Preparation of Novel Carbenes and their Catalytic Application to the Cross-Benzoin, Aza-Benzoin and Stetter Reactions

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By

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Abstract

N-Heterocyclic carbenes (NHCs) derived from bicyclic triazolium salts possessing a fused 6 membered ring were found to induce chemoselectivity in the cross-benzoin between aromatic and aliphatic aldehydes. Use of these catalysts gave rise to predominantly one cross-benzoin product which could be isolated in good to excellent yield (68-99%). Consistently high chemoselectivity was realized across a wide range of substrates. Examples were shown using benzaldehyde and several different unbranched aliphatic aldehydes. The reaction was also effective with *ortho*, *meta* or *para* substituted aromatic aldehydes (possessing either electron donating or withdrawing substituents) and was tolerant to α and β branched aliphatic aldehydes as well.

A library of bis(amino)cyclopropenium salts were prepared, and the corresponding bis(amino)cyclopropenylidenes (BACs) generated in situ were screened in the Stetter reaction. Among those tested, bis(diethylamino)cyclopropenylidene (EtBAC) was found to be the most efficient BAC catalyst for the Stetter reaction. EtBAC was also found to be superior to common NHCs in reactions with β-alkyl ketone acceptors or electron rich aromatic aldehydes. A chiral bis-1,4-dimethylpyrrolidine derived BAC catalyst demonstrated superior enantioselectivity (73% *ee*) compared to triazolium systems. Reaction monitoring and crossover experiments revealed no formation of benzoin product with EtBAC, unlike other carbenes.

EtBAC was found to be an excellent catalyst for aza-benzoin reactions with *N*-phosphinoyl imines and their derivatives. Anhydrous conditions were necessary, but the reaction was otherwise robust and afforded good yields (69-96%) with a number of aromatic and heteroaromatic aldehydes. Substitution on the *N*-phosphinoyl imine was also tolerated. An excess of aldehyde improved reactivity in some instances, and no homo-benzoin side-products were observed in aza-benzoin reactions with EtBAC.

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List of Schemes

List of Abbreviations

$[\alpha]_D$	Specific rotation (units are implied)
Å	Angstrom(s)
Ac	Acetyl
AIBN	2,2'-azobisisobutyronitrile
aq	Aqueous
Ar	Aryl
BAC	Bis(amino)cyclopropenylidene
Bn	Benzyl
BnBAC	Bis(dibenzylamino)cyclopropenylidene
Boc	*tert*-Butoxycarbonyl
bp	Boiling point
br	Broad (spectral)
t-Bu	*tert*-Butyl
°C	Degrees Celsius
calcd	Calculated
CI	Chemical Ionization
CIF	Crystallographic Information File
COSY	Correlation spectroscopy
Cy	Cyclohexyl
m-CPBA	*meta*-Chloroperoxybenzoic acid
δ	Chemical shift in parts per million
d	Day(s); doublet (spectral)
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DMAP	4-(*N*,*N*-Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
EDG	Electron-donating group
ee	Enantiomeric excess
equiv	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EtBAC	Bis(diethylamino)cyclopropenylidene
EWG	Electron-withdrawing group
FCC	Flash column chromatography
FTIR	Fourier transform infrared
g	Gram(s)
h	Hour(s)
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infrared

i-PrBAC	Bis(diisopropylamino)cyclopropenylidene
J	Coupling constant (in NMR spectroscopy)
LDA	Lithium diisopropylamide
lit.	Literature value (abbreviation used with period)
M	Molar (moles per litre)
M^+	Parent molecular ion
m	Multiplet (spectral)
Me	Methyl
MeBAC	Bis(dimethylamino)cyclopropenylidene
Mes	Mesityl (2,4,6-trimethylphenyl)
MHz	Megahertz
min	Minute(s)
mol	Mole(s)
mp	Melting point
MS	Molecular Sieves; mass spectrometry
MW	Microwave irradiation; molecular weight
m/z	Mass-to-charge ratio
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
N. R.	No reaction
Pd/C	Palladium on charcoal
Ph	Phenyl
PipBAC	Bis(dipiperidino)cyclopropenylidene
ppm	Part(s) per million
PPTS	Pyridinium *para*-toluenesulfonate
i-Pr	*iso*-Propyl
Pr	Propyl
PTLC	Preparative thin-layer chromatography
PyBAC	Bis(dipyrrolidino)cyclopropenylidene
q	Quartet (spectral)
R	Any substituent
R_f	Retention factor (in chromatography)
r.t.	Room temperature
s	singlet (spectral); second(s)
t	Triplet (spectral)
t	Time
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin-Layer Chromatography
TMG	*N*,*N*,*N'*,*N'*-Tetramethylguanidine
TOF	Time-of-flight (in mass spectrometry)
Ts	Tosyl(*para*-toluenesulfonyl[*p*-CH_3-C_6H_4-SO_2])

Chapter 1: Introduction

1.0 Synthons and Umpolung

The construction of carbon-carbon bonds is fundamental to organic chemistry. To categorize the multitude of ways these bonds may be formed Corey and Seebach have introduced the concept of *synthons*; structural units within molecules that can be formed by known synthetic operations.[1] When considering potential *synthons,* the effects of heteroatoms must be taken into account. With the exception of 3 membered rings, heteroatoms induce alternating donor/acceptor reactivity which propagates along carbon chains. For instance, in considering a Grignard reaction with an enone, direct (1, 2) and conjugate (1, 4) addition is reasonable, while α-addition (1, 3) is not. Dienols are nucleophilic at the α and γ positions, but not the β site. Consequently, preparing molecules with an odd number of carbon atoms between heteroatoms (1,3; 1,5; etc.) is generally more straightforward than preparing molecules with an even number of atoms linking them (1,2 1,4 etc.). Efficiently forming even-numbered attachments usually requires 3-membered rings, radical transformation, redox transformations, or reagents capable of inverting the normal mode of reactivity of a molecule to generate the desired *synthon*. The concept of inverting the normal mode of reactivity has been termed *umpolung*.[2]

Cyanohydrins and dithioacetals are examples of stoichiometric *umpolung* reagents. They can be deprotonated with base to give nucleophilic anions (acting as donors), but can afterwards be converted back to acceptor functionalities. This can also be accomplished catalytically with the use of carbenes. In biological systems the thiamine coenzyme serves this function, performing reactions *in vivo* which are vital for life (such as being a cofactor for pyruvate dehydrogenase in sugar metabolism).[3] Studying carbenes and *umpolung* reactivity is of interest for preparing biologically relevant molecules and for studying the chemistry of life.

1.01 General Discussion of Carbenes

Carbenes are molecules which contain carbon atoms that are charge-neutral, divalent, and possess 6 electrons in their outer shell. The unbonded electrons may occupy two half filled orbitals and react in a manner akin to diradicals; these are called triplet carbenes (**Figure 1.1**, **1**).[4] Alternatively both electrons may occupy the same orbital, leaving one filled and one empty orbital on the same atom (**Figure 1.1**, **2**). These are known as singlet carbenes and they may react as both nucleophiles and electrophiles depending upon the circumstances. The chemical ambivalence of singlet carbenes is the basis of their *umpolung* reactivity. Whether the carbene occupies primarily a singlet or triplet electronic state, and the energetic gap between states is determined by the stabilizing influences of substituents.[5,6,7] Substituents which are σ-electron-withdrawing and capable of π-donation increase the singlet triplet gap and therefore stabilize singlet carbenes (as depicted in **Figure 1.1**, **3**).[8] This is accomplished with heteroatoms, or some stabilising π-systems. The ideal R-C-R angle for triplet carbenes is 180°, whereas the ideal angle for singlet carbenes is around 120°. Thus singlet carbenes are stabilized by cyclic substituents which constrain the bond angle towards 120°. Bulky substituents also prolong the lifetimes of carbenes by shielding the carbene center from reactions.[9]

Figure 1.1 Representations of Carbenes

The first carbene to be unambiguously isolated was bisadamantyl imidazolylidene, an *N*-heterocyclic carbene (NHC) reported by Arduengo and coworkers in 1991.[10] It met all the above criteria. Bertrand and coworkers reported a (phosphino)-(silyl)carbene in 1988 however key

evidence for that structure followed Arduengo's work.[11] As carbenes have become popular as ligands on transition metals, a wide variety of carbenes have since been isolated for study.[12] Persistent carbenes with only one α-heteroatom are known, but are generally considered less stable that those with two α-heteroatoms.[13] Anti-Bredt carbenes, where the carbene is inductively stabilized by two heteroatoms but only receives π-donation from one (because stabilization from the other violates Bredt's rule), are known but are much less stable than isomers with π-donation by both heteroatoms.[14] Acyclic carbenes are also known but are generally less stable than cyclic carbenes.[15] Thus NHC's, which in general satisfy these criteria, are stable enough to serve as organocatalysts in the benzoin, Stetter, aza-benzoin reaction as well as other *umpolung* transformations.[16,17]

1.02 Bis(amino)cyclopropenylidenes

Cyclopropenylidene has been detected in interstellar space and as part of combustion, but is much less stable in condensed media (outside of an argon matrix at >40 Kelvin).[18] Adding amino substituents was found to improve the stability of this carbene considerably, and to date Bis(amino)cyclopropenylidenes (BACs) are the only persistent carbenes not directly stabilized by a heteroatom (**Figure 1.1**, **4**).[19]

Yoshida and coworkers came close to isolating a BAC-type carbene in the 70s, which would have predated Arduengo substantially.[20] Instead they isolated a lithium adduct, but Bertrand and coworkers revisited the reaction and reported isolation of the first BAC-type carbene in 2006.[21] It was persistent enough for characterization by X-ray crystallography and was thermally stable at elevated temperatures. Based on X-ray crystal data and computational modelling it was concluded BACs are singlet carbenes with high singlet-triplet energy barriers (~153 kJ/mol), like NHCs.[22] This is due to substantial stabilization by the amino groups and Hückel aromaticity.[23] Sterically, BACs are less constrained than imidazolinium-, imidazolium-,

or triazolium-derived NHC's with the substituents positioned further away from the carbene center.[24] Interestingly, homo-dimerization has not been observed with bis(diisopropylamino)-cyclopropenylidene (*i*-PrBAC), unlike other unhindered carbenes.[25]

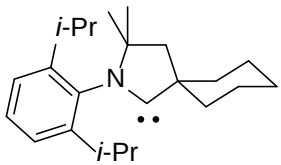
The relative nucleophilicity of BACs and NHCs is of great interest however there is debate about what metrics are most relevant and how best to go about measurement. The kinetics of carbene formation via deprotonation of corresponding azolium salts (such as thiazolium) has been studied to this end, but not with BACs.[26] A popular approach compares the donor strength of carbenes (which may be correlated with nucleophilicity) by examining bond lengths and the IR stretching frequencies of *syn* or *anti* CO groups of transition metal derivatives.[27] These values can be correlated to Tolman's electronic parameter for phosphines.[28]

Comparison of the rhodium CO stretching frequencies found *i*-PrBAC to be slightly more electron donating than CAACs, as well as imidazolinium, imidazolium and triazolium NHC's (**Table 1.1**). A lower value indicates stronger bonding by an *anti* carbene ligand. Similar derivatization of BACs was done using palladium and molybdenum by Yoshida, though these values are more difficult to directly compare to NHC's.[29] Tamm and coworkers prepared series of tungsten pentacarbonyl complexes and found *i*-PrBAC to have an intermediate bond length and ^{13}C NMR chemical shifts, (between imidazolium and oxazolium NHC's) which is consistent with the rhodium system.[30] One drawback of these approaches is that they do not separate the effect of σ-bonding from π-backbonding. Presumably only σ-bonding information is relevant to assessing nucleophilicity.

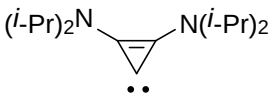
To look at the sigma donor component of carbenes, Bertrand and coworkers prepared CO_2 adducts of carbenes and assessed changes in CO stretching frequencies which are due to σ-bonding in this system (**Table 1.1)**. They concluded that *i*-PrBAC was more electronically

donating than several NHCs. Bertrand and coworkers also looked at carbene-phosphine adducts to explore backbonding interactions, as phosphorus is capable of partial π-backbonding with carbenes and its ^{31}P NMR shift is responsive to changes in electron density. Phosphorus bonded to *i*-PrBAC was found to be more shielded and thus have weaker back-bonding interaction than any other carbene surveyed. Considering *i*-PrBAC's ability to stabilize cationic phosphonium species, this assessment seems reasonable.[31]

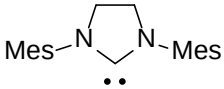
Table 1.1 Spectroscopy of Carbene Derivatives



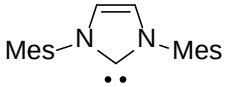
5
CAAC



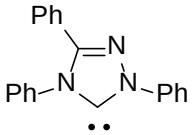
6
i-PrBAC



7
Imidazolinylidene



8
Imidazolylidene



9
Triazolylidene

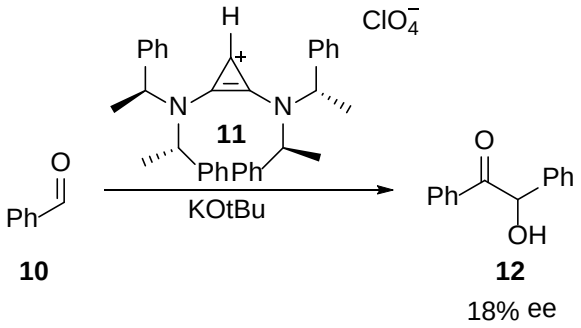
compound[a]	**5**	**6**	**7**	**8**	**9**
cis-(RhCl(CO)$_2$L ave CO stretch (cm^{-1})	2036[32,b]	2031[33]	2039[34]	2041[34]	2049[35]
LCO$_2$ CO stretch (cm^{-1})	1676[36]	1660[34]	1684[37]	1675	-
*L=PPh ^{31}P Value[38] (ppm)	68.9	-34.9	-10.4	-23.0	-

a) Where L is the carbene; b) From a 2-isopropyl-4 methyl substituted cyclohexane derivative.

1.03 Bis(amino)cyclopropenylidenes as Catalysts

Several transition metals complexes with BAC ligands have been characterized. Of note, Grubbs-type catalysts have been prepared with *i*-PrBAC taking the place of an NHC.[39] Along similar lines, a nickel-BAC complex was explored for aldehyde-alkyne reductive couplings along with several NHC's.[40] Cazin and coworkers used a copper-BAC complex to catalyze some azide-alkyne click reactions.[41] The only report of organocatalysis with BACs comes from Tamm and coworkers. They prepared chiral bis(amino)cyclopropenium salt **11** as a ligand to a silver

complex, but found it could catalyze the homo-benzoin reaction (**Scheme 1.1**), with unreported efficiency and poor enantioselectivity.[42]



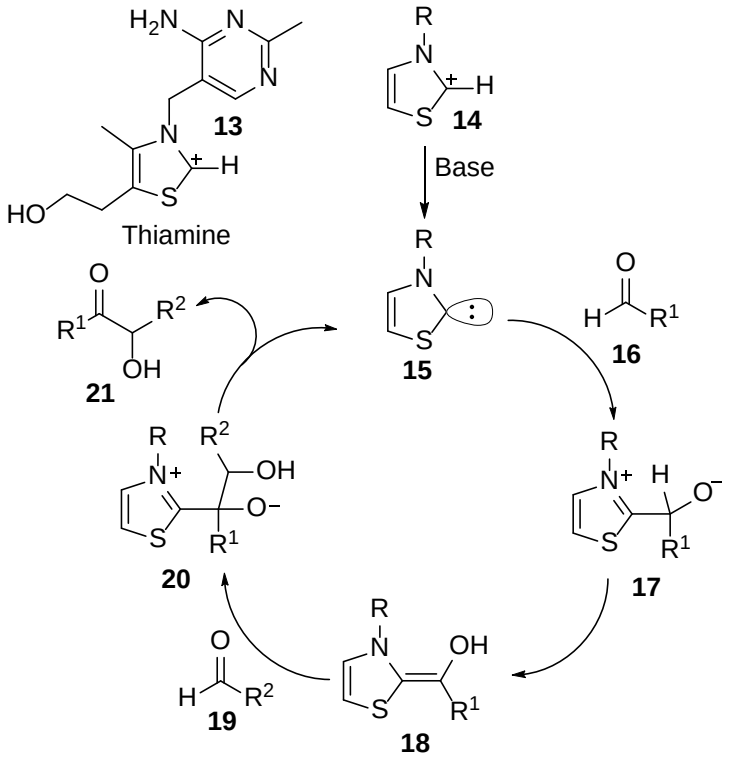
Scheme 1.1 BAC Catalyzed Benzoin Reaction by Tamm and Coworkers

To summarize, BACs are known to be stable carbenes with properties similar to NHCs. They are more strongly σ-donating than NHCs, and this property may correlate to higher nucleophilicity. Unlike NHCs they have not been explored significantly for umpolung organocatalysis.

1.1 Cross Benzoin Reaction

The benzoin reaction is one of the earliest known organic reactions. Its discovery is often attributed to Whöler and Liebig (1832) and their work with the oil of bitter almonds,[43] though Stange (1824) reported a similar transformation.[44] Zinin found that the cyanide source in this reaction could be used in substoichiometric quantity.[45] Lapworth (1903) proposed the α-deprotonation of cyanohydrins and their addition to aldehydes as the mechanism for this transformation.[46] This proposal was validated by the kinetic studies of Schowen and coworkers who found neither the deprotonation nor the aldehyde addition step to be fully rate limiting with cyanide.[47] Realizing the potential applications for homo-benzoin products was limited, Buck and Ida attempted to selectively prepare crossed acyloin products from mixtures of aldehydes but the

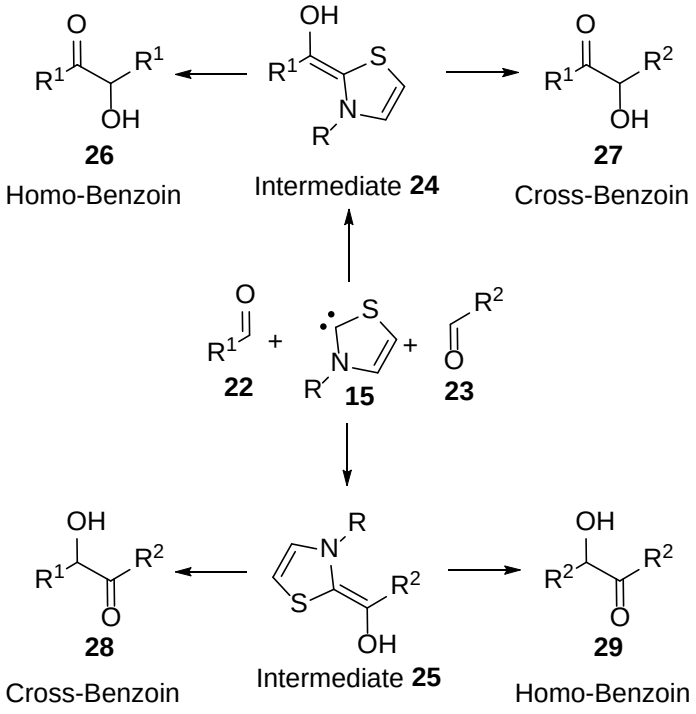
results of these early studies were ambiguous.[48] Ukai, Tanaka and Dowaka reported the first NHC catalyzed benzoin reaction using thiamine.[49]



Scheme 1.2 Mechanism of the Benzoin Reaction Proposed by Breslow

Breslow proposed the currently accepted mechanism for this reaction which is analogous to the one put forth by Lapworth (**Scheme 1.2**). Breslow's key insight was that the thiazole ring could be deprotonated to give a carbene, which was demonstrated by isotopic labelling experiments.[50] Carbene **15**, like cyanide, is nucleophilic and reacts with the aldehyde forming an adduct (**17**). Proton transfer (presumably stepwise) in adduct **17** forms intermediate **18**, now called a Breslow intermediate. The former carbonyl carbon is now nucleophilic, and adds to another aldehyde (**19**). Intermediate **20** subsequently ejects the catalyst to give the benzoin product **21**, and regenerates the catalyst. When $R^1 \neq R^2$ this process is referred to as a cross-benzoin reaction.

The main challenge of attempting to couple two different aldehydes is producing and isolating the desired product with reasonable efficiency. If the aldehydes are similar, either Breslow intermediate (**24** or **25**, *E or Z*) can form (**Scheme 1.3**). These intermediates can then react with either aldehydes indiscriminately (**22** or **23**), to give rise to four different products (**26-29**, two homo-benzoin and two cross-benzoin), when only one product is desired. If one aldehyde is substantially more reactive than the other, homo-benzoin processes will dominate the reaction.

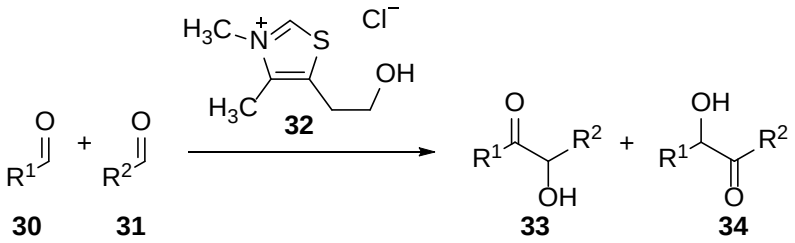


Scheme 1.3 Possible Cross-Benzoin Products

Stetter and Dämbkes (1977) discovered that thiazolium catalyzed cross-benzoin reactions using α-branched aliphatic aldehydes or *o*-chlorobenzaldehyde could form one cross-benzoin product with negligible (entry 5) to excellent (entry 2) chemoselectivity (**Table 1.2**, entries 1-8, homo-coupled products not reported).[51] Other aldehydes gave rise to near statistical mixtures.

Three strategies have since arisen to attempt to direct the cross-benzoin reaction towards generating a single cross-benzoin product. These are: using substrates which can only act as acyl donor or acceptor (but not both), biasing reaction stoichiometry, and using catalysts to introduce chemoselectivity between dissimilar aldehydes.

Table 1.2 The First Report of a Chemoselective Cross-Benzoin Reaction by Stetter[51]

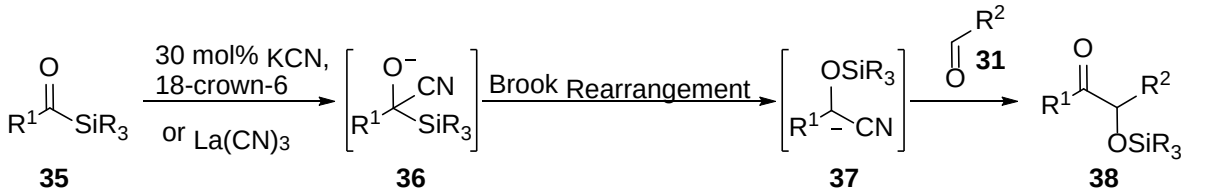


entry	R^1 =	R^2 =	ratio **33**:**34**[i]
1	Ph	*i*-C_3H_7	35:65
2	*o*-ClC_6H_4	*i*-C_3H_7	100:0
3	*o*-ClC_6H_4	$(CHCH_3)$n-C_3H_7	100:0
4	*o*-ClC_6H_4	CH_3	0:100
5	*p*-ClC_6H_4	*i*-C_3H_7	45:55
6	2-furyl	*i*-C_3H_7	95:5
7	2-thiophene	*i*-C_3H_7	100:0
8	*n*-C_7H_{15}	*i*-C_3H_7	30:70

The most straightforward strategy is to use a substrate incapable of competing in the desired reaction. For the acyl donor this can be done in a non-catalytic fashion using dithianes, cyanohydrins or *O*-silyl thiazolium carbinols (*O*-silyl protected **17**).[52] This has also been

[i] It has since been pointed out entries 2 and 3 are likely misassigned as the alternate cross-acyloin product[63]

accomplished catalytically with cyanide by Linghu, Bausch, and Johnson who used acyl silanes as aldehyde surrogates to achieve chemoselectivity (**Scheme 1.4**).[53] They found acyl silanes competitively form Breslow intermediate analogues following a Brook rearrangement.[54] This methodology is only successful with some acyl silanes, which can be difficult to prepare, but is otherwise general.



R_3 = Me_3, Et_3, Me_2Ph
R^1 = Ph, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$, *n*-hex, Me
R^2 = Ph, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$, *p*-$Me_2NC_6H_4$, Mes, 2-furyl, *N*-Me-2-pyrrole, *i*-Pr, cyclohexane, CH_2CH_2Ph, CH=CHPh, *n*-hex, *t*-Bu

Scheme 1.4 Cross-Benzoin Reactions via Brook Rearrangement

1.11 Cross-Benzoin Reaction with Ketones

Regarding non-competitive acyl acceptors, cross-benzoin reactions with ketone acceptors are known (representative products **39-47** in **Figure 1.2**). As these ketones cannot undergo an umpolung processes, only a single cross-benzoin product is possible. The reaction has been performed intramolecularly to generate 5- or 6-membered rings in good yield and enantiomeric excess.[55] It has also been used to desymmetrize 1, 3-diketones[56] and in the synthesis of complex natural products.[57] Intermolecularly, more activated carbonyl acceptors are required such as trifluoromethyl ketones, α-keto esters and isatins.[58,59,60] Acyl silanes as well as acyl phosphonates have also been used in cross-benzoin reactions with phenyl ketones.[61]

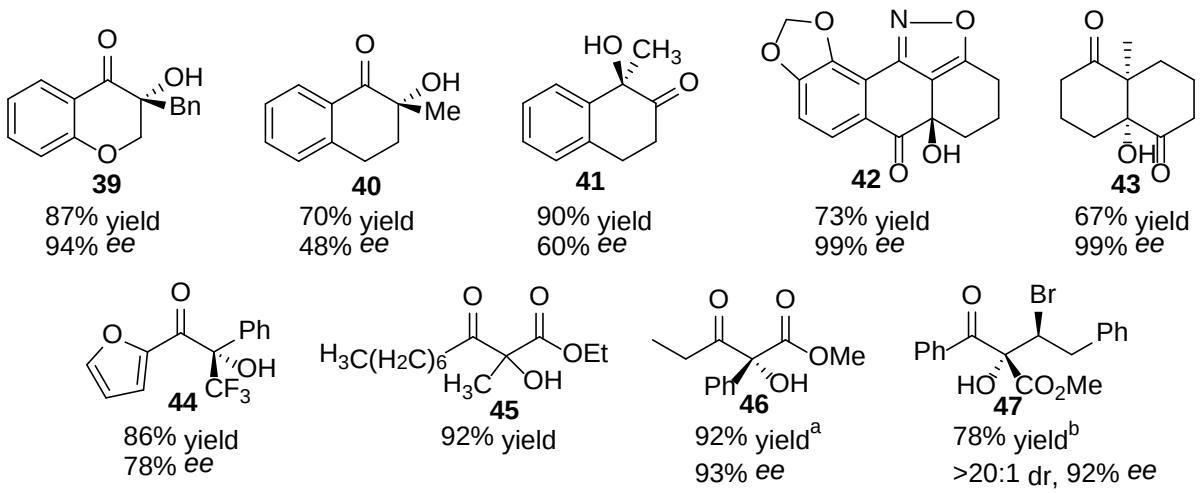
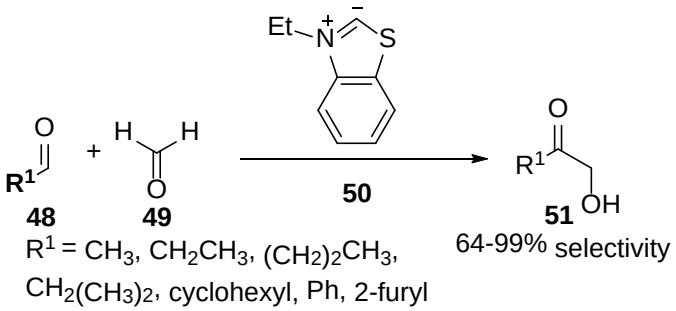


Figure 1.2 Examples of Aldehyde-Ketone Cross-Benzoin Products

a) From the work of our own Dr. Thai b) from the dynamic resolution of racemic bromide substrates.

Inoue and coworkers observed excellent chemoselectivity for cross-benzoin product **51** in reactions using formaldehyde (**Scheme 1.5**).[62] Chemoselectivity was rationalized to be due to the inability of a hydride group to stabilize a Breslow intermediate to the same extent an alkyl or aryl group can. Thus this is also a reaction with a non-competitive acceptor.



Scheme 1.5 Cross-Benzoin Reactions with Formaldehyde[ii]

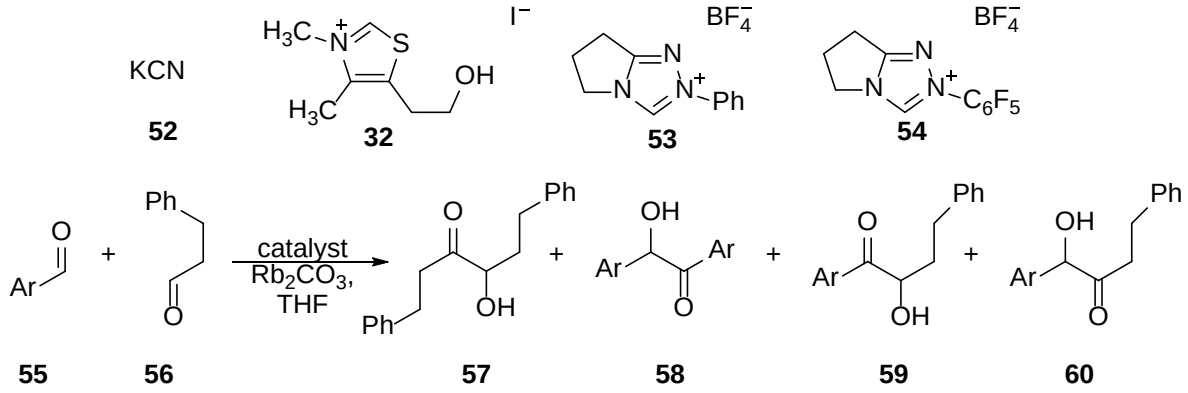
1.12 Catalyst Control

O'Toole, Rose, Zeitler and Connon revisited the cross-benzoin reaction and found the chemoselectivity reported by Stetter could be improved through use of *N*-pentafluorophenyl triazolium catalyst **54** (**Table 1.3**, entries 4-11).[63] Reactions between aliphatic aldehydes and aromatic aldehydes with bulky groups in the *ortho* position selectively formed cross-benzoin

[ii] Selectivity was determined using Gas-Liquid chromatography on silated reaction mixtures containing **51**

product (**60**) in reasonable yield (50-83%). More than other catalysts (entries 1-3) there was a bias towards the product derived from the Breslow intermediate of the aliphatic aldehyde.

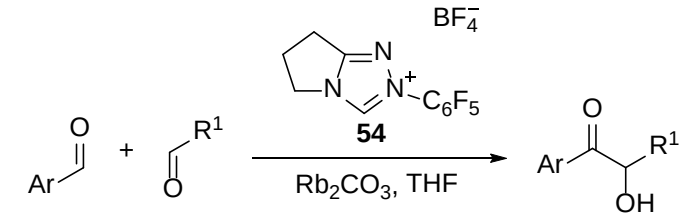
Table 1.3 Cross-Benzoin Selectivity Observed by Connon and Zeitler[62]



			ratio of products			
entry	Ar =	catalyst	**57**	**58**	**59**	**60**
1[a]	*o*-ClC_6H_4	CN	-	-	-	<5
2[a]	*o*-ClC_6H_4	**32**	-	-	-	38
3	Ph	**53**	<2	8	<2	10
4	Ph	**54**	26	20	11	48
5	*p*-ClC_6H_4	**54**	53	44	2	43
6	*o*-ClC_6H_4	**54**	8	15	9	51
7	*o*-FC_6H_4	**54**	52	45	14	34
8	*o*-$CH_3OC_6H_4$	**54**	20	16	21	59
9	*o*-$CF_3C_6H_4$	**54**	8	6	10	81
10[b]	*o*-BrC_6H_4	**54**	0	9	8	49
11[b]	*o*-BrC_6H_4	**54**	31	4	7	84

a) In these reactions Connon and Zeitler used the conditions originally reported by Buck and Stetter respectively.

The same group observed high chemoselectivity in reactions with aliphatic aldehydes possessing α-branched substituents (**Scheme 1.6**). In these cases the aliphatic aldehyde was more hindered. Interestingly, heteroaromatic aldehydes were unselective in this reaction. Crossover experiments found every product except the aromatic homo-benzoin was formed irreversibly under these conditions, meaning the reaction was under kinetic control.



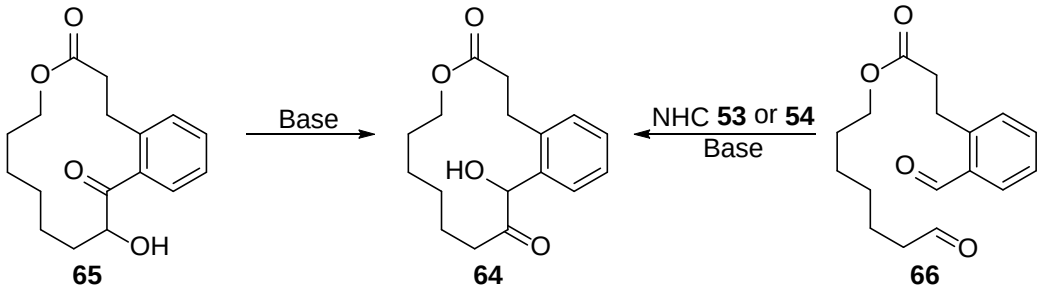
61 **62** **63**

Ar = *o*-BrC_6H_4, *o*-ClC_6H_4, *o*-IC_6H_4,*o*-$CF_3C_6H_4$, *o*-Br-*mp*-$(CH_3O)C_6H_2$, *o*-Br-*p*-$CH_3C_6H_3$, *p*-BrC_6H_4, *p*-ClC_6H_4, *p*-$CH_3OC_6H_4$
R^1 = cyclohexyl, cyclopropyl, *i*-Pr

36-80% yield

Scheme 1.6 Cross-Benzoin Reactions with α-Substituted Aliphatic Aldehydes

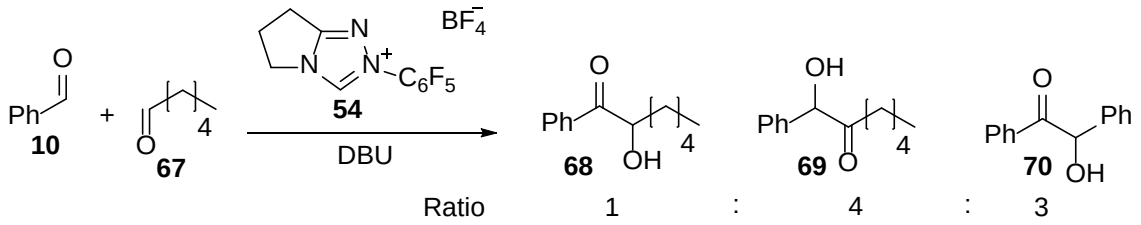
High chemoselectivity was also observed intramolecularly by Mennen and Miller in their preparation of acyloin macrolactones (**Scheme 1.7**).[64] Triazolium **53** and **54** successfully reacted with the dialdehyde **66** to form acyloin **64** (30% and 48% yield respectively). The opposite cross-benzoin product (**65**) could be converted to **64** using base, indicating it to be the most thermodynamically stable product.



65 **64** **66**

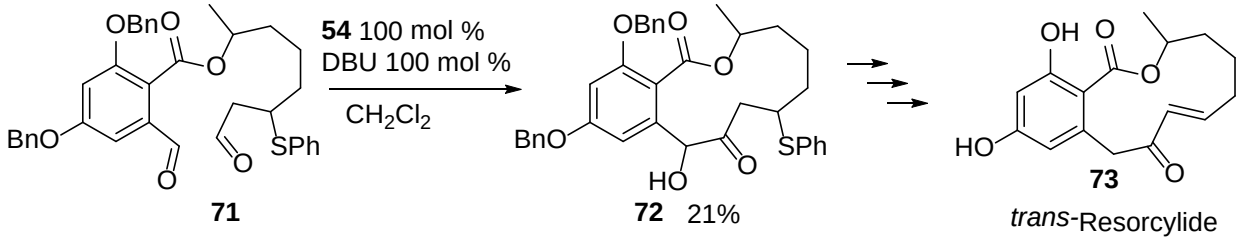
Scheme 1.7 Intramolecular Cross-Benzoin Reactions

It was presumed that **64** was the thermodynamic product because of a minimization of ring strain, however an acyclic version of the reaction on a model system had a similar outcome with benzaldehyde (**Scheme 1.8**). The reaction was then used to produce 11- to 13-membered macrocycles in modest (16-47%) yield.



Scheme 1.8 Acyclic Cross-Benzoin Reactions by Mennen and Miller

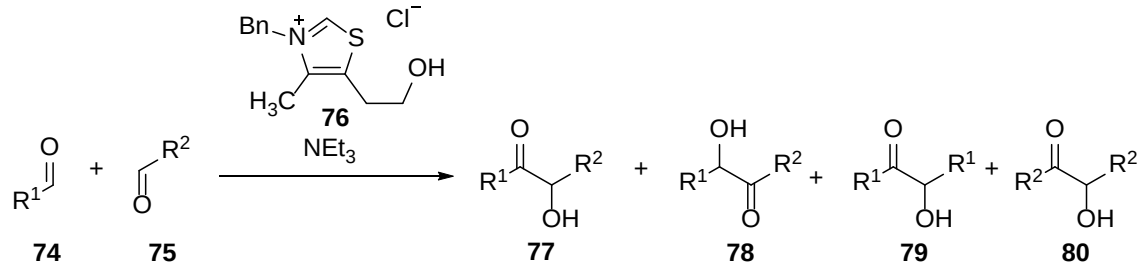
This methodology was applied to a formal synthesis of *trans*-resorcylide, the only natural product synthesis containing an NHC-catalyzed aldehyde-aldehyde cross-benzoin reaction to date (**Scheme 1.9**).



Scheme 1.9 Synthesis of *trans*-Resorcylide via Cross-Benzoin Reaction

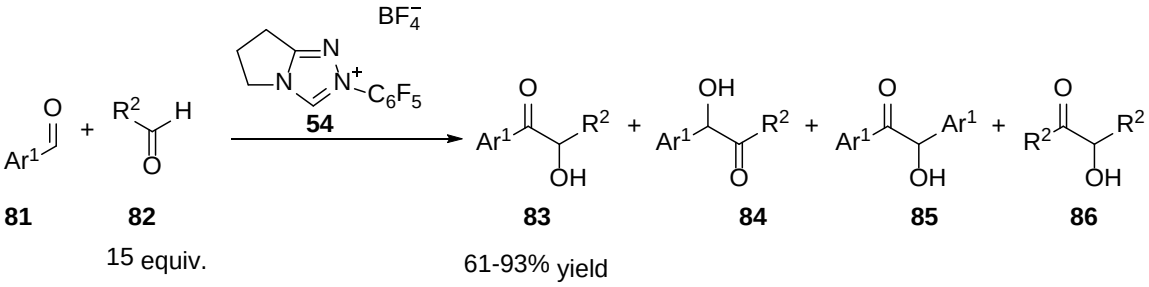
1.13 Chemoselective Cross-benzoin Reactions Using Substrate Stoichiometry

Following Stetter's example, Retéy and Golding used aldehyde stoichiometry as the main chemoselectivity directing influence in the cross-benzoin reaction (**Scheme 1.10**).[65] They found a 3:1 stoichiometry of aldehydes under thermodynamic conditions biased the reaction heavily towards both cross-benzoin products (**77** and **78**), with respect to the limiting aldehyde.



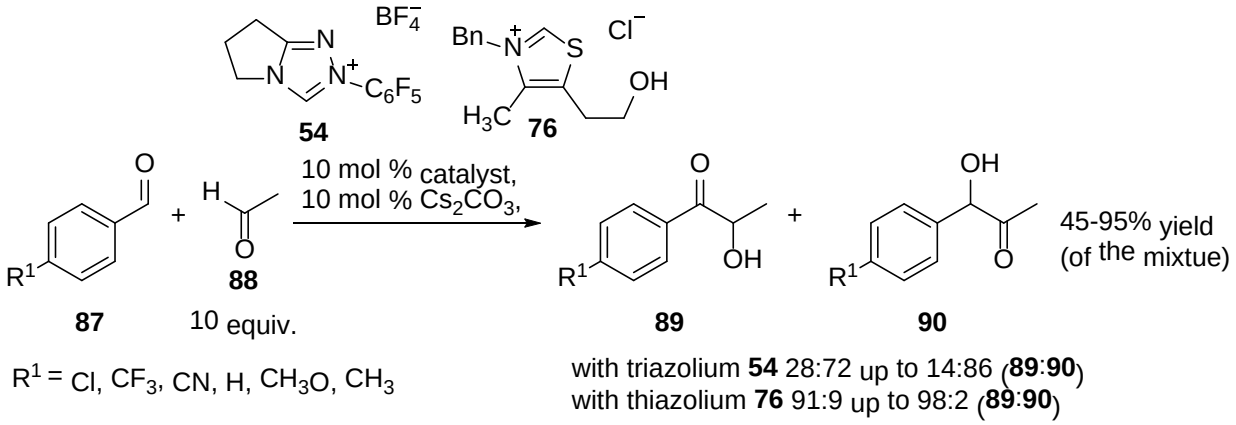
Scheme 1.10 Alkyl-Alkyl Cross-Benzoin Reactions Reported by Retéy and Golding

Song and Yang took this approach further (**Scheme 1.11**).[66] Using 15 equivalents of aliphatic aldehyde they obtained a number of aliphatic-aromatic cross-benzoin products in synthetically attractive yields, with relatively minor quantities of compounds **84** and **85** produced (the amount of compound **86** was not reported).

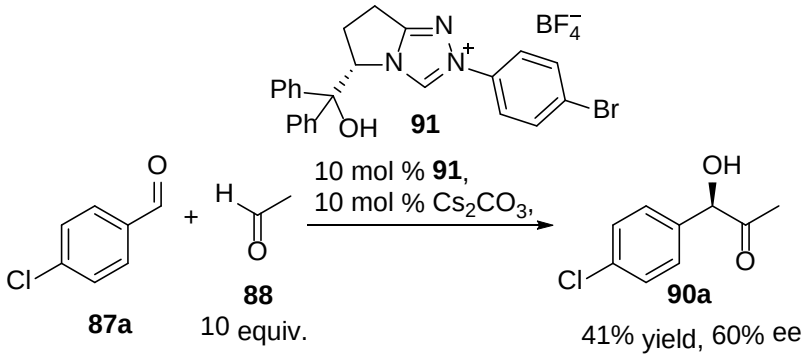


Scheme 1.11 Cross-Benzoin Products Reported by Song and Yang

Using acetaldehyde Han, Yang and coworkers were able to exploit both stoichiometry control and aldehyde selectivity to produce either cross-benzoin product **89** or **90** (**Scheme 1.12**).[67] They were also able to perform the reaction enantioselectively (**Scheme 1.13**).



Scheme 1.12 Cross-Benzoin by Han, Yang and Coworkers



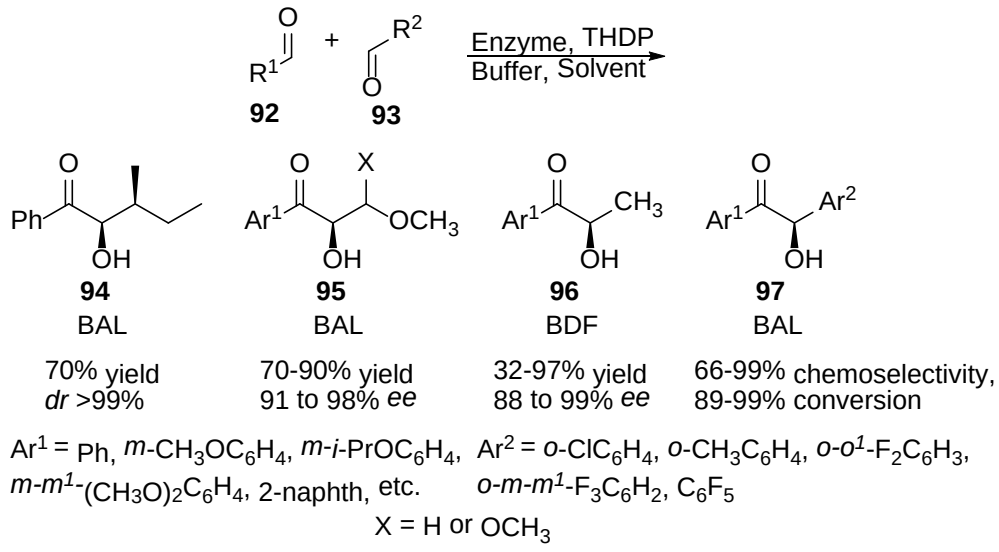
Scheme 1.13 Enantioselective Cross-Benzoin Reactions with Acetaldehyde

An analogous reaction using trifluoroacetaldehyde instead of acetaldehyde was reported by Anand and coworkers.[68]

1.14 Cross-Benzoin Reactions Catalyzed by Enzymes

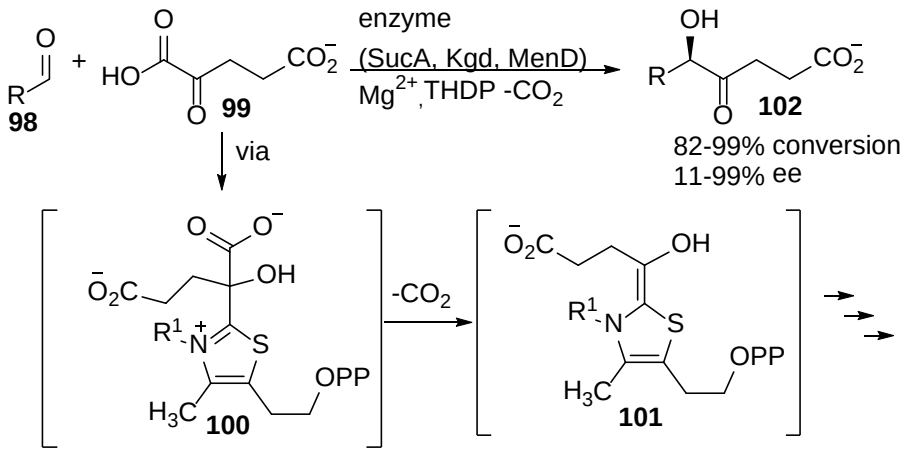
Biologically significant carbon-carbon bond forming or cleaving reactions are performed *in vivo* by thiamine diphosphate (ThDP) dependent enzymes, such as pyruvate decarboxylase, α-ketoglutarate dehydrogenase, benzaldehyde lyase (BAL) and benzoylformate decarboxylase (BFD).[69] In a synthetic setting, the groups of Müller, Demir, and Domínguez de María have achieved good to excellent chemoselectivity for the cross-benzoin reaction between branched aliphatic aldehydes and aromatic aldehydes using BAL or BFD enzymes, as well as mutants

thereof (**Scheme 1.14**).[70,71,] These reactions were often highly enantioselective given the chiral nature of the enzyme pocket. Excellent chemoselectivity has been achieved between aromatic aldehydes and *o*-halo aromatic aldehydes using BAL or a mutant of BFD.[72]



Scheme 1.14 Enzymatic Cross-Benzoin Reactions between Aldehydes

Cross-benzoin products have also been generated using α-keto acids in combination with decarboxylase enzymes (**Scheme 1.15**). Rather than deprotonation, decarboxylation generated the acyl anion in these cases. Müller and coworkers found enantiomeric excess with aromatic aldehydes was very good (76-99% *ee*), but α-β-unsaturated aldehydes were more modest (63-61% *ee*) and the *ee* with aliphatic aldehydes was negligible using a MenD enzyme.[73] When other α-keto acids (methyl, ethyl, α-carboxyl, δ-carboxyl) were used, SucA was the only decarboxylase to show any reactivity (conversion <53%). Despite these drawbacks, this reaction has been modified to produce (S)-phenylpropionylcabinol on scale.[74] These enzymes have also been used to perform cross-benzoin reactions with ketones.[75]



Scheme 1.15 Enzymatic Cross-Benzoin Reactions with α-Keto Acids

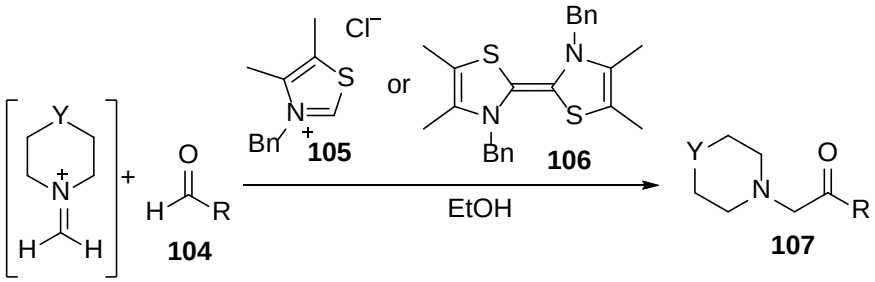
1.15 Cross-Benzoin Summary

To summarize the above examples, achieving high chemoselectivity in the cross-benzoin reaction is a well known problem. Strategies to obtain highly chemoselective reactions have made use of specialized substrates, enzymes and reaction stoichiometry. These approaches have inherent limitations in substrate scope and/or material throughput.

1.2 The Aza-Benzoin Reaction

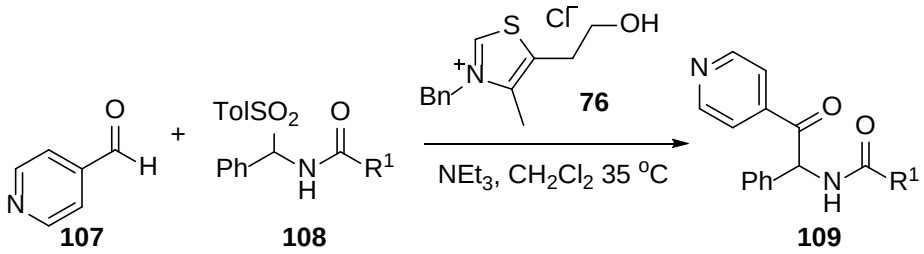
As the benzoin reaction is the addition of an aldehyde to a carbonyl, the aza-benzoin reaction is the addition of an aldehyde to an imine. Castells, Bassedas, Urrios, and López-Calahorra reported the first aza-benzoin reactions with thiazolylidene catalysts and iminium salts derived from paraformaldehyde and morpholine or piperidine **103** in 1988 (**Scheme 1.16**).[76] Rovis and co-workers reported that stable adducts formed when triazolylidines were combined with dialkyl iminium salts, instead of the intended *umpolung* reactions.[77] This demonstrates the challenge of aza-benzoin reactions, as catalysts can be inhibited or even poisoned by imine substrates. Successful strategies have addressed this issue by varying catalysts and reaction conditions to be compatible with a type of imine or varying the imine to be compatible with

catalyst and conditions. These approaches have lead to specialized methods possessing substantial limitations.

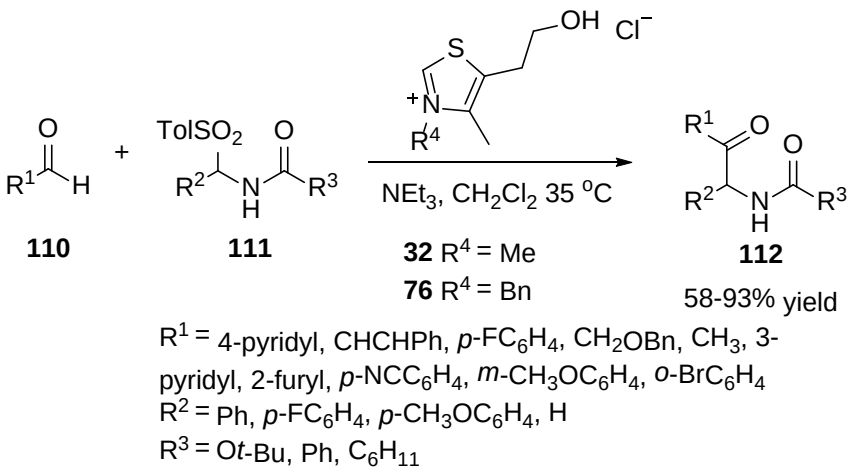


Scheme 1.16 The First Reported Aza-Benzoin Reaction

Murry, Reider and co-workers made use of arylsulfonylamides, which can eliminate sulfinic acid to give acylimines under mild conditions (**Scheme 1.17, 1.18**). [78] The concentration of imine was, in theory, kept low which minimized inhibition. The nature of the base had a strong influence in this reaction as triethylamine and potassium carbonate were effective while DBU, tetramethyl-guanidine and DABCO gave low conversion or no product. The reaction generally worked well except with an aliphatic imine (R^2 = *c*-C_6H_{11}) which isomerized to an enamide under reaction conditions (**Scheme 1.18**).

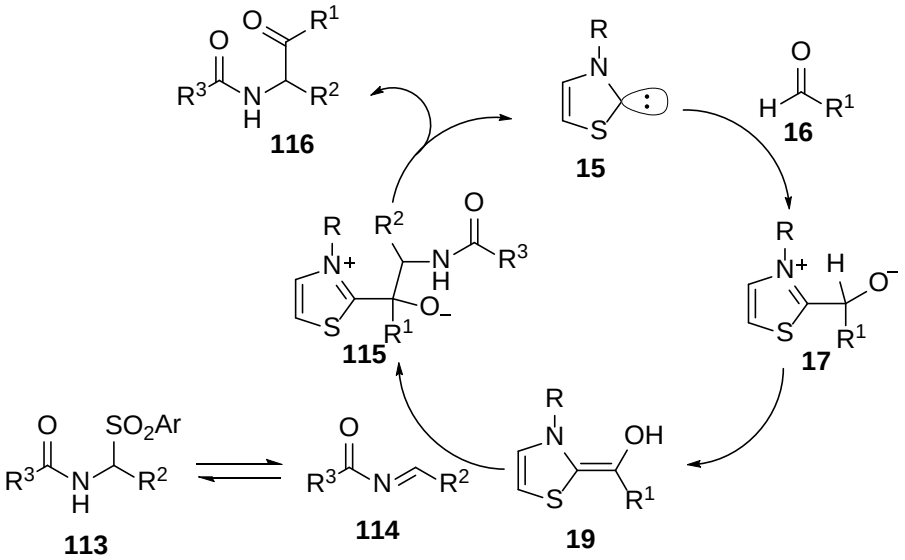


Scheme 1.17 *N*-Protecting Groups Explored by Murry and Reider



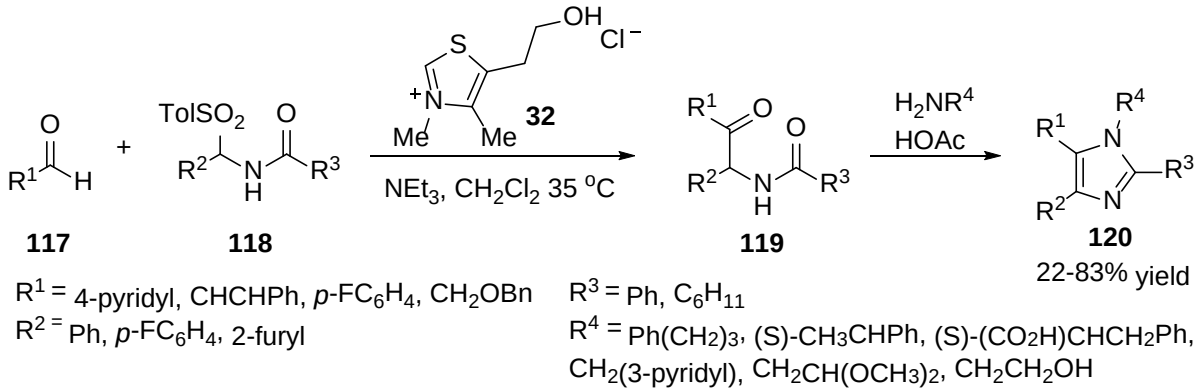
Scheme 1.18 Substrate Scope of Aza-Benzoin Reactions Explored by Murry and Reider

The mechanism proposed for the aza-benzoin reaction by Murry and Reider is analogous to the mechanism proposed for the benzoin reaction (**Scheme 1.19**). NMR studies were able to detect the imine-sulfonylamide equilibrium between species **113** and **114**. An alternate mechanism where the acyl anion formed with the imine first, then tautomerized, was ruled out by isotope labelling experiments. Crossover experiments found the reaction to be under kinetic control.



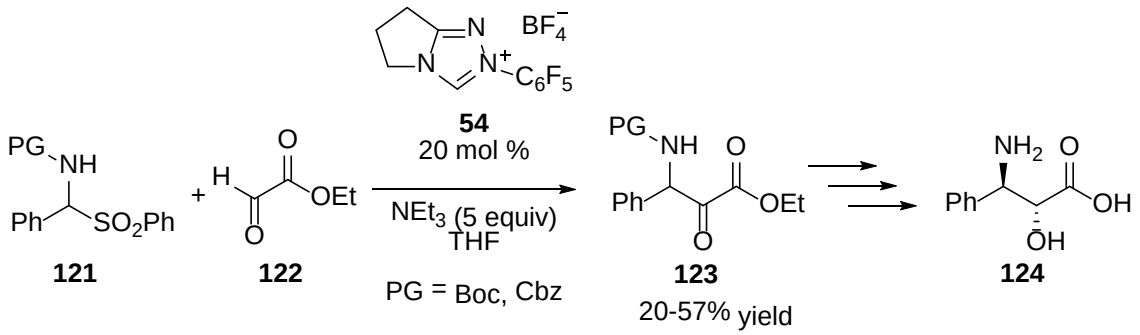
Scheme 1.19 Proposed Mechanism for the Aza-Benzoin Reaction

Murry and coworkers demonstrated the usefulness of this motif for forming heterocycles by condensing aza-benzoin products with amines to give di-, tri- and tetra-substituted imidazoles in a one pot process (**Scheme 1.20**).[79] Thiazoles or oxazoles could also be formed using Lawesson's reagent or iodine/triphenylphosphine respectively. This reaction could also be performed with resin bound arylsulfonylamindes.[80]



Scheme 1.20 Aza-Benzoin Reaction Forming Imidazoles

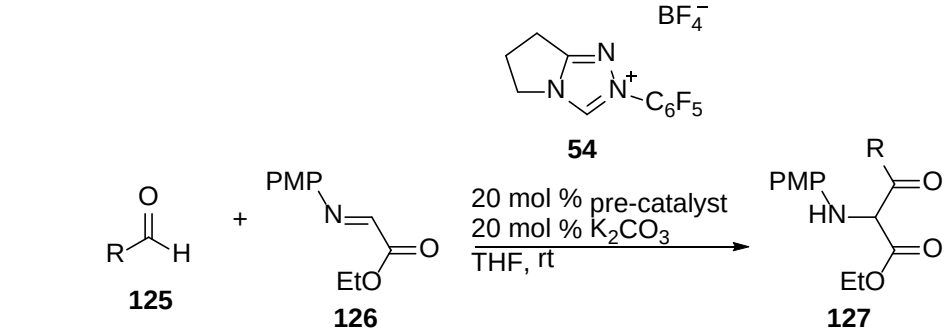
Johnson and coworkers used a similar reaction with ethyl glyoxylate and a triazolium catalyst **54** followed by enantioselective reduction for the preparation of *anti*-α-hydroxy-β-amino acids (**124**).[81]



Scheme 1.21 Aza-Benzoin Reactions Reported by Johnson and Coworkers

The group of Takemoto performed aza-benzoin reactions using *N*-methoxyphenyl imino acetates, which were activated by an α-ester group instead of an *N*-substituent (**Scheme 1.22**).

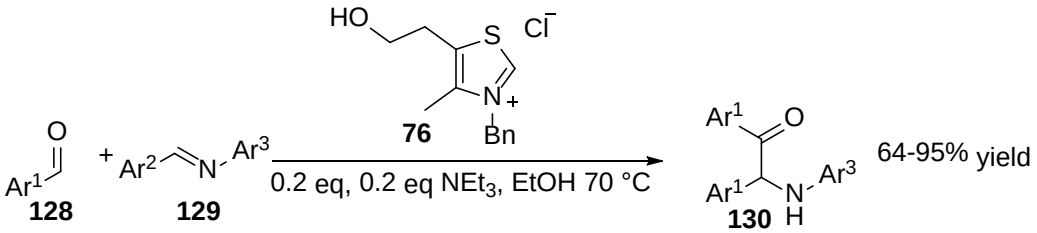
Pentafluorophenyl triazolium **54** was found to be more reactive than phenyl triazolium **53** or thiazolium **32**. The reaction preceded using potassium *tert*-butoxide or carbonate bases.



R = *p*-ClC_6H_4, *m*-ClC_6H_4, *o*-ClC_6H_4, *p*-$NO_2C_6H_4$, *p*-NCC_6H_4, *p*-$CH_3OOCC_6H_4$, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, 2-furan, 3-thiophene, CH_3, CH_2OBn, CH_2NHBoc, CH_2CH_2Ph

Scheme 1.22 Aza-Benzoin Reactions Reported by Takemoto and Coworkers

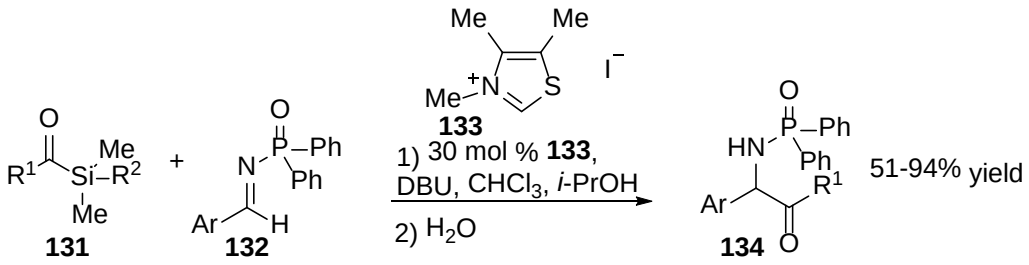
You and co-workers developed an aza-benzoin reaction under thermodynamic control using *N*-aryl imine substrates without activating groups in refluxing ethanol for extended periods (**Scheme 1.23**).[82] These reactions were modest yielding with aromatic or heteroaromatic aldehydes. This process was found to be reversible. The reaction is specific to thiazolium catalysts but the main drawback to this method is that harsh conditions are required to cleave *N*-aryl groups.



Ar^1 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, 2-benzofuran, 2-furan, 2-thiophene
Ar^2 = Ar^1 = Ph, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$
Ar^3 = Ph, *p*-ClC_6H_4, *p*-$CH_3C_6H_4$, *o*-ClC_6H_4

Scheme 1.23 Aza-Benzoin Reactions under Thermodynamic Control

Rather than focus on highly electrophilic acyl imines, or less reactive aryl imines, Scheidt and co-workers sought modestly electrophilic imines (**Scheme 1.24**). *N*-Benzyl, *N*-sulfinyl and *N*-sulfonyl imines were explored unsuccessfully. Reactions with *N*-phosphinoyl imines gave aza-benzoin product however these reactions were low yielding and complicated by benzoin side-products.[83] To counter this issue Scheidt and co-workers used acyl silanes as aldehyde surrogates.[84] Imidazolium and triazolium salts afford no reaction with this system and DBU was the optimal base. The reaction was effective with aromatic (80-95%) and aliphatic acyl silanes (51-83%) including those with α-branching. To demonstrate the usefulness of this methodology, the product ketone was reduced with BH_3SMe_2 to give good (15:1) diastereoselectivity and reasonable (70%) yield of the *trans*-amino alcohol. The *N*-phosphinoyl group could be efficiently cleaved and replaced with a Boc group under mild conditions (74% yield).



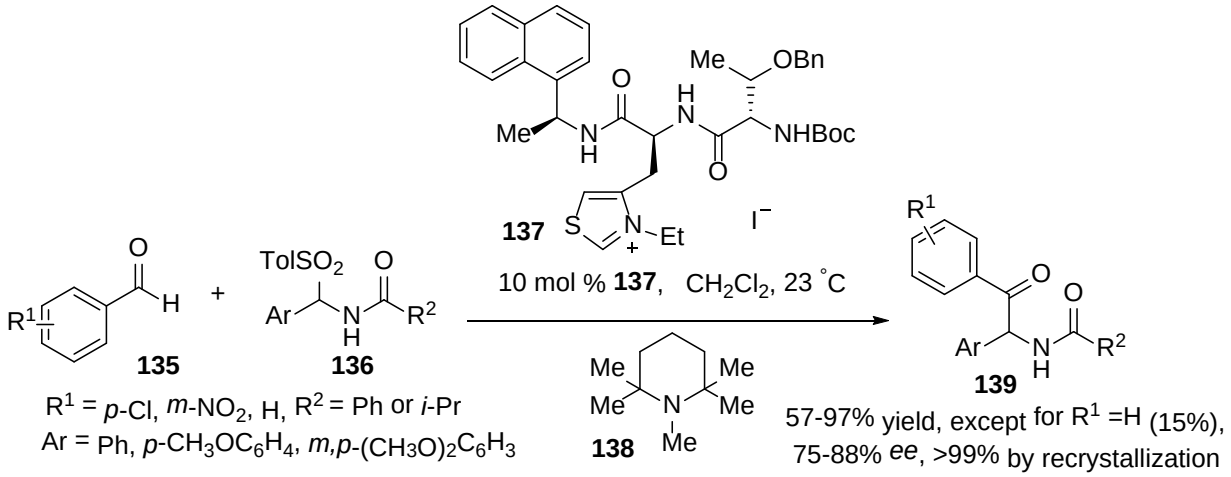
R^1 = Ph, *p*-ClC_6H_4, *p*-$CH_3C_6H_4$, Me, $CH_3(CH_2)_4$, $BnOCH_2CH_2$, *i*-Pr
R^2 = Me or Ph
Ar = Ph, *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *o*-$CH_3OC_6H_4$, 2-Naphthyl, *m*-*p*-$Cl_2C_6H_3$, *o*-Cl-C_6H_4, 2-thiophene

Scheme 1.24 Aza-Benzoin Reactions with *N*-Phosphinoyl Imines

1.21 Enantioselective Aza-benzoin Reactions

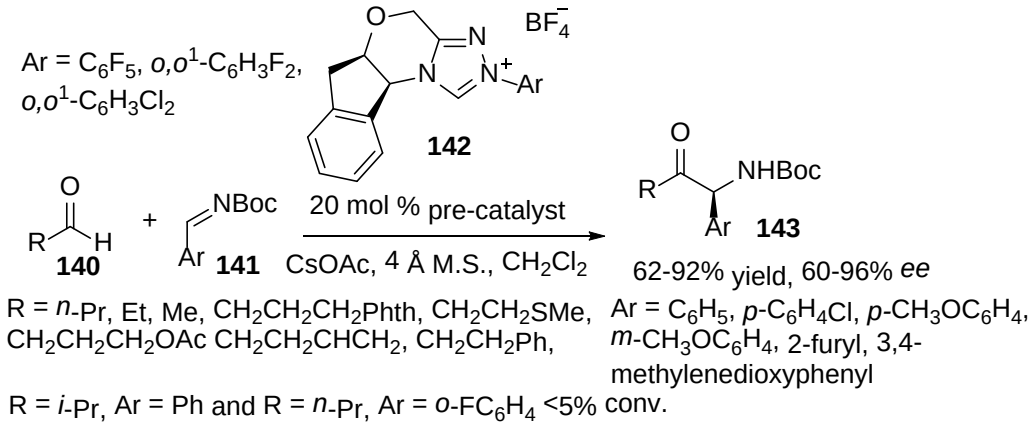
The first enantioselective aza-benzoin reactions were performed using peptide inspired thiazolium salt **137** with hindered amine bases (**Scheme 1.25**).[85] This reaction exhibited a time dependent erosion of enantioselectivity as well as a noticeable kinetic isotope effect. Both things indicated that the reaction was under kinetic control. The authors posited a secondary mode of

action, such as a hydrogen bond between the peptide backbone and the imine, as the origin of the observed enantioselectivity.



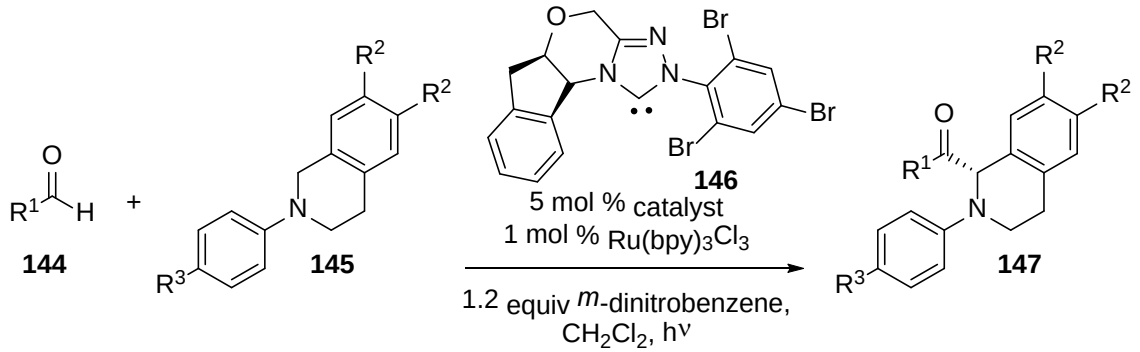
Scheme 1.25 Enantioselective Aza-Benzoin Reactions Catalyzed by Thiazolium **137**

The Rovis group has also explored the enantioselective aza-benzoin reaction using more widely known chiral triazolium catalysts (**Scheme 1.26**).[86] Acetic acid was used to overcome the catalyst inhibition observed in this system. Molecular sieves were required to suppress imine hydrolysis from trace water. Post reaction epimerization could be suppressed by lowering reaction temperature to -20 °C. *o*-Halo-phenyl imines and α-branched aldehydes were not tolerated, and no examples with aromatic or heteroaromatic aldehydes were reported.



Scheme 1.26 Enantioselective Aza-Benzoin Reactions Performed by Rovis and Coworkers

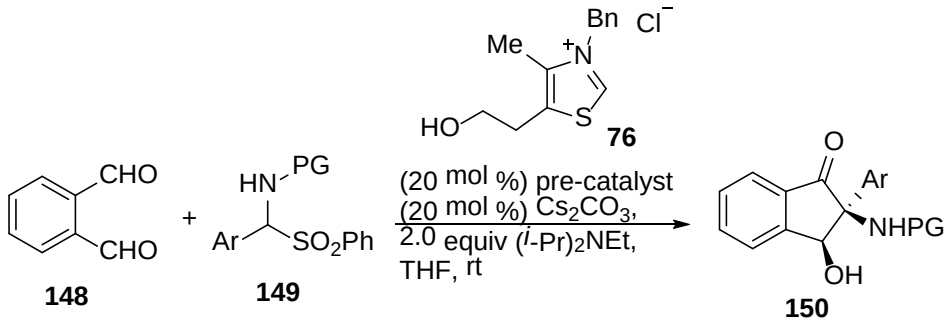
The Rovis group recently demonstrated an aza-benzoin reaction with the imine generated *in situ* via a ruthenium photo-redox process (**Scheme 1.27**).[87] Excellent yield and enantioselectivity were obtained with a number of aliphatic aldehydes. Only easily oxidized *N*-aryl benzylic tertiary amines (**145**) can be used.



Scheme 1.27 Photo-Redox Aza-Benzoin Reactions

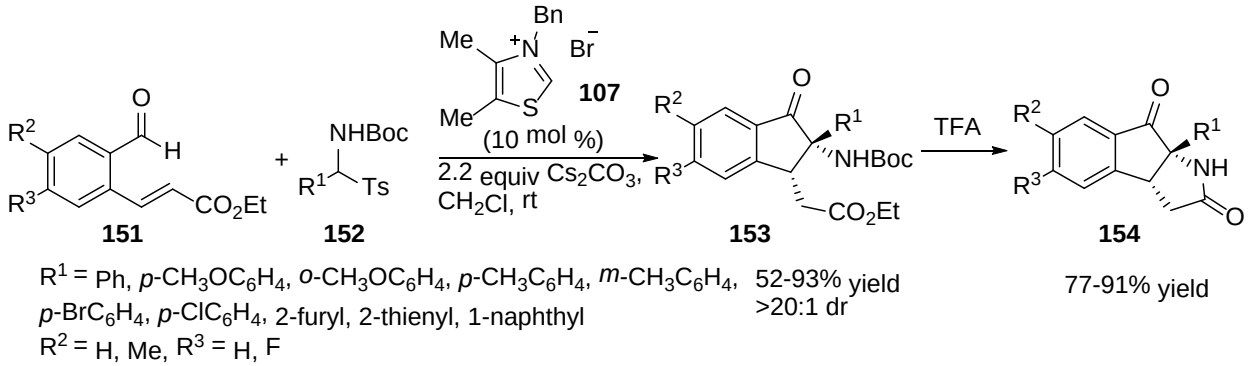
1.22 Cascade Aza-benzoin Reactions

Sun and Ye reported aza-benzoin-aldol reactions with phthalaldehyde, to give formal [4+1] annulated products (**150**, **Scheme 1.28**).[88]



Scheme 1.28 Aza-Benzoin-Aldol Reactions

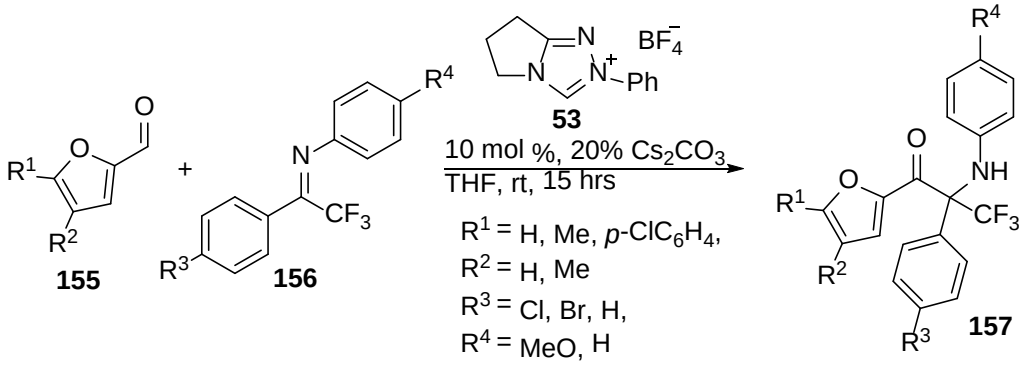
You and coworkers reported the first aza-benzoin-aza-Michael reaction to form dihydroindenones and pyrrolidinone containing tricyclic molecules (**Scheme 1.29**).[89] Cheng and coworkers later worked on a similar scaffold with the addition of an oxygen atom between the phenyl and vinyl groups of compound **151**.[90]



Scheme 1.29 Aza-Benzoin-Aza-Michael Reactions

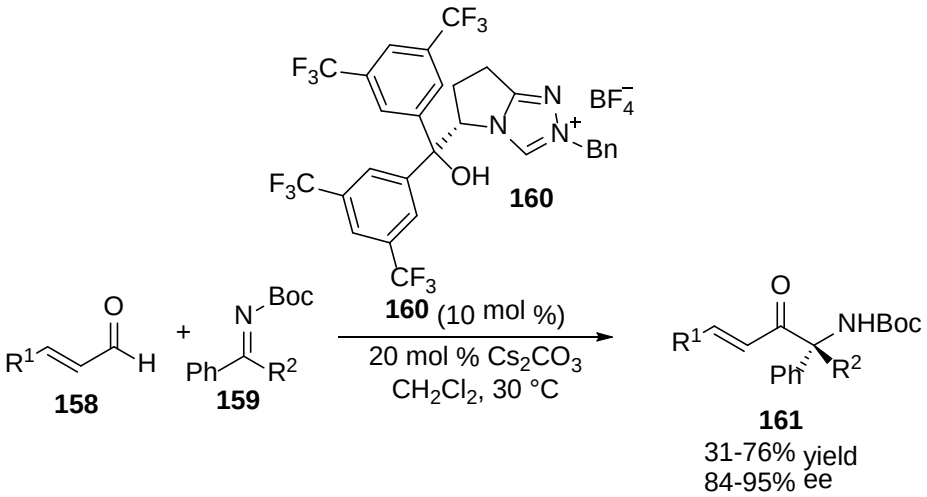
1.23 Ketimines

Ketimines have been explored to expand the scope of the aza-benzoin reaction. These species can be very electrophilic without forming NHC-imine adducts. The group of Enders found a reaction with *N*-aryl-trifluoromethyl-aryl ketimines which was only reported with furfural derivatives (**Scheme 1.30**).[91]



Scheme 1.30 Aza-Benzoin Reactions with Ketimines Reported by Enders

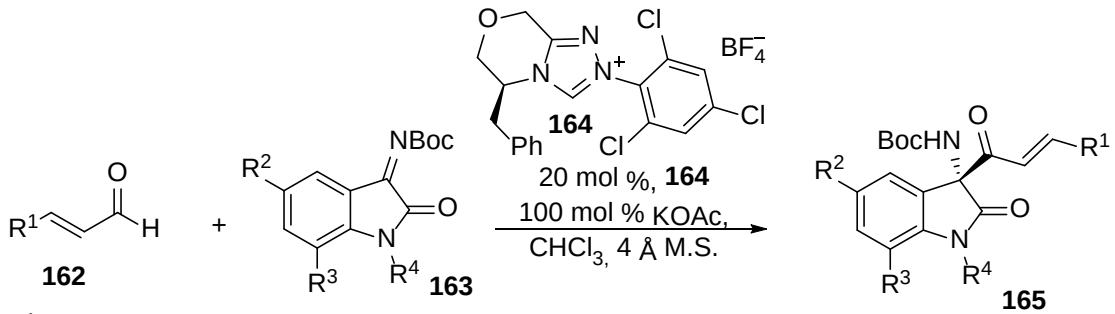
Ye and coworkers presented a more general solution by using α-β-unsaturated aldehydes (**Scheme 1.31**).[92] Aromatic and aliphatic alkynals could be used in highly enantioselective but low yielding reactions. α-Imino-esters and α-imino-nitriles were also demonstrated as suitable ketimine partners.



R^1 = Ph, *n*-C_5H_{11}, *p*-ClC_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, 2-furyl, $(CH_2)_4CH_3$, $(CH_2)_6CH_3$
R^2 = CF_3, CO_2CH_3, CN

Scheme 1.31 Aza-Benzoin Reactions with Ketimines Reported by Ye and Coworkers

The Chi group has extended this methodology to isatins (**163**, **Scheme 1.32**).[93]



R^1 = Ph, p-$CH_3C_6H_4$, p-$CH_3OC_6H_4$, m-FC_6H_4, p-ClC_6H_4, p-BrC_6H_4, 2-furyl, 2-thiophenyl, Me, propyl,
R^2 = Me, OMe, H; R^3 = Me, H; R^4 = Me, Allyl, Bn, Ph

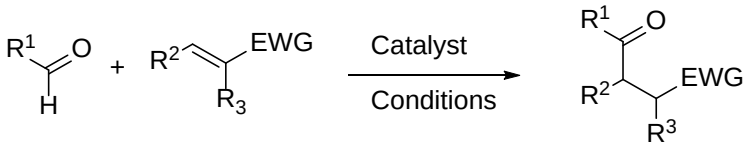
Scheme 1.32 Aza-Benzoin Reactions with Isatins

1.24 Aza-Benzoin Summary

To summarize, the most general approach to the aza-benzoin reaction to date made use of thiazolium salts. These reactions could be performed enantioselectively using peptide derived thiazolium catalyst **137**, which imposed other limitations upon the reaction. Rovis and coworkers have successfully performed enantioselective aza-benzoin reactions using triazolium catalysts. However, these reactions have not been shown with aromatic aldehydes. Other approaches have been more specialized such as using reactive ketimines or generating reactive imines through photo-redox activation. Consequently, more general enantioselective methods of performing the aza-benzoin reactions are desirable.

1.3 The Stetter Reaction

In 1973 Stetter and Schreckenberg reported the first carbene catalyzed addition reaction of an acyl anion equivalent onto an electrophilic alkene (**Figure 1.3**).[94] This process has come to be called a Stetter reaction. This reaction can serve as an efficient route to 1,4 dicarbonyl compounds (when EWG = COR), potentially in an enantio- or diastereoselective manner, which can further be used to generate substituted heterocycles such as furans, thiophenes, and pyrroles as well as other biologically relevant molecules.[95] Notably, 1,4 dicarbonyl compounds can serve as precursors to substituted 2-cyclopentenones (via aldol reaction), and related compounds such as prostaglandins.[96]

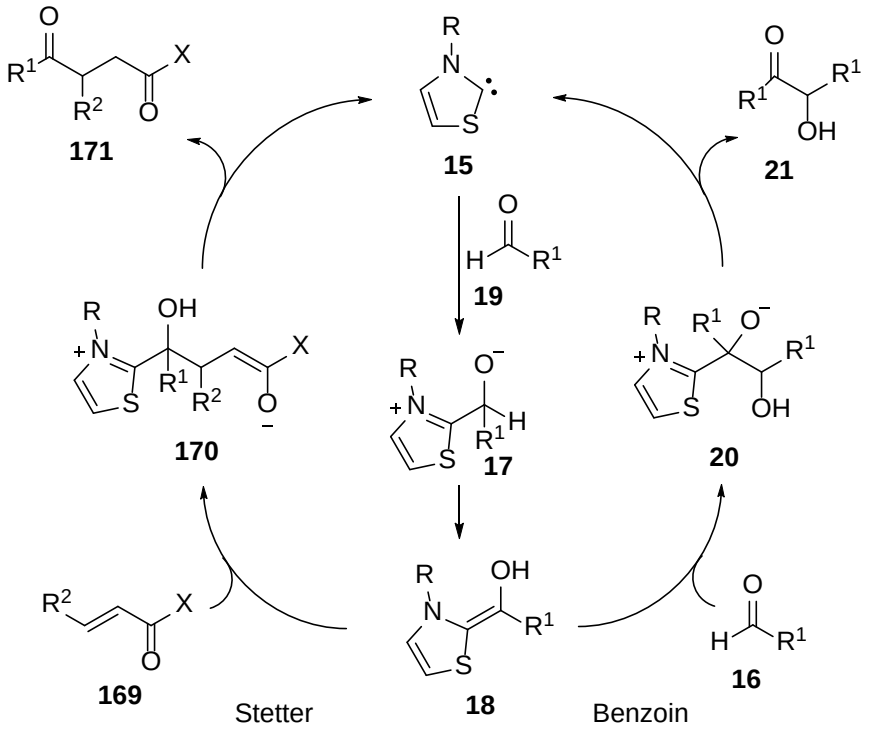


166 **167** **168**

Figure 1.3 A Generic Stetter Reaction

Stetter proposed that this reaction proceeds similarly to the benzoin reaction, via the formation of a Breslow intermediate (**18**) which attacks an electrophilic alkene (**169**) in a conjugate fashion (**Scheme 1.33**).[97] Following proton transfer, the catalyst is ejected to give the Stetter product (**171**) and regenerate the carbene. Computational DFT studies performed by Hawkes and Yates are consistent with this depiction.[98]

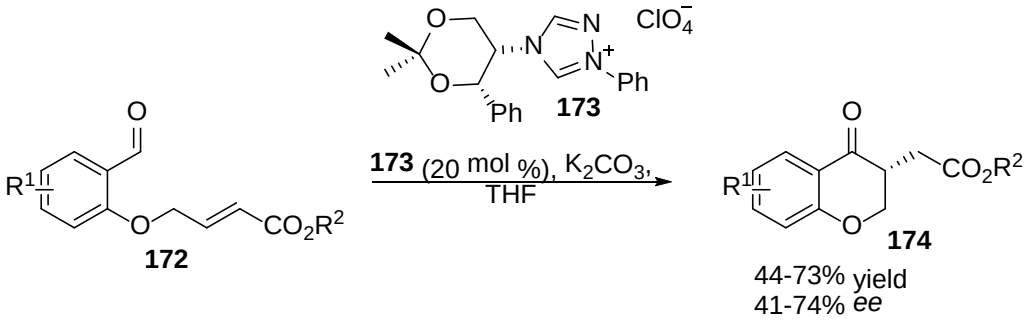
Because this process shares a common intermediate (**18**) with the benzoin reaction, benzoin side-products can also be formed (often reversibly) and consequently α-hydroxy ketones have been used as aldehyde surrogates in some instances.[99] Stetter reactions can categorized as intermolecular or intramolecular.



Scheme 1.33 Mechanism for the Stetter Reaction with Competing Benzoin Pathway

1.31 Intramolecular Stetter Reactions

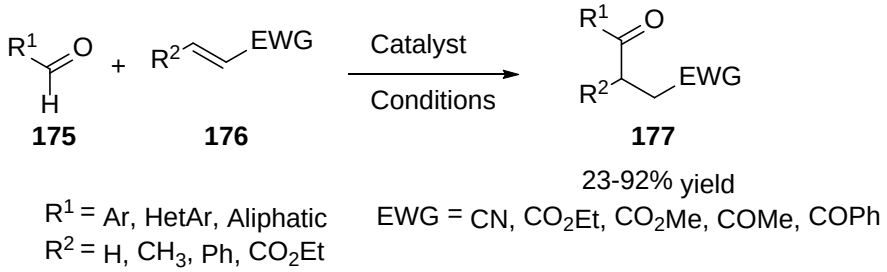
The intramolecular Stetter Reaction was first explored by the groups of Trost and Ciganek.[100,101] Enders and coworkers performed the first enantioselective intermolecular Stetter reactions (**Scheme 1.34**), ascribing the high enantioselectivity in intramolecular Stetter reactions to highly ordered transition states.[102] The intramolecular Stetter reaction has been extensively developed and has been the subject of reviews which can be consulted for more information.[103,104,105,106,107]



Scheme 1.34 The First Enantioselective Stetter Reaction

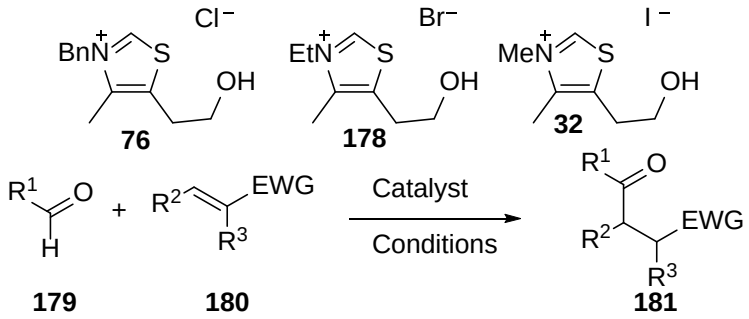
1.32 Intermolecular Stetter Reactions

Stetter and coworkers developed the intermolecular Stetter reaction with numerous substrates, as summarized in **Scheme 1.35**. Reactions initially used cyanide as a catalyst. However cyanide could not catalyze Stetter reactions with aliphatic aldehydes and switching to thiazolium salts removed this constraint.[108,109,110] Nitriles, esters, methyl ketones, and aryl ketones can all serve as suitable electron withdrawing groups for Michael acceptors in this reaction. β-Substitution (R^2) was found to have a large influence on reactivity.[111] Unsubstituted acceptors such as acrylonitrile and other acrylates worked well, as did acceptors bearing aromatic or heteroaromatic substituents. However, acceptors bearing aliphatic substituents proved more challenging.



Scheme 1.35 Stetter Reactions Reported by Stetter and Coworkers

Table 1.4 Benzoin Reactions Reported by Stetter and Coworkers with Alkyl Substituents

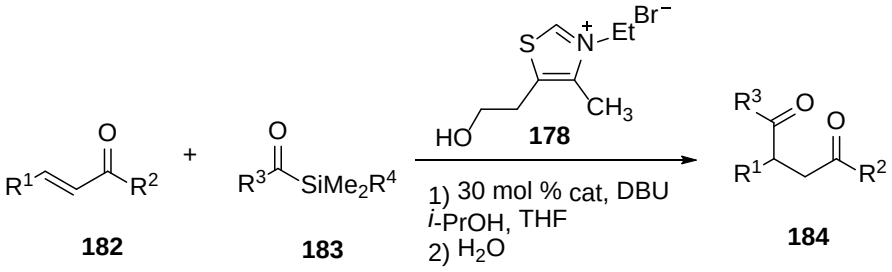


entry	R^1	R^2	R^3	EWG	yield (%)
1[a]	*p*-ClC_6H_4	CH_3	H	CO_2*t*-Bu[112]	64
2[a]	2-thienyl	CH_3	H	CN[113,114]	76
3	2-furyl	CH_3	H	$COCH_3$[115]	34
4	2-furyl	Ph[b]	H	$COCH_3$[115]	80
5	*n*-Pr	CH_3	CO_2CH_3	$COCH_3$[116]	32
6	2-furyl	CO_2Et	H	COPh	70
7	*n*-Pr	CO_2Et	H	$COCH_3$	74
8	Me	CH_2R[b]	CO_2CH_3	$COCH_3$[117]	46
9	$CONC_4H_8$	CH_3	H	CO_2Et[118]	56

a) Sodium cyanide as catalyst; b) acetal R= $C(OCH(CH_3)CH(CH_3)O)H$.

Stetter performed several reactions with alkyl-substituted Michael acceptors, most of which were modestly yielding (best outcomes entries 1-9, **Table 1.4**). The reactions in entries 3 and 4 only differ by the R^2 substituent, with the methyl substituent giving much lower yield than the phenyl substituent. Reactions were modestly yielding with more electrophilic acceptors (alkenyl malonates, entry 8) as were reactions with ester functionality in the R^2 position (entries 6 and 7). Using a more reactive glyoxamide, Stetter reactions could also be performed on crotonate derivatives (entry 9).

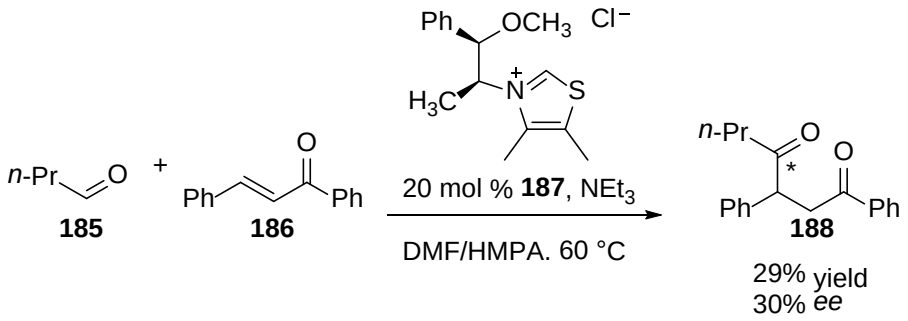
Demonstrating the efficiency of this reaction on chalcone derivatives (R^2 = Ar, R^3 = H, EWG = COPh), Müller and coworkers reported a three step sequence to prepare substituted pyrroles via palladium coupling, intermolecular Stetter reaction, and condensation with an amine. [119] Scheidt and co-workers also reported a high yielding, though not enantioselective, sila-Stetter reaction with a range of substrates (**Scheme 1.36**).[120]



Scheme 1.36 Sila-Stetter Reactions Reported by Scheidt and Coworkers

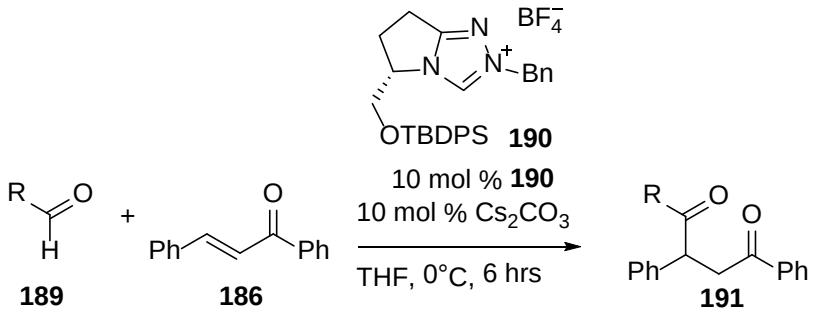
1.33 Enantioselective Intermolecular Stetter Reactions

The Stetter reaction can generate new stereocenters. Enders reportedly was the first to perform enantioselective intermolecular Stetter reactions, though the yield and enantiomeric excess in these reactions were poor (**Scheme 1.37**).[121]



Scheme 1.37 Intermolecular Enantioselective Stetter Reaction Reported by Enders

Table 1.5 Enantioselective Stetter Reactions by Enders and Coworkers

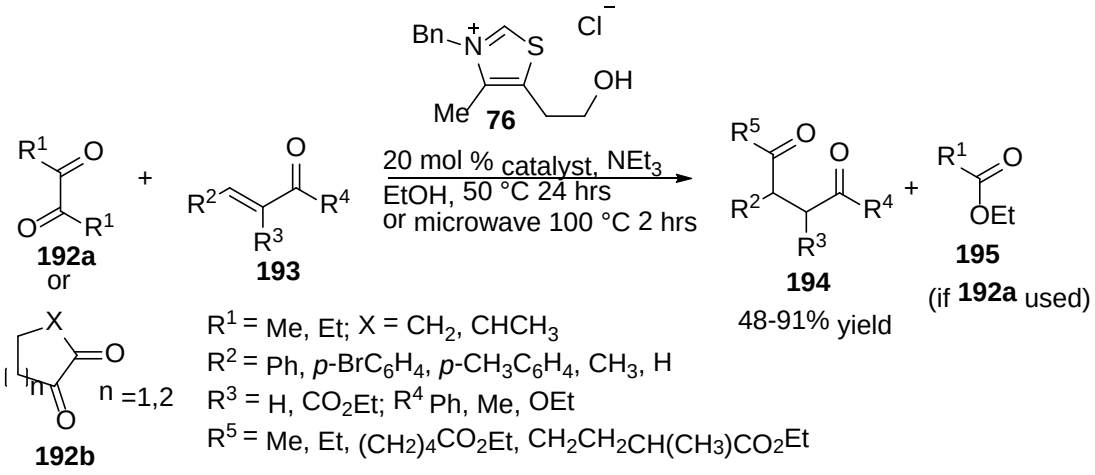


entry	R	yield (%)[a]	*ee* (%)[a]
1	Ph	65 (40)	66 (>99)
2	*p*-$CH_3C_6H_4$	43 (31)	78 (>99)
3	*m*-$CH_3C_6H_4$	50 (32)	70 (98)
4	*p*-ClC_6H_4	55	67
5	*p*-BrC_6H_4	68	56
6	2-Naph	65 (41)	70 (90)
7	2-furyl	98	56
8	Ph[b]	55	64
9	Ph[c]	57 (21)	56 (94)

a) following recrystallization in brackets; b) (*E*)-1-phenyl-3-(*p*-tolyl)-prop-2-en-1-one instead of chalcone; c) (*E*)-1-phenyl-3-(*p*-chlorophenyl)-prop-2-en-1-one instead of chalcone.

The first highly enantioselective, NHC-catalyzed intermolecular Stetter reaction was reported by Enders using an *N*-benzyl triazolium catalyst **190** (entries 1-9, **Table 1.5**).[122] Following optimization, modest to good yields and enantiomeric excesses were obtained with a wide range of aromatic aldehydes (as well as furfural) and chalcone (**186**) or its derivatives. Enantioselectivities were among the best reported to date for the Stetter reaction and *ee* could often be improved through recrystallization.

Following this work there have been a few more specialized advances in the intramolecular Stetter reaction on the chalcone scaffold. Yang and co-workers developed an enantioselective Stetter reaction using acetaldehyde.[123] Massi performed an analogous reaction using symmetric diketones as aldehyde surrogates with a much improved scope (**Scheme 1.38**).[124] One equivalent of the diketone is consumed in this reaction to generate the corresponding ethyl ester as a by-product.



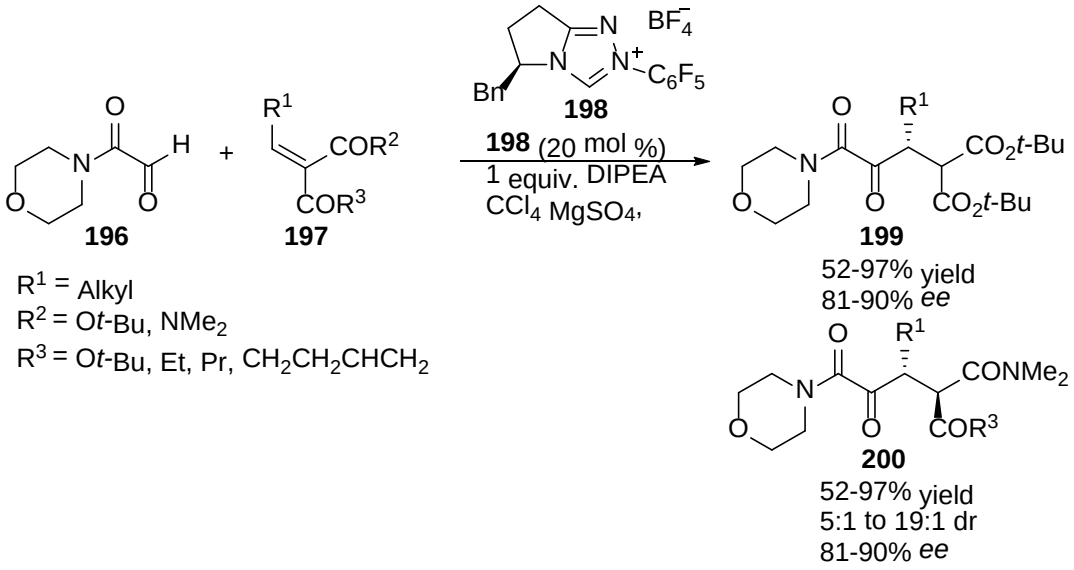
Scheme 1.38 Stetter Reactions using α-Diketones as Aldehyde Surrogates

Later the group of Takaki extended this methodology to aryl diketones as aldehyde surrogates, which also underwent subsequent aldol reactions with the enone acceptors.[125]

Recently the group of Chi found reducing sugars could act as formyl group equivalents for the intermolecular Stetter reaction.[126]

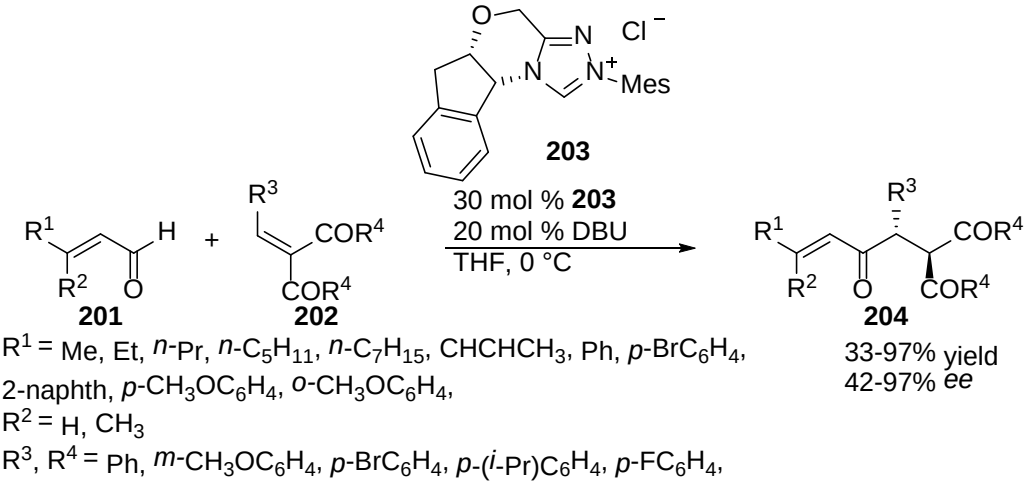
1.34 Stetter Reaction on Alkylidene Malonates

Rovis and coworkers explored electrophilic alkylidene malonates (**Scheme 1.39**).[127] Using di-*tert*-butyl alkylidene malonates a high yielding and highly enantioselective Stetter reaction was accomplished with reactive glyoxamides. This reaction was later extended to a variety of β-keto-amides and this reaction was reasonably diastereoselective as well.[128]



Scheme 1.39 Stetter Reactions on Alkylidene Malonates Reported by Rovis and Coworkers

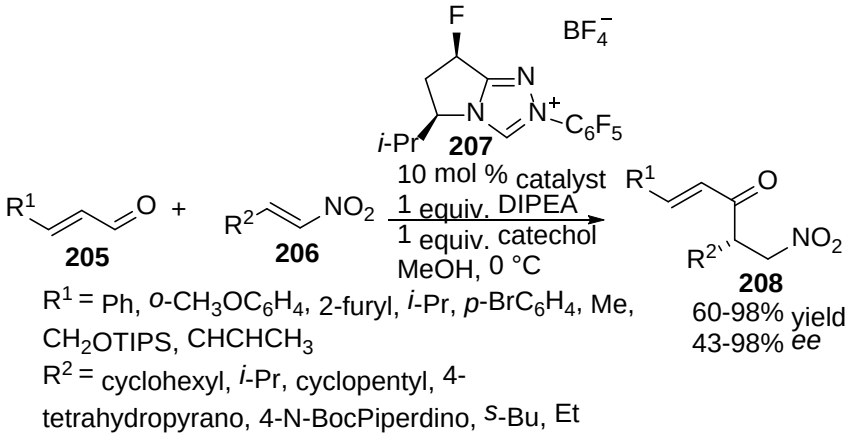
Enders reported a similar reaction between alkylidene malonate derivatives (**201**) and heteroaromatic aldehydes.[129] Shi and coworkers performed similar reactions with a range of malonates and crotonaldehyde derivatives (**Scheme 1.40**).[130]



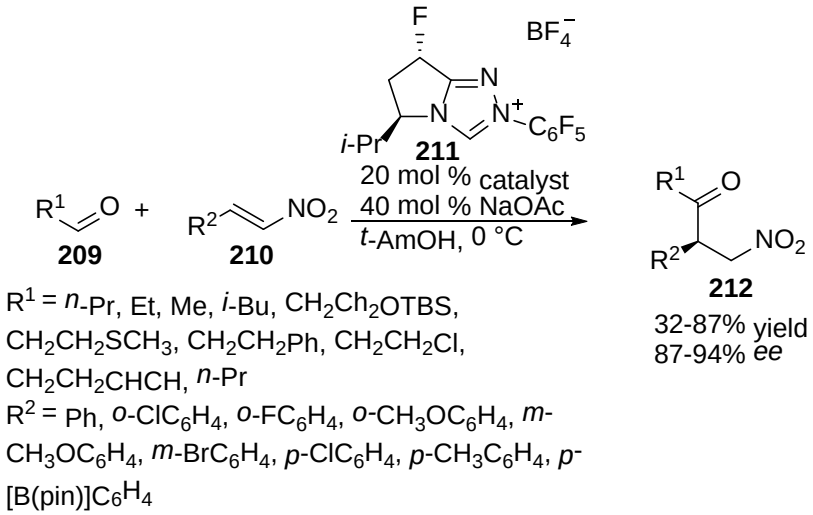
Scheme 1.40 Stetter Reactions on Alkylidene Malonate Derivatives by Shi and Coworkers

1.35 Stetter Reactions on Nitroalkenes

Rovis and coworkers were the first to perform catalytic Stetter reactions with nitroalkenes (**Scheme 1.41**).[131] Initial reports used aliphatic nitro-alkenes with heteroaromatic aldehydes or cinnamaldehyde derivatives in the presence of catechol.[132,133] Aliphatic aldehydes were later reported with nitrostyrene derivatives (**Scheme 1.42**).[134] Interestingly, these catalysts demonstrated a stereoelectronic effect in that reactions using a triazolium catalyst with a fluorine atom *trans* to the isopropyl group (**211**) were lower yielding than reactions using a nearly identical catalyst where the two groups were *cis* (**207**).



Scheme 1.41 Stetter Reactions with Nitroalkenes and Unsaturated Aldehydes



Scheme 1.42 Stetter Reactions with Nitroalkenes and Aliphatic Aldehydes

1.36 Other Activated Acceptors

A number of groups have studied the Stetter reaction on more activated acceptors (**Figure 1.4**). The group of Shi reported a Stetter reaction with 3-(1-arylsulfonylalkyl)indoles.[135] Biju and coworkers revisited the Stetter reaction of vinyl sulfones and achieved reasonable yields.[136] In a similar work Biju and coworkers found *N*-mesityl imidazolium salts catalyze Stetter reactions with vinyl phosphonates though Cullen and Rovis demonstrated the same reaction intramolecularly years earlier. [137,138] McErlean and coworkers reported some high yielding intermolecular Stetter reactions of vinyl amides.[139]

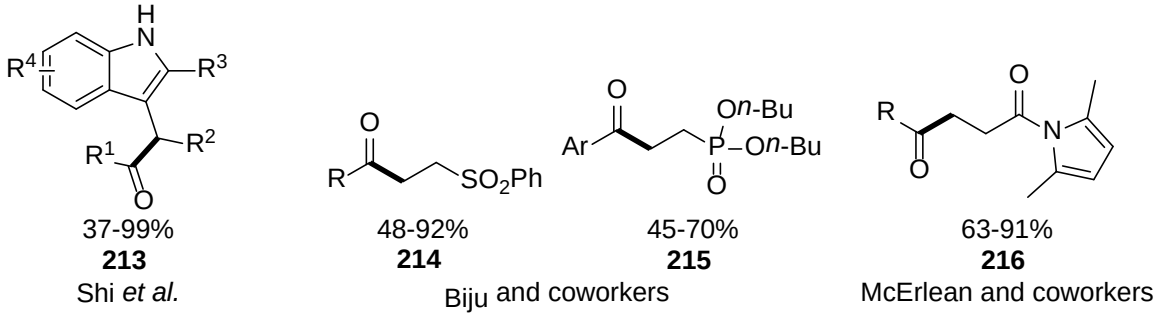
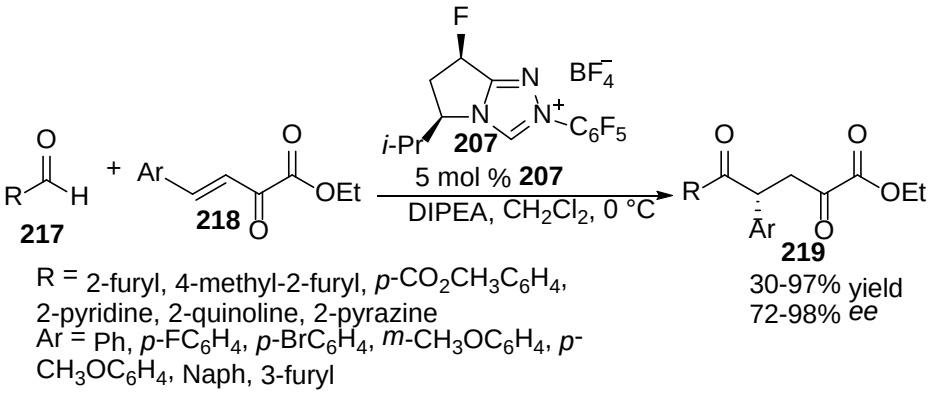


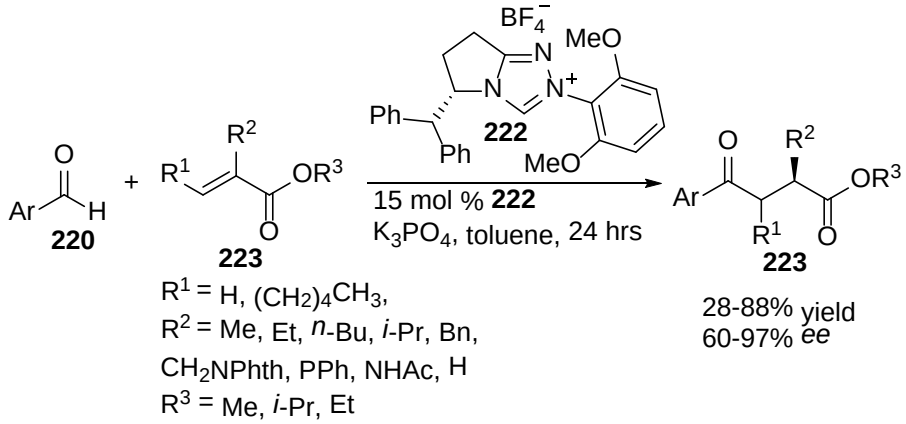
Figure 1.4 Other Acrylate Stetter Acceptors

Gravel and coworkers reported a highly stereoselective Stetter reaction upon unsaturated α-keto esters (**Scheme 1.43**).[140]



Scheme 1.43 Stetter Reactions with α-Keto Esters by Gravel and Coworkers

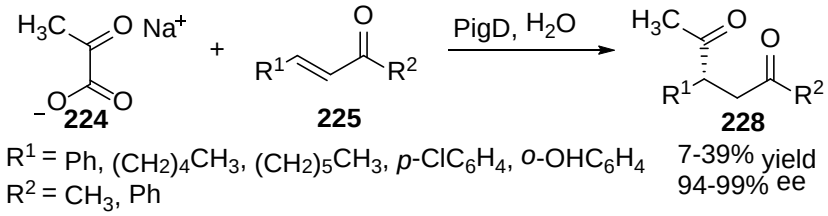
Using less activated acceptors Glorius and coworkers reported a Stetter reaction with α-β-unsaturated esters **223** (**Scheme 1.44**).[141] This was later used in an enantioselective preparation of α-amino acid derivatives (where R^1 = H and R^2 = NHAc), via enantioselective protonation.[142,143]



Scheme 1.44 Stetter Reactions with α-β-Unsaturated Esters by Glorius and Coworkers

1.37 Enzymatic Stetter Reaction

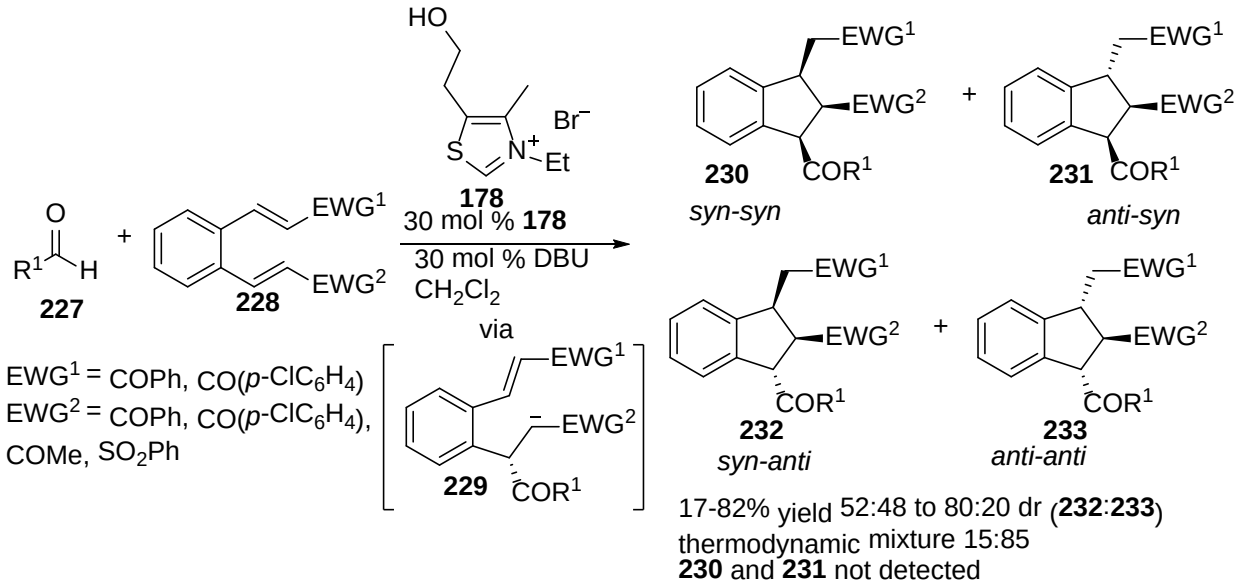
The enzyme-catalyzed intermolecular Stetter reaction is known with PigD (a thiamine diphosphate-dependent enzyme extracted from *Serratia Marcescens*).[144] Thus far the reaction is limited to pyruvate as an acetaldehyde surrogate and, though very enantioselective, yields are low (**Scheme 1.45**).



Scheme 1.45 Enzymatic Stetter Reactions

1.38 Domino Stetter Reactions

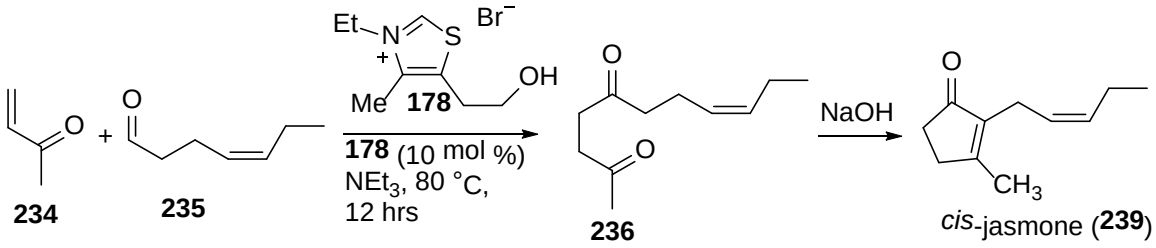
Several groups have explored combining the Stetter reaction with other reactions including domino Stetter-aldol-Michael, Stetter-Stetter, and Stetter-aldol-aldol reactions.[145,146] In 2011, Gravel and coworkers developed a highly diastereoselective Stetter-Michael reaction using acceptor **228** (**Scheme 1.46**).[147] In this reaction, intermediate **229** is an enolate (when EWG ^{2} = COR) and cyclizes in a Michael fashion. Though there are four different diastereomers accessible the *syn-syn* diastereomers (**230**) and *anti-syn* diastereomers (**231**) were not detected and were computed to be much higher in energy than the *syn-anti* (**232**) or *anti-anti* (**233**) stereoisomers. *Syn-anti* diastereomers (**232)** were found to be the products of kinetic control, with the diastereomeric ratio being good (80:20) in most cases. Equilibration favors the *anti-anti* stereoisomers (**233**), suggesting them to be the thermodynamic products.



Scheme 1.46 Domino Stetter-Michael Reaction

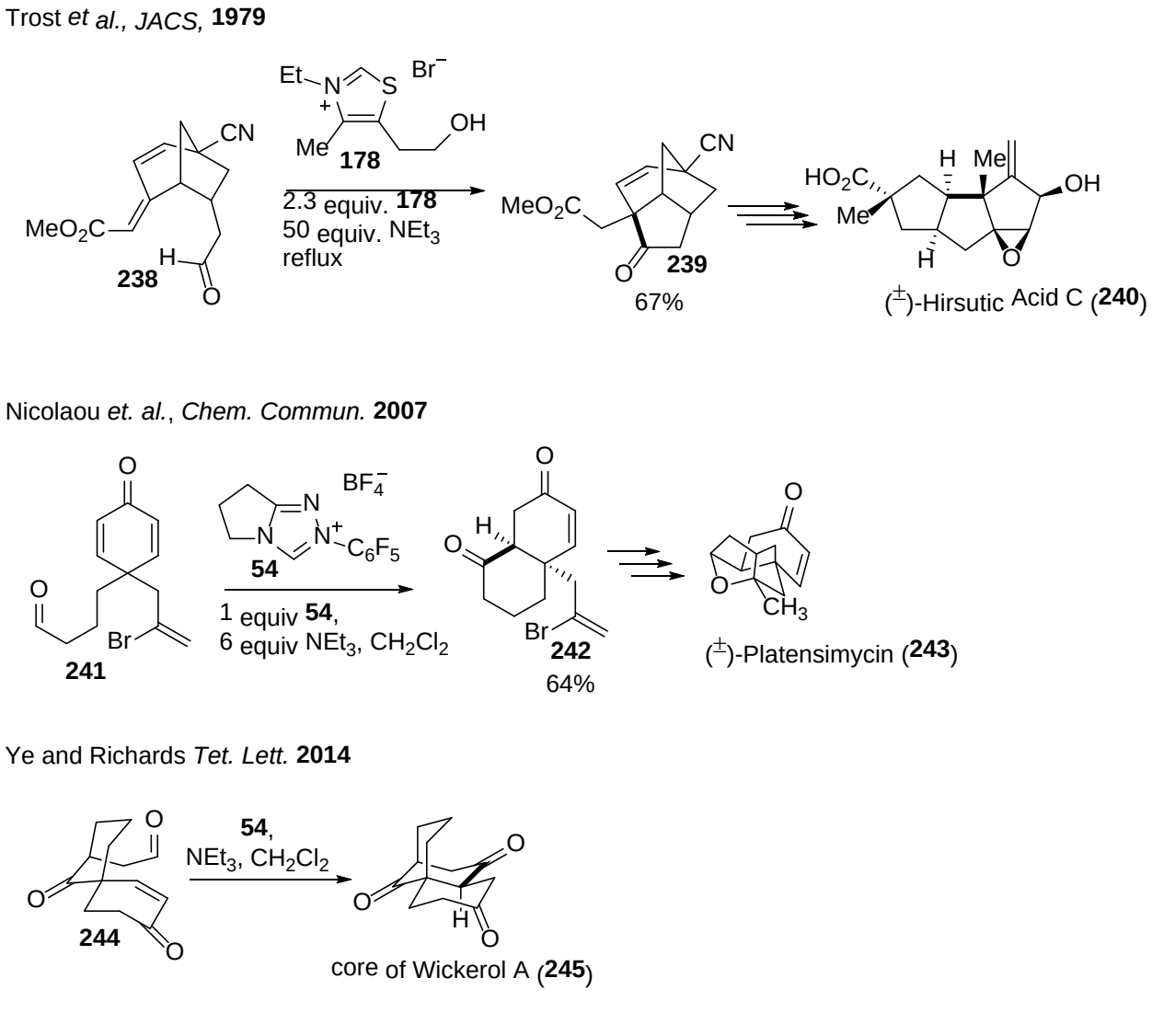
1.39 Stetter Reactions in Total Synthesis

The intermolecular Stetter reaction has been used in several total syntheses to date, primarily with vinyl ketones (such as **234**).[148] The first total synthesis to incorporate a Stetter reaction was a preparation of *cis*-jasmone and dihydrojasmone by Stetter and Kuhlman (**Scheme 1.47**).[149] Coupling methyl vinyl ketone **234** with the aldehyde **235**, followed by aldol cyclization and dehydration gave *cis*-jasmone in excellent yield. Subsequent Stetter reactions with vinyl ketones have been used in preparation of roseophilin,[150] (±)-*trans*-sabinene hydrate,[151] (-)-englerin A,[152] haloperidol,[153] two unnamed indolizidine alkaloids,[154] and a formal synthesis of marineosin A.[155]



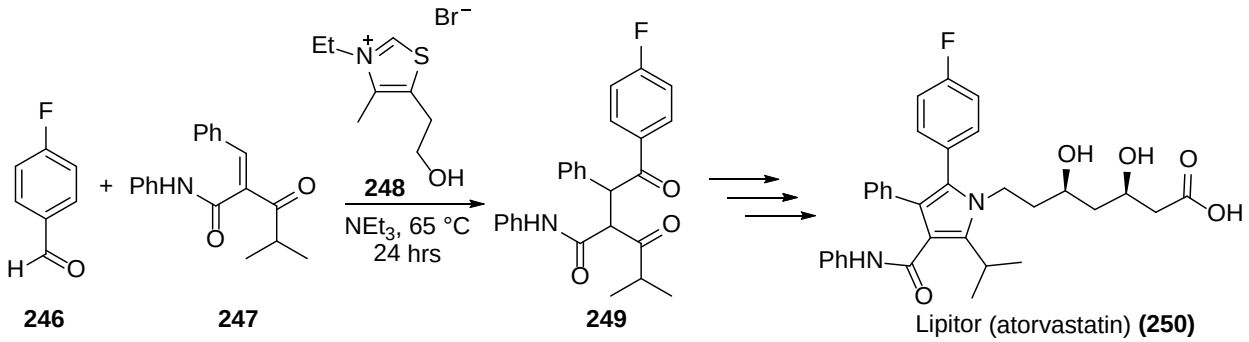
Scheme 1.47 Stetter and Kuhlman's Preparation of *cis*-jasmone

There have only been a few intramolecular Stetter reactions reported in total synthesis (**Scheme 1.48**). Trost and co-workers used a Stetter reaction on an alkyl substituted enone, to form the central cyclopentane ring in their total synthesis of hirsutic acid C.[100] Nicolaou and co-workers used pentafluorophenyl triazolium for a formal synthesis of (±)-platensimycin using an intramolecular Stetter reaction to desymmetrize substrate **241**.[156] Ye and Richards used an intermolecular Stetter reaction to prepare the core of wickerol A.[157]



Scheme 1.48 Stetter Reactions in Total Synthesis

Industrially, the intermolecular Stetter reaction has been used to prepare the substituted pyrrole functionality in the blood cholesterol lowering drug Lipitor **250** (**Scheme 1.49**).[158] Despite several examples in methodology, there have been no reports of catalytic enantioselective intermolecular Stetter reaction in synthesis.



Scheme 1.49 Stetter Reaction in the Synthesis of Atorvastatin

1.4 Conclusions and Objectives

There have been many significant, and recent, advances in the area of carbene organocatalysis. New catalysts and non-intuitive ways of combining substrates are being discovered on an ongoing basis. Exciting breakthroughs and advancements were reported as this work took place. One example of such an advance is the combination of an aza-benzoin reaction with photo-redox catalysis reported by Rovis and coworkers.[87] With the recent (2012) isolation of Breslow intermediates, we can understand the minutiae of carbene-mediated reactions better than ever before.[159] However, there is a dichotomy in this field between the effective scope of methodologies developed to date and the requirements of reactions in complex synthetic settings. There have been some useful overlaps, such as the preparation of *trans*-resorcylide or the industrially viable synthesis of atorvastatin (Lipitor TM, **250**). But considering the amount of work done in total synthesis and carbene catalysis, there is surprisingly little overlap between the

two. There is still untapped potential in carbene catalysis, as nature demonstrates and we have begun to find with isolated enzymes.[62-68,137] Broadly, the objective of this work is to study carbenes and *umpolung* reactions, and in doing so to improve upon their effectiveness and scope. Specifically deficiencies in the cross-benzoin, aza-benzoin and Stetter reactions will be addressed.

The biggest challenge in the cross-benzoin reaction is that of chemoselectivity. Though several strategies exist, they depend upon substrates which are sterically hindered, bypass the problem with specific substrates (such as acyl silanes) or use a significant excess of one of the aldehydes. There are examples of modest chemoselectivity (Connon and Zeitler or Miller and Mennen) being achieved in reactions with triazolium catalysts, however achieving consistently high chemoselectivity in reactions has not yet been realized.[63,64] The objective in this reaction was to improve upon existing triazolium catalysts to find the best chemoselectivity possible for the cross-benzoin reaction between two aldehydes, with as few substrate limitations as possible.

For the aza-benzoin reaction, the primary challenge is that of reactivity. The most general and enantioselective method reported to date makes use of a complex thiazolium-containing peptide derivative which is not widely available. Reactions using triazolium salts demonstrate substrate inhibition and are generally limited to using aliphatic aldehydes, glyoxylates or impractical imines such as compound **126**. Reactions with thiazolium derived catalysts can be wasteful of material, low yielding and difficult to make enantioselective. With few exceptions, neither option is practical in synthesis. In this reaction BACs may represent an untapped middle ground between these extremes. The objective of this work was to explore the potential of BACs in the aza-benzoin reaction, and if possible develop a more general, high yielding, aza-benzoin reaction on a scaffold easily made chiral.

In principle, the Stetter reaction can be an extremely efficient method of creating 1,4 dicarbonyl compounds. Practically, these reactions often have severe substrate limitations resulting in complex mixtures and low yields. Despite great advances with triazolium derived catalysts in model systems, nearly all examples in synthesis use large amounts of simple achiral thiazolium salts. In the intermolecular Stetter reaction there are only a few examples of reactions with β-alkyl enones and yields are modest, despite this motif being far more synthetically relevant than β-aryl enones. Reactions reported using electron rich aromatic aldehydes such as alkoxy-benzaldehyde derivatives are modestly yielding, and no method addresses this limitation despite phenols being biologically relevant as well as useful handles for further synthetic operations. Unlike the intramolecular Stetter reactions, the enantioselectivity in intermolecular Stetter reactions has been modest except for a few examples. Bis(amino)cyclopropenylidenes are not NHCs. The electronic differences between these two carbene families may be beneficial with some substrates, such as electron rich aromatic aldehydes. The substituents are further away from the carbene center, and this may be beneficial in reactions with some hindered and/or unreactive acceptors, such as β-alkyl enones. It is straightforward to introduce chiral moieties into BACs and this may be beneficial in enantioselective applications. The objective of this work was to explore BACs as carbene organocatalysts, and ascertain what challenges these molecules may be suitable to overcome.

Chapter 2: Development of a Chemoselective Cross-Benzoin Reaction

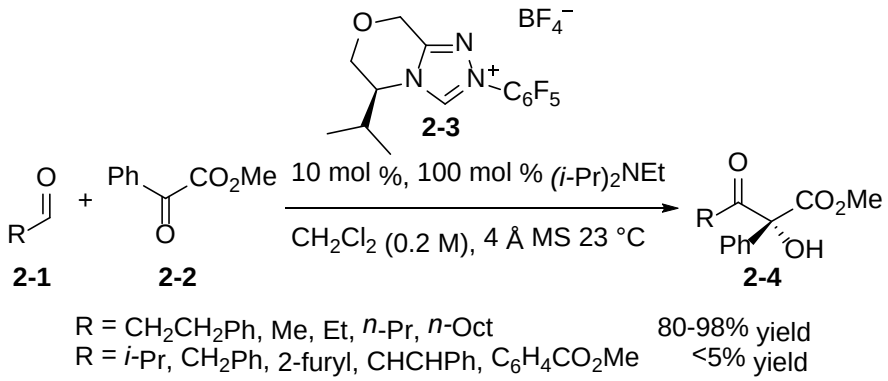
This project was done in collaboration with Steven Langdon.

Preliminary investigations were performed by Dr. Karen Thai.

2.1 Background and Objective

The cross-benzoin reaction is a mild and efficient way to construct carbon-carbon bonds. In the process it generates an α-hydroxy ketone, potentially enantioselectively, a motif which is found in numerous natural products.[160] The key obstacle in cross-benzoin chemistry is that the reaction typically generates mixtures: two homo-benzoin products and two cross-benzoin products may be formed by combining two different aldehydes. The maximum obtainable yield of a single cross-benzoin product is often low as homo-benzoin formation expends starting material non-productively. Additionally, separation of the desired cross-benzoin product from its isomer can be difficult. This is material inefficient and not suitable in complex synthetic settings. Methodologies have been developed to overcome these obstacles and aldehydes surrogates, such as acyl silanes, have been used to this effect.[83,84] Aldehyde-ketone cross-benzoin reactions can be effective, either intramolecularly or else intermolecularly though this often requires using more activated ketones such as trifluoromethyl ketones or α-keto-esters. The substrates for these methods are chosen to avoid acyl anion reactivity in one partner. In reactions involving two aldehydes, the use of one partner in large excess has been shown to bias the reaction towards a particular cross-product, though this is not a general solution.[65,66,67] Recently the groups of Connon and Zeitler as well as Mennen and Miller have reported triazolium catalysts which can induce a chemoselective reaction between hindered and non-hindered aldehydes.[63,64] Hence, prior to this work there was no general method of performing a chemoselective intermolecular cross-benzoin reaction.

Thai *et al.* recently demonstrated a highly chemoselective cross-benzoin reaction using aldehydes and α-keto esters (**Scheme 2.1**).[59c] In the course of this work, it was observed that triazolium precatalyst **2-3** gave high yielding reactions with aliphatic aldehydes but not aromatic aldehydes.[161] It was hypothesized that there may be molecular interactions limiting either the formation of a Breslow intermediate from triazolium **2-3** with aromatic aldehydes or the Breslow intermediate's ability to react with electrophiles. Furthermore, these interactions could impart a bias into cross-benzoin reactions between two aldehydes which would result in chemoselectivity. The objective of this work was to explore carbenes derived from triazolium salts, such as **2-3** or its derivatives, as a means of achieving chemoselectivity in the cross-benzoin reactions.



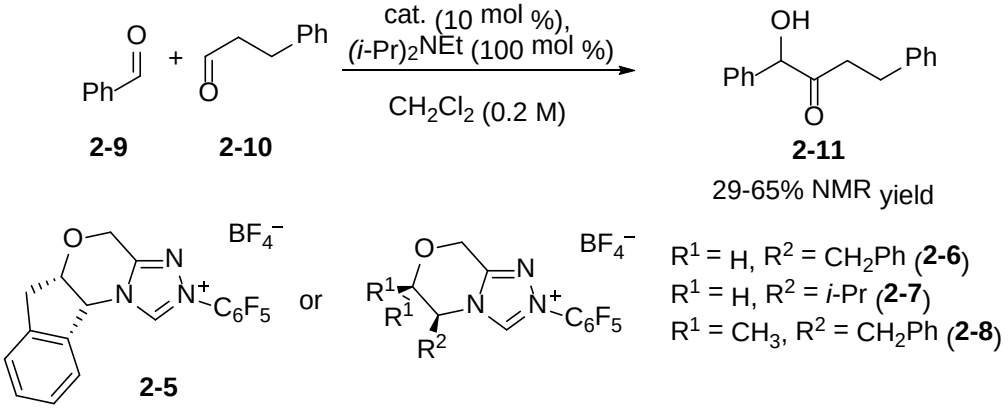
Scheme 2.1 Aldehyde-Ketone Cross-Benzoin Reactions Reported by Gravel *et. al*.

2.2 Preliminary Results

A portion of the hypothesis regarding an aldehyde selection bias with the carbene derived from triazolium **2-3** was validated when benzaldehyde was reacted with hydrocinnamaldehyde. Cross-benzoin product **2-11** was highly favored over other benzoin products using triazolium salts **2-6** to **2-8** (**Scheme 2.2**).[iii] Each of these catalysts features a fused morpholine-triazole core, an *N*-pentafluorophenyl substituent, as well as a sterically bulky R^1 group situated near the

[iii] Thai, K.; Gravel, M. *Unpublished Results*

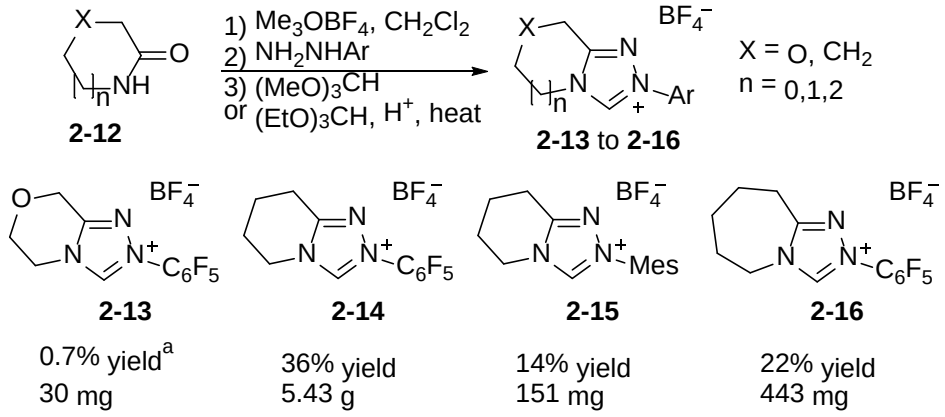
reacting site. To resolve which of these features are important in achieving chemoselectivity, simplified analogues were prepared.



Scheme 2.2 First Demonstration of Catalyst Chemoselectivity by Dr. Thai[162]

2.3 Catalyst Preparation

The established protocol for preparing triazolium salts generates them from lactams (or amides) already possessing the desired functionality via alkylation, amidrazone formation, formylation and *in situ* cyclization.[163] This strategy was utilized in preparing novel triazolium salts **2-13** to **2-16** (**Scheme 2.3**) in modest to poor yield. This process could be optimized, but sufficient quantities of material for study were accessed without optimization.

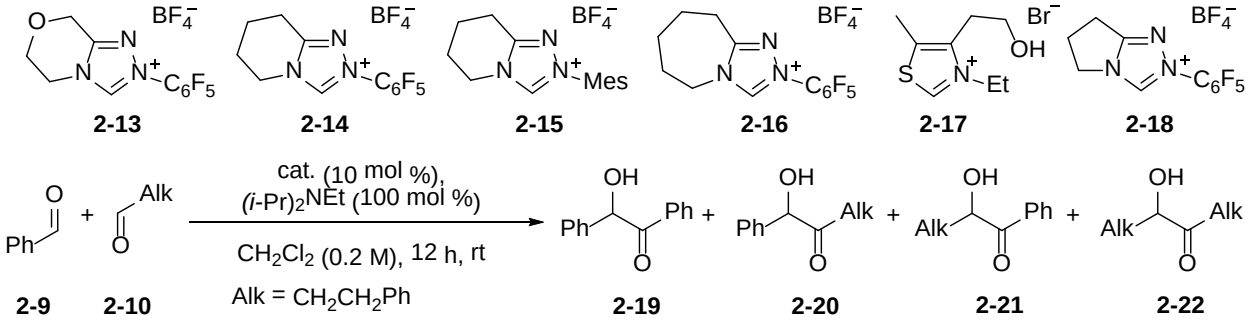


a) Prepared by Dr. Thai[164]

Scheme 2.3 Triazolium Pre-catalyst Preparation

2.4 Identification of the Structural Factors Affecting Chemoselectivity[iv]

Table 2.1 Catalyst Screening for Chemoselectivity in the Cross-Benzoin Reaction



entry	pre-catalyst	product-ratio (**2-19:2-20:2-21:2-22**)				^{1}H NMR
		2-19	**2-20**	**2-21**	**2-22**	yield (%)[a]
1[b]	**2-17**	6	12	21	61	<5
2	**2-18**	2	59	25	14	43
3	**2-13**	2	93	0	5	19
4	**2-14**	2	94	0	4	16
5	**2-15**	-	-	-	-	<5
6	**2-16**	21	68	9	2	26

a) Determined by ^{1}H NMR through use of dimethyl terephthalate as internal standard; b) Performed using 10 mol % of DBU as base instead of (*i*-Pr)$_2$NEt,

The prepared triazolium salts, along with thiazolium **2-17,** were tested in reactions involving benzaldehyde and hydrocinnamaldehyde (**Table 2.1**).[165] Reactions with thiazolium derived catalyst **2-17** did not show selectivity towards the cross-benzoin products, consistent with prior reports.[51] Reactions with well known triazolium **2-18** showed some chemoselectivity,

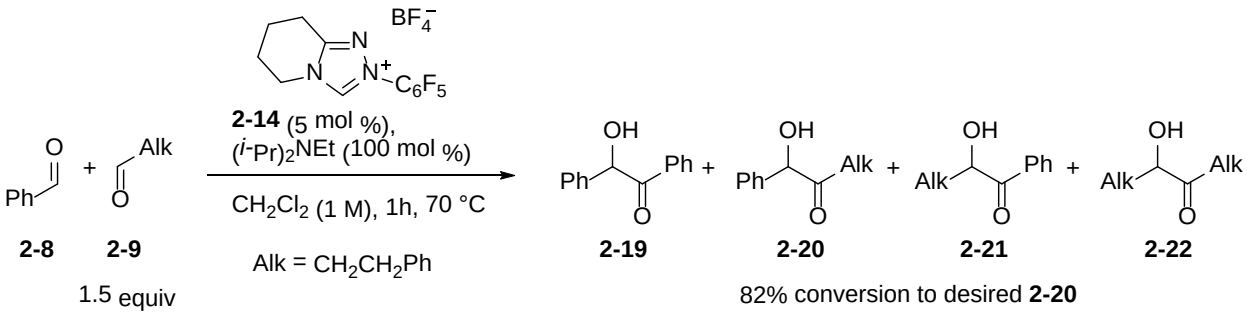
[iv]This section was done collaboratively by S. Langdon and the author. Entries 1-4 in **Table 2.1** were obtained by S. Langdon. Entries 5 and 6 were a joint effort.

consistent with Mennen and Miller's work.[64] Remarkably, reactions with novel triazolium **2-14** displayed high chemoselectivity without the catalysts possessing a bulky substituent, such as the isopropyl group of **2-3** or benzyl group of **2-6**. Similar selectivity to reactions with triazolium **2-13** was observed in reactions using triazolium **2-14**, which lacks the oxygen heteroatom. Reactions using the catalyst with the 7 membered ring (**2-16**) showed diminished selectivity, although improved reactivity, in the same time frame. Use of the pre-catalyst possessing an electron rich *N*-mesityl group (**2-15**) did not afford cross-benzoin products.

Triazolium **2-14** was chosen to carry forward for optimization as it was much easier to obtain in gram quantities than triazolium **2-13**.

2.5 Reaction Optimization

Reaction conditions were established for obtaining optimal conversion and chemoselectivity (**Scheme 2.4**).[v] These conditions were utilized while isolating cross-benzoin products and exploring the scope of the reaction.



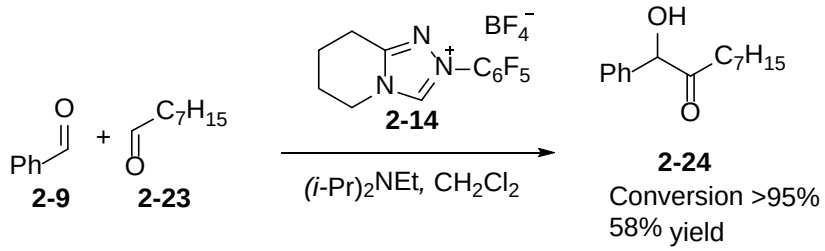
Scheme 2.4 Optimized Reaction Conditions with Pre-catalyst **14**

[v] This optimization was performed by S. Langdon with pre-catalyst provided by the author.

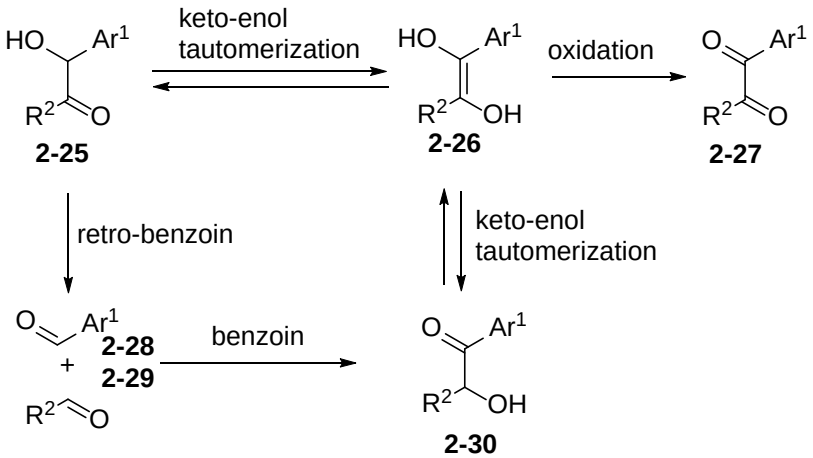
2.6 Isolation of Cross-Benzoin Products

With chemoselectivity well demonstrated efforts shifted toward demonstrating the utility of this methodology, which required isolation of cross-benzoin products. Given the sensitive nature of these compounds, their purification required additional development.

Purification via flash column chromatography resulted in isolated yields which were not consistent with the high conversion observed for this transformation (see **Scheme 2.5**). Isomerization and decomposition both may have led to a decrease in isolated yield of the desired products, and were observed to occur during chromatography. The isomerization could occur in a manner which involves a retro-benzoin/benzoin sequence or via tautomerism catalyzed by acid or base (**Scheme 2.6**). Additionally intermediates such as **2-26** were easily oxidized to diketone sideproducts and so a way to purify these reactions while minimizing decomposition was sought.

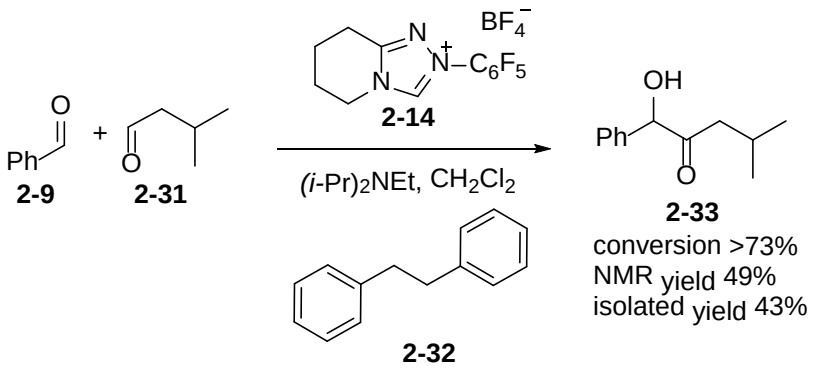


Scheme 2.5 First Indication of Isolation Problems



Scheme 2.6 Decomposition Pathways for α-Hydroxy Ketones

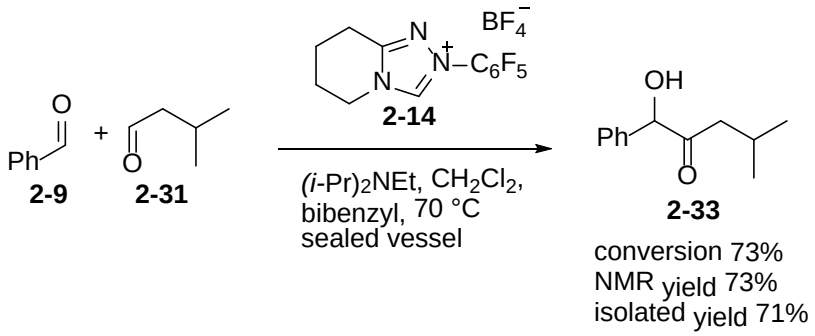
In a reaction with multiple products, yield assessed by NMR (from internal standard) can be more informative than isolated yields, as material may be unequally lost during purification. In this case the internal standard used (dimethylterephthalate) was found to coelute with the desired product, adding an unnecessary challenge to the purification. An approach was explored wherein reactions were run in duplicate. The NMR yield was measured with internal standard from one reaction, while purification was done on the other. This approach proved to be flawed as it complicated the issue of conversion being inconsistent with yield. The first improvement came from switching internal standards to bibenzyl **2-32** (1,2-diphenylethane), which was easily separable so that yield and conversion could be assessed on the same material (**Scheme 2.7**).



Scheme 2.7 Cross-Benzoin Reaction with Bibenzyl Internal Standard

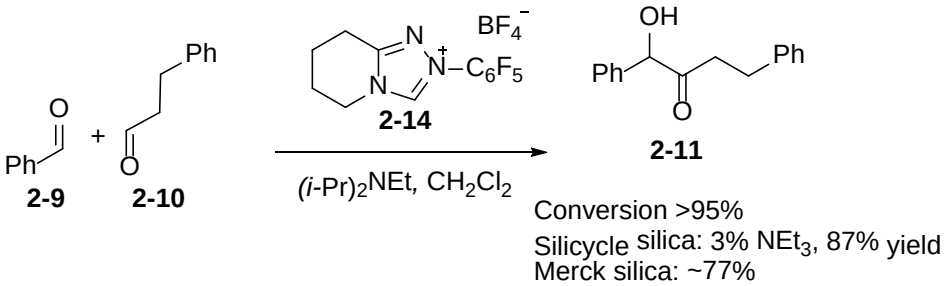
With more consistent results, it was discovered that the most substantial source of material loss occurred prior to the purification (**Scheme 2.7**). The NMR yields using the new internal standard were close to the isolated yields and inconsistent with the high conversions observed. Conversion is a measure of starting material relative to product, so if the starting materials is consumed and the NMR yield of the product is low, there must be another pathway by which starting material is lost. Decomposition was suspected, however decomposition products were not detected in the crude reaction mixture.

It was hypothesized that the experimental setup could be accelerating loss of the aldehydes via evaporation. In order to avoid evaporation of the starting aldehydes, the reaction was run in a sealed vessel. With this change, NMR yield became consistent with conversion, and the material loss issue was resolved. (**Scheme 2.8**)



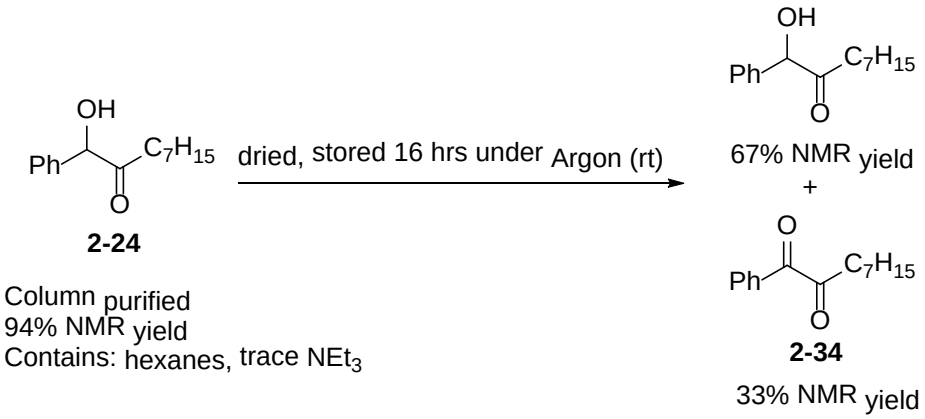
Scheme 2.8 Sealed Vessel Cross-Benzoin Reactions

With the conversion and yield now consistent, efforts moved towards substrates for which oxidative degradation was found to be more problematic. Using Merck brand silica for the chromatography improved the isolated yield significantly (**Scheme 2.9**). A similar outcome was achieved using Silicycle silica provided triethylamine was added to the eluent (as was used in the isolation of **2-33**, **Scheme 2.8**). However, use of triethylamine was not a general solution as it was found to accelerate degradation of the desired cross-benzoin product (**Scheme 2.10**).



Scheme 2.9 Minimizing Oxidation of α-Hydroxy Ketones upon Purification

Based on these observations the reaction quenching protocol was re-evaluated. Passing the crude reaction mixture through a short pad of silica to remove the polar triazolium salts was also not effective as decomposition still occurred (**Scheme 2.10**). Washing the crude reaction mixture with 1N HCl was found to be the best way of quenching reactions as it also removed residual DIPEA. Once purified, products were stable in the freezer under argon for months without isomerization or oxidation products being detected.



Scheme 2.10 Effect of Amines on α-Hydroxy Ketones

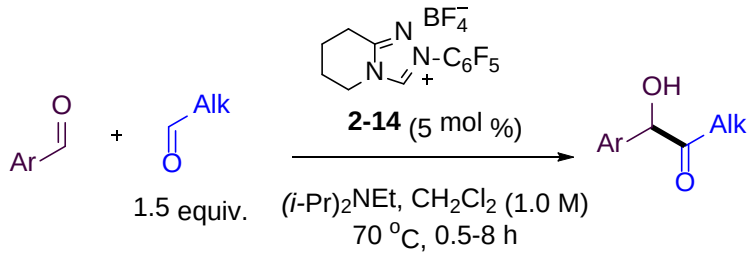
Using these modified purification conditions (bibenzyl internal standard, workup with 1N HCl and chromatography using Merck silica) a large number of different cross-benzoin products were isolated.

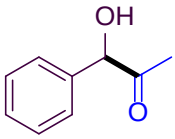
2.7 Substrate Scope

The scope of this reaction was found to be quite broad (**Table 2.2**). [vi] The reaction worked quite well with acetaldehyde (**2-35)** as well as longer chain aliphatic aldehydes (**2-36**, **2-24)**. The reaction was high yielding with β-substituted aliphatic aldehydes (**2-33**), and α-substituted aldehydes could also be used with longer reaction times and a larger excess of aldehyde (**2-37**).

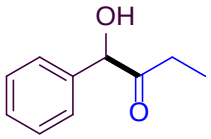
[vi] S. Langdon and the author both explored the substrate scope. General observations regarding reactivity refer to work done by both the author and S. Langdon. Unless stated otherwise, all data presented here (yields with corresponding procedures and characterization data in the experimental) was contributed by the author.

Table 2.2 Substrate Scope in the Cross-Benzoin Reaction with Catalyst **2-14**

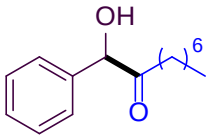




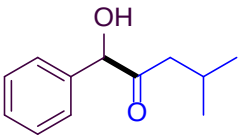
2-35 : 73%



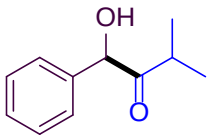
2-36: 89%[b] (62%)[c]



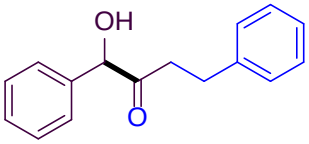
2-24 : 88%



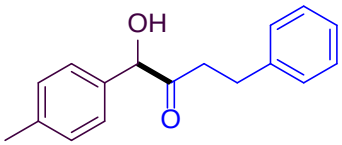
2-33 : 71%



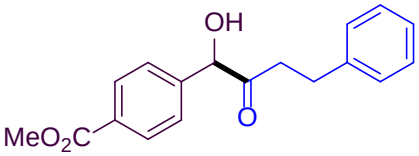
2-37 : 68%[d]



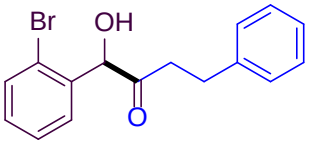
2-11 : 84%[b]



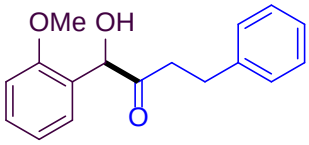
2-38 : 91%[c]



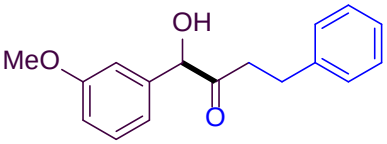
2-39 : 61%



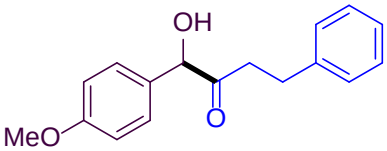
2-40 : 89%



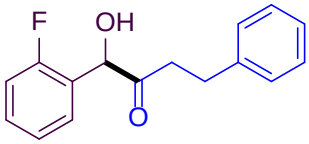
2-41 : 99%



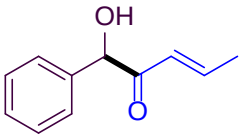
2-42 : 82%



2-43 : 99%



2-44 : 64%

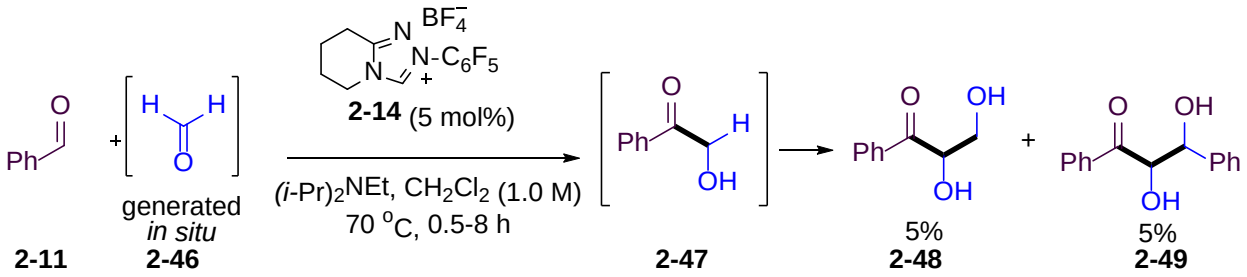


2-45 : 11%

a) Yields are of isolated products after chromatography; b) Yield determined by mass of a known mixture of benzoin products. **2-36**: 3% benzoin and 5% of the homo-benzoin of propanal, **2-11**: 13% of the homo-benzoin of hydrocinnamaldehyde and 3% of the opposite cross-benzoin product, **2-38**: 14% of the homo-benzoin of hydrocinnamaldehyde; c) Yield in brackets is of the acetylated derivative d) 5 equivalents of isobutyraldehyde used.

The reaction was effective with a large variety of aromatic aldehydes. Reactions with *ortho*, *meta*, or *para* substituted aromatic aldehydes possessing electron donating or withdrawing substituents (**2-38** to **2-44**, **Table 2.2**) provided good yields. Some cross-benzoin products could not be fully separated from their isomers (**2-11**, **2-36**, **2-38**), highlighting the necessity of forming these products in a chemoselective manner.

Although the scope of the reaction was quite broad, there were some aldehydes for which the reaction was not as effective. Attempting a cross-benzoin reaction with paraformaldehyde gave no desired product (**Scheme 2.11**). Instead two materials were isolated which corresponded to the products of a cross-benzoin reaction followed by an aldol reaction (**2-48**, **2-49**). This outcome was similar to what Kuhl and Glorius reported using *N*-alkyl thiazolium salts.[166]

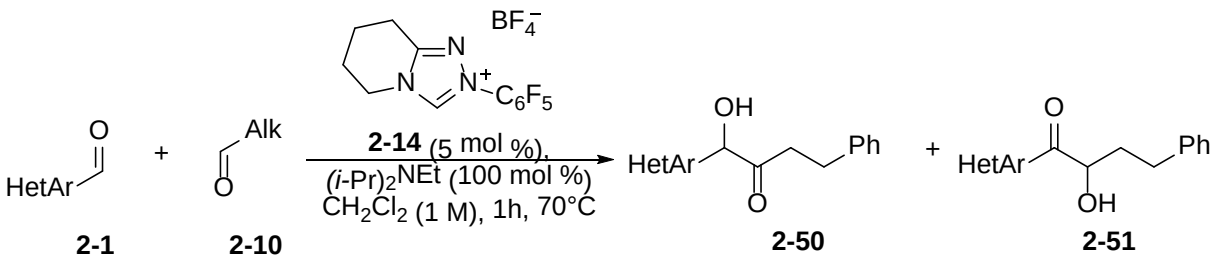


Scheme 2.11 Cross-Benzoin Reaction using Paraformaldehyde

Reactions with α-β unsaturated aldehydes (**2-45**) also gave a significantly reduced yield, as well as substantially more homo-benzoin product. Heteroaromatic aldehydes were especially problematic with this methodology (**Table 2.3**). Pyridine-3-carboxaldehyde (entry 1, **Table 2.3)** gave diminished yield and the product oxidized upon purification even with the improved purification protocol. Derivatives of these compounds could be isolated following acetylation of the crude α-hydroxy ketone mixture. Interestingly, reactions using pyridine-2-carboxaldehyde (entry 2), indole-2-carboxaldehyde (entry 3), and furfural (not shown) all demonstrated substantially reduced chemoselectivity between cross-benzoin products. The low

chemoselectivity observed in reactions when there is a heteroatom at the 2 position of the heterocycle could be due to isomerization of the cross-benzoin product or a more facile retro-benzoin reaction. Loss of selectivity between the two possible cross-benzoin products with heteroaromatic aldehydes is the largest limitation to this methodology encountered to date.

Table 2.3 Cross-Benzoin Reactions with Heteroaromatic Aldehydes



2-1 **2-10** **2-50** **2-51**

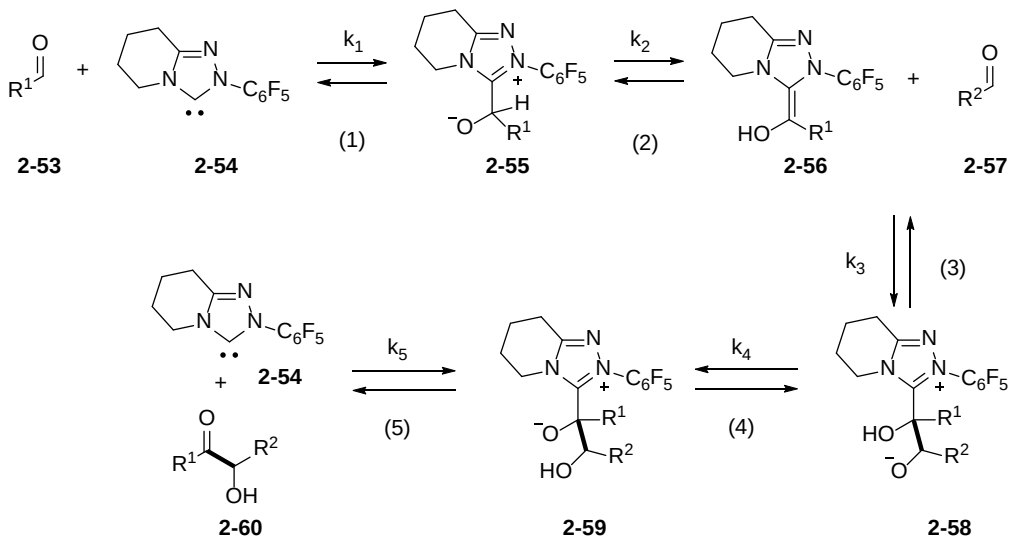
entry	HetArCHO	Ratio **2-50** : **2-51**	Yield **2-50**[a] (%)	Yield **2-51**[a] (%)
1	Pyridine-3-carboxaldehyde	1 : 0	45	0
2	Pyridine-2-carboxaldehyde	-[b]	21	20
3	Indole-2-carboxaldehyde	1.4 : 1	-	-

a) Isolated yield of acetylated derivative; b) complex mixture.

2.8 Mechanistic Discussion

Thus far a highly chemoselective cross-benzoin reaction between aromatic and aliphatic aldehydes using triazolium salts bearing a fused 6-membered ring has been demonstrated without discussing the origin of this selectivity. Following the publication of this work; Du, Bi and coworkers reported a computational study of this reaction which did not adequately address the issue.[167] Within the Gravel group, kinetic and crossover experiments as well as quantum mechanical modeling has recently resulted in a publication exploring this phenomenon.[168]

It appears three of the four cross-benzoin products are formed irreversible under the reaction conditions (the aromatic homo-benzoin product being the exception).[165] Connon and Zeitler observed similar results in reactions with triazolium **2-18**, which supports this observation.[63] If three of the four products are formed irreversibly, the chemoselectivity between these products must be governed by kinetic control. This hypothesis is consistent with the near statistical, thermodynamic distribution of products observed with cyanide and unhindered thiazolium salts for the same transformation.[51] Under kinetic control chemoselectivity becomes a question of which step is rate limiting. Following the general mechanism of Breslow (**Scheme 2.12**), there are three candidates for the rate limiting step: tautomerization to the active Breslow intermediate (2), the addition of this intermediate to the second aldehyde (3), and the catalyst ejection (5).[20] The carbene addition step (1) is often reversible and the proton transfer (4) is expected to have no substantial energy barrier.[169] Indeed, steps 3 and 4 have been found to be concerted in several computational studies. Early computational studies of the homo-benzoin reaction catalyzed by cyanide from Schowen concluded that the pre-Breslow to Breslow conversion (2) and aldehyde addition (3) step appear to have similar high energy barriers. If the same steps are assumed with triazolylidene catalysts to have comparable energy barriers, then either step could be rate limiting depending upon the substrate and catalyst.



Scheme 2.12 Detailed Cross-Benzoin Mechanism

Langdon, Gravel and Legault confirmed the reaction to be under kinetic control, using kinetics studies and quantum mechanical modeling using DFT.[170] These computations found the aldehyde addition (step 3) and catalyst ejection (step 5) have transition states (TS) of comparable energies which are candidates to be rate limiting. The aldehyde addition step (3) was found to have a significantly lower energy TS for the formation of the alkyl-aryl cross-benzoin product and aryl-aryl cross-benzoin product relative to the other products. However the formation of the aryl-aryl homo-benzoin product was found to have a very high TS energy barrier to catalyst ejection (step 5), while formation of the alkyl-aryl cross-benzoin product did not. Thus the alkyl-aryl cross-benzoin product (R^1 = Alk, R^2 = Ar) was found to have the energetically lowest rate limiting step overall (step 3), explaining the selectivity observed.

2.9 Future Work in the Cross-Benzoin Reaction

A highly chemoselective and broadly applicable cross-benzoin reaction has been presented. In this reaction a stereocenter was created, but efforts to perform the reaction enantioselectively, while maintaining chemoselectivity, have not been successful to date. Computations done on the

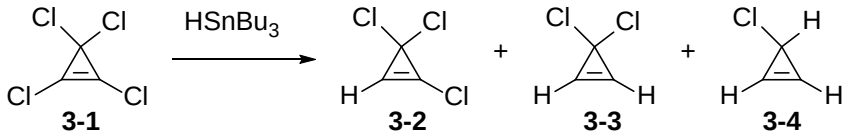
relevant transition states may serve as a predictive tool for which chiral catalysts to try. However, finding the optimal catalyst for enantioinduction in this reaction will involve bench-work, as relatively minor interactions which are difficult to model and anticipate can play a large role in the stereochemical outcome.

Current methodology focuses upon generation of α-hydroxy ketones with the ketone out of conjugation with the aromatic substituent, however with a sufficient understanding of the relevant intermediates and transition states it may be possible to chemoselectively produce the opposite cross-benzoin product and simultaneously direct stereochemistry at that site.

Chapter 3: Preparation of Bis(amino)cyclopropenium Salts and Exploration of Bis(amino)cyclopropenylidenes in *Umpolung* Reactions

3.0 Background

Studying bis(amino)cyclopropenylidenes requires the preparation of bis(amino)-cyclopropenium salt precursors. To date, all bis(amino)cyclopropenium salts have been prepared from tetrachlorocyclopropene via a substitution reaction, functional group interconversion (if necessary) and reduction. Reduction of tetrachlorocyclopropene has been reported with tributyltin hydride but resulted in a mixture of tetra-, tri-, di- and monochlorocyclopropenes (such as **3-2** to **3-4**) which can be difficult to separate (**Scheme 3.1**).[171] For this reason substitution has been typically performed first. Tetrachlorocyclopropene has undergone substitution reactions with a wide variety of nucleophiles, including halogens, alkenes and arene derivatives in the presence of halophilic Lewis acids.[172,173,174,175]

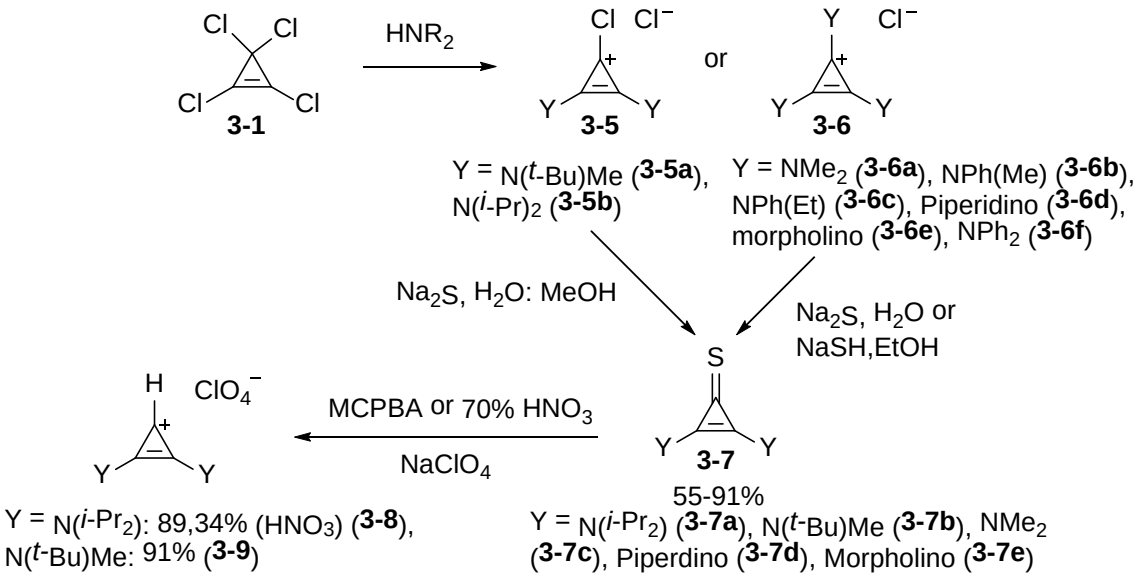


3-1 **3-2** **3-3** **3-4**

Scheme 3.1 Reduction of Tetrachlorocyclopropene

Yoshida and coworkers reported the first preparation of bis(diisopropylamino)-cyclopropenium perchlorate (**3-8**) via a disubstitution of tetrachlorocyclopropene with diisopropylamine to give chloro-bis(diisopropylamino)-cyclopropenium chloride **3-5b**.[176] The chloro-cyclopropenium salt could be reacted with sodium sulfide to give thione **3-7a** (**Scheme 3.2**). Oxidation of the thione with *m*-CPBA or nitric acid gave an unstable SO_2 or SO_3 species which fragmented to produce salt **3-8**.[177] Bis(methyl-*t*-butylamino)-cyclopropenium perchlorate **3-9** was prepared in the same manner. Some tris(amino)cyclopropenium salts could also be reacted with sodium sulfide or sodium hydrogen sulfide to afford the analogous thiones, though

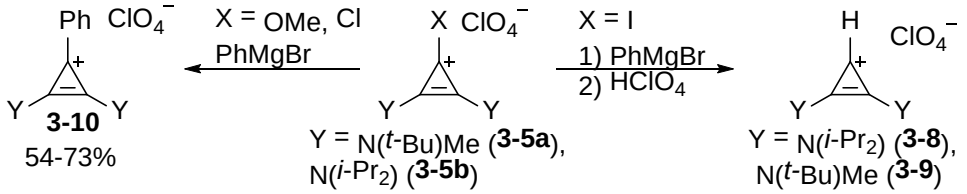
no examples of these being converted to cyclopropenium salts were presented. Regarding the order of substitution on tetrachlorocyclopropene (to give **3-5** or **3-6**), steric arguments were originally dismissed as a smaller amine (diethylamine) was found to substitute twice while a larger amine (diphenyl) substituted three times. The result with diethylamine has since proven difficult to reproduce and the outcome with *N*-phenyl analine can be explained with conformational freedom (the phenyl groups can rotate to minimize steric repulsion), making sterics the best predictor for order of substitution.[178]



Scheme 3.2 Yoshida's Route to Cyclopropenium Salts

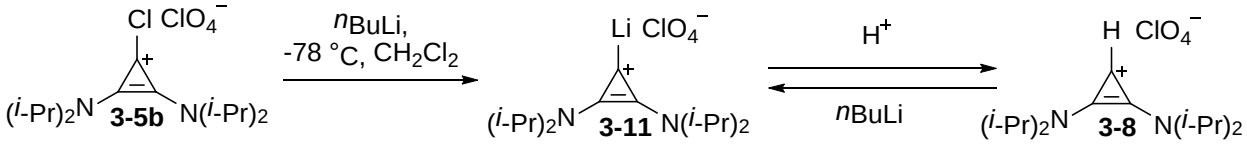
Yoshida and coworkers found a second way of preparing cyclopropenium salts while attempting Grignard reactions on chloro-bis(amino)cyclopropenium salts (**Scheme 3.3**).[179] They found that upon reaction with phenylmagnesium bromide the chloro-bis(amino)cyclopropenium salt **3-5a** gave a small amount of cyclopropenium salt **3-8** as a side product, presumably due to chloride magnesium exchange followed by protic quench. This reactivity could be suppressed by using a bis(amino)methoxy-cyclopropenium salt to give **3-10**, or enhanced by using a

bis(amino)iodo-cyclopropenium salt (prepared by salt metathesis with KI) to give exclusively salts **3-8** or **3-9**.



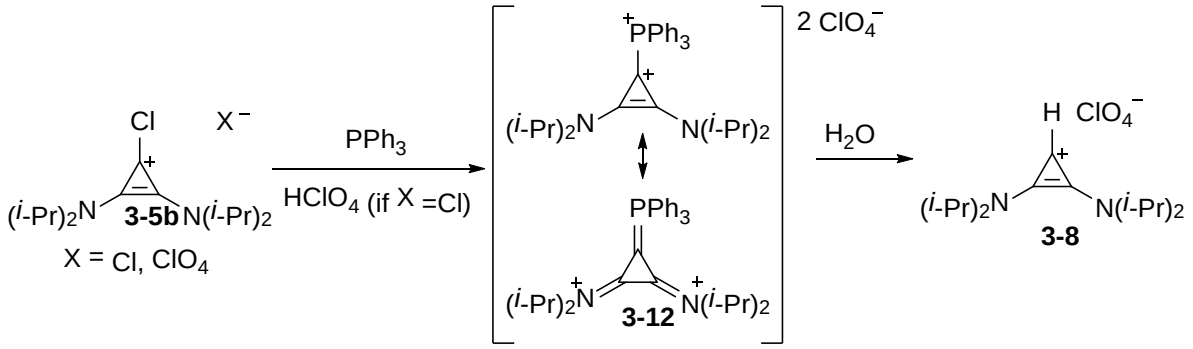
Scheme 3.3 Grignard Reaction on Chloro-cyclopropenium Salts

Weiss, Priesner and Wolf demonstrated the preparation of bis(diisopropylamino)-cyclopropenium perchlorate from the chloro-bis(amino)cyclopropenium salt **3-5b** using lithium halogen exchange with protic quench to effect reduction (**Scheme 3.4**). Their solvent choice was unusual and dichloromethane may have played an additional role in the reaction.[180] The reversible deprotonation of bis(diisopropylamino)cyclopropenium perchlorate has been reported by Yoshida and coworkers previously.[181]



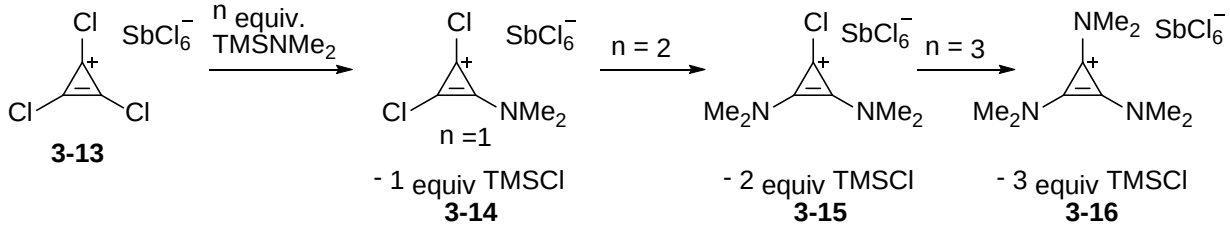
Scheme 3.4 Reduction of Chloro-cyclopropenium Salts via Lithium Halogen Exchange

Using much milder conditions Weiss and Priesner reported the phosphine reduction of chloro-bis(diisopropylamino)-cyclopropenium chloride to form bis(diisopropylamino)-cyclopropenium perchlorate (**Scheme 3.5**).[182] Further study revealed an unusual dicationic phosphine-cyclopropenium adduct, which could be isolated.[31] Upon hydrolysis this species gives bis(diisopropylamino)cyclopropenium perchlorate as well as triphenylphosphine oxide. Phosphine reduction was used by Bertrand in the preparation of bis(diisopropylamino)-cyclopropenium tetraphenylborate and by Tamm.[21,24,42]



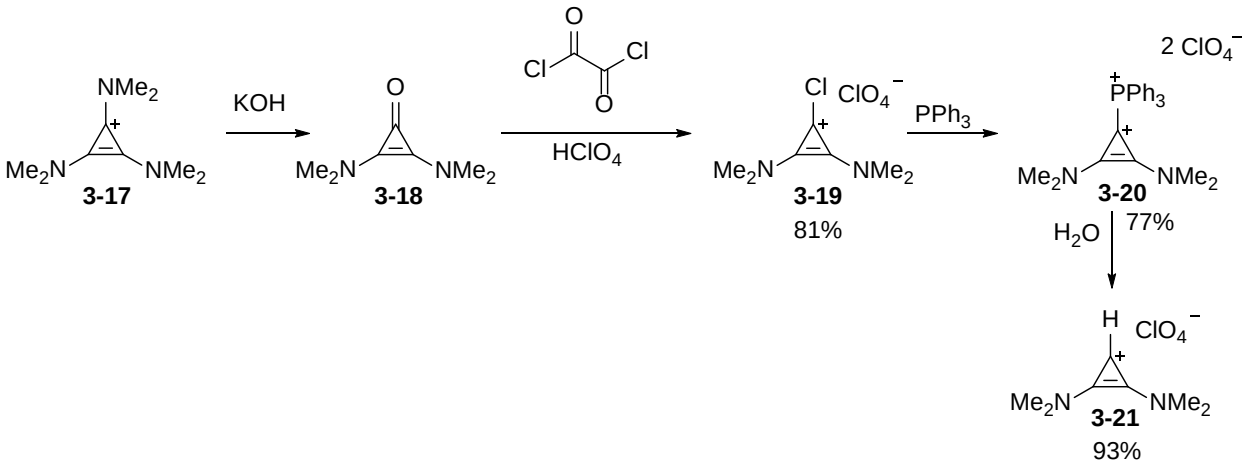
Scheme 3.5 Phosphine Reduction of Chloro-cyclopropenium Salts

Seeking to better direct the substitution reaction Weiss and coworkers found that electrophilic antimony(V) chloride salts can be reliably mono or di-substituted, with less nucleophilic *N*-silyl amines (**Scheme 3.6**).[183] These compounds eventually disproportionated to **3-16** and starting material **3-13** upon standing.



Scheme 3.6 Substitution Reactions upon Trichlorocyclopropenium Antimony(v) Chloride

Another approach to preparing cyclopropenium salts is by regeneration of chloro-bis(amino)-cyclopropenium salts. Tris(amino)cyclopropenium salts can be easily prepared from unhindered secondary amines, and react with hydroxide to form a bis(amino)cyclopropenone.[176c] Bis(dimethyl)cyclopropenone **3-18** was found to form chloro-bis(dimethylamino)-cyclopropenium perchlorate **3-19** when reacted with oxalyl chloride and perchloric acid (**Scheme 3.7**). It was subjected to phosphine reduction to give bis(dimethylamino)cyclopropenium perchlorate (**3-21**) in reasonable yield.[184]



Scheme 3.7 Cyclopropenone Route to Bis(amino)cyclopropenium Salts

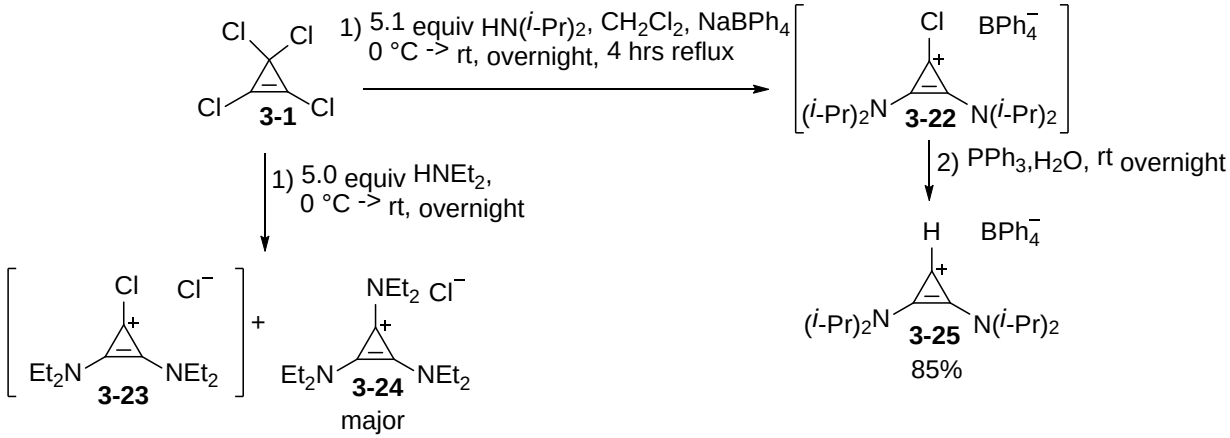
3.1 Objectives for Bis(amino)cyclopropenium Salt Synthesis

Bis(amino)cyclopropenylidenes (BACs) possess interesting properties (outlined in **Sections 1.02** and **1.03**), which may make them useful in some types of organocatalysis, but further study is required. BACs, like other carbenes, are inherently unstable and thus short lived. They can be generated *in situ* from more stable species such as bis(amino)cyclopropenium salts by reaction with base. Prior to this work, two BACs and four bis(amino)cyclopropenium salts had been reported. Unlike NHC's, there was no general method to their preparation. Studying these molecules required their preparation, which posed unique challenges given their unusual structure and reactivity. The objective of this work was to first duplicate the known methodologies to produce bis(amino)cyclopropenium salts and then produce a library of bis(amino)cyclopropenium salts for further study of BACs, ideally to establish a relationship between structure and catalytic activity. Catalysts derived from dimethylamine, diethylamine, pyrrolidine, piperidine, morpholine, *N*-methylaniline, and dibenzyl amine were targeted to probe steric and electronic effects upon reactivity. BACs possessing stereogenic elements were targeted

to explore enantioselective applications with this scaffold. What follows is an exploration of the different preparations of cyclopropenium salts, and suggestions for future innovation.

3.2 Stoichiometry Control and Phosphine Reductions

The most direct preparation of a bis(amino)cyclopropenium salt to date was Bertrand's preparation of bis(diisopropylamino)cyclopropenium tetraphenylborate[21] based upon the independent reports of Yoshida[25] and Weiss.[31] It entailed a one pot di-substitution reaction with the desired amine followed by *in situ* phosphine reduction. This protocol was replicated and afforded bis(diisopropylamino)cyclopropenium tetraphenylborate **3-25** in 85% yield (**Scheme 3.8**).[vii] An analogous procedure was unsuccessful with other amines (such as pyrrolidine); this protocol required modification to be successful with less hindered amines. Bis(diethylamino)cyclopropenium tetraphenylborate was targeted since its precursor, chloro-bis(diethylamino)cyclopropenium perchlorate can be accessed through a known procedure.[179]



Scheme 3.8 Substitution Reactions on Tetrachlorocyclopropene

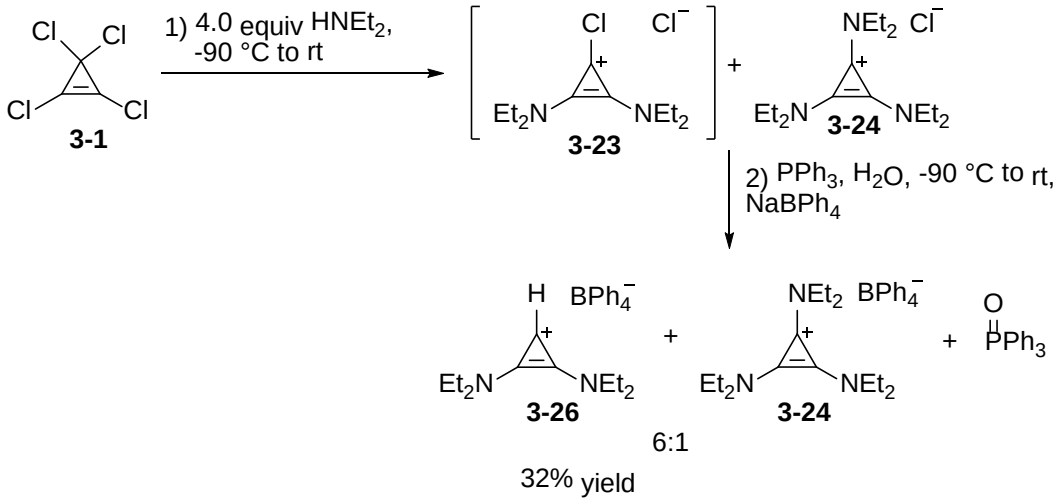
Yoshida and coworkers reported 56% yield of chloro-bis(diethylamino)cyclopropenium perchlorate (**3-23**) at low temperatures, and a quantitative yield was reported using excess amine

[vii] The tetraphenylborate salt **3-25** was prepared by Gravel, M., the perchlorate salt was prepared by the author.

at 0 °C.[176a,b,177] The reaction performed at 0 °C produced exclusively tris(diethylamino)-cyclopropenium **3-24**, which is consistent with other reports (**Scheme 3.8**).[185]

Experimental details of the low temperature procedure are unavailable, however performing the reaction at 0 °C and using 4 equivalents of diethylamine produced a mixture of cyclopropenium species enriched in salt **3-23**. The mixture was subjected to reducing conditions which generated the desired cyclopropenium salt **3-26**. Di-substituted salt **3-26** could not be purified due to the large amount of tri-substituted salt **3-24** and phosphine by-products present. Chromatography was unsuccessful, as salts **3-26** and **3-24** co-elute, and most of the material was retained by the column. Similarly salts **3-26** and **3-24** were found to co-crystallize, though this may be due to the triphenylphosphine oxide by-product which is known to co-crystallize with a large number of organic molecules.[186]

In order to produce more of the desired product **3-26** and minimize formation of side-product salt **3-24** the reaction was optimized. Presumably with more **3-26** and less **3-24** co-crystallization would be less of an issue which would simplify the purification of product **3-26**. To decrease the amount of secondary amine used, DIPEA was used as the base. This surprisingly caused an increase in the amount of tris(amino)cyclopropenium salt **3-24** formed. Lowering the temperature of the amine addition further (−78 °C), and slowing the rate of addition was found optimal for minimizing the formation of the tris(amino)cyclopropenium side product, and a >6:1 mixture of **3-23**:**3-24** was achieved (**Scheme 3.9**). Slow addition at low temperature improved the efficiency of triphenylphosphine reduction of this mixture. This procedure generated mixtures which could be crystallized to afford **3-26**, in 32% yield, on gram scale. Key to this purification was the use of methanol to remove phosphine by-products.



Scheme 3.9 Preparation of Bis(diethylamino)cyclopropenium Tetraphenylborate

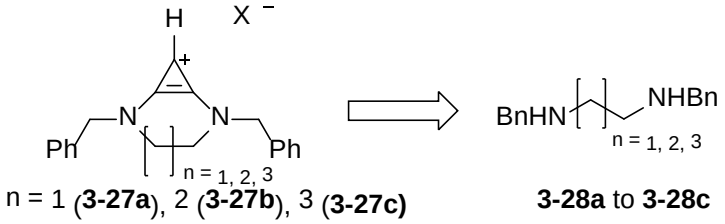
Attempting to replicate this procedure with other amines (pyrrolidine, morpholine, and *N*-methyl aniline) afforded mixtures rich in tris(amino)cyclopropenium salts which could not be satisfactorily purified to give any of the desired cyclopropenium salts. This is consistent with the literature, as yields for low temperature di-substitution varied greatly depending on the amine used.[176]

3.3 Attempts to Prepare Achiral Bicyclic Bis(amino)cyclopropenium Salts

It was hypothesized that it may be easier to control the degree of substitution in this reaction with diamines (**3-28a** to **3-28c**). Low level computations found an 8-membered ring to be the smallest ring capable of accommodating the wide N-C=C angle present in bis(amino)cyclopropenes without introducing substantial strain.[viii] It was unknown what the effect a smaller, more strained, ring would have on BAC catalysts. This could serve as another variable to explore in search of more active catalysts. The desired diamines **3-28a** to **3-28c** for these reactions were accessed without difficulty, however the corresponding pre-catalysts **3-27a** to **3-27c** could not be prepared except for a chiral variant of **3-27c** (n = 3) discussed in **Section**

[viii] Molecular mechanics calculations performed by Gravel, M.

3.8. All attempts instead yielded oligomeric materials. Thus, while conceptually intriguing, an alternate methodology will be required before these molecules become accessible.

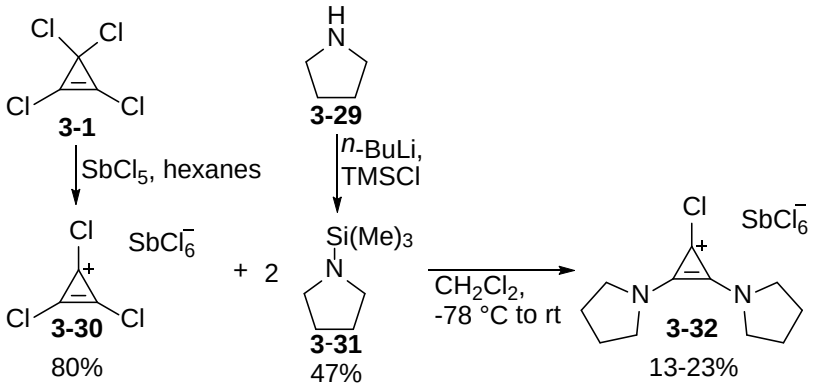


n = 1 (**3-27a**), 2 (**3-27b**), 3 (**3-27c**) **3-28a** to **3-28c**

Figure 3.1 Acyclic Bis(amino)cyclopropenium Salts Targeted

3.4 Preparation of Bis(amino)cyclopropenium Antimony Hexachloride Salts

The primary obstacle to the formation of a series of cyclopropenium salts at this stage was controlling the extent of amine substitution (i.e. di- vs. tri-substitution). Weiss and coworkers reported that better control could be obtained by reacting 1,2,3 tri(chloro)cyclopropenium antimony hexachloride with *N*-silyl amines. This protocol was attempted with pyrrolidine, to generate salt **3-32** cleanly in low yield (13-23%). Presumably this could be improved with optimization (**Scheme 3.10**).



Scheme 3.10 Preparation of Chloro-bis(amino)cyclopropenium Antimony(v) Chloride

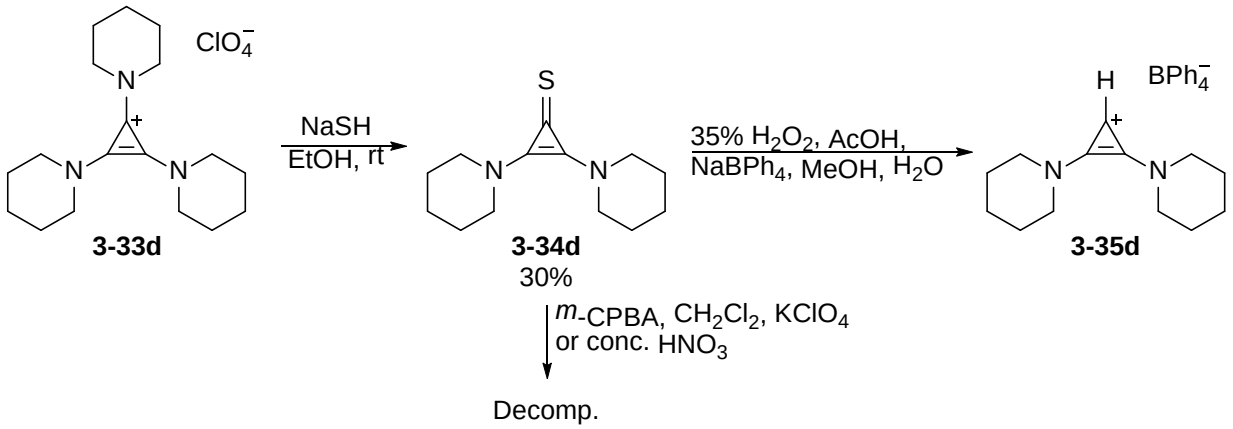
Unfortunately salt **3-32** was found to be inert to, or decompose under, reducing conditions. None of the desired product was formed with triphenylphosphine reduction. Reduction of **3-32** via lithium halogen-exchange and protonation, reducing metal (zinc) conditions or sodium borohydride also failed to generate the desired cyclopropenium salt.[ix] Exchanging antimony(v) chloride for another counterion was also unsuccessful. While reductions with antimony (v) chloride salts failed, this method did provide effective di-substitution and may be amenable to the use of other halophilic Lewis acids.

3.5 Preparation of Bis(amino)cyclopropenium Salts via Bis(amino)cycloprop-2-enethiones

Yoshida and coworkers reported a potential route to bis(amino)cyclopropenium salts via oxidation of bis(amino)cycloprop-2-enethiones, using *m*-CPBA or nitric acid. A number of bis(amino)cycloprop-2-enethiones have been prepared by reacting tris(amino)cyclopropenium salts with sodium hydrogen sulfide. The oxidation step was reported with bis(diisopropylamino)cycloprop-2-enethione and bis((methyl)*t*-butyl)cycloprop-2-enethione and not with any of the less bulky cycloprop-2-enethiones.

To probe this methodology, salt **3-33d** was prepared and subjected to sodium hydrogen sulfide following literature conditions (**Scheme 3.11**). The yield (30%) for this reaction was far below the reported 75%, but otherwise satisfactory.[176c] Attempts at oxidation of thione **3-34d** with *m*-chloroperoxybenzoic acid did not produce the desired product. Attempted oxidation with nitric acid on small scale decomposed the starting material. Hydrogen peroxide, which has long been known to de-sulfurize ureas and convert azole-2-thiones to imidazolium salts, was found to be an effective oxidant generating the desired cyclopropenium salts.[187]

[ix] Zinc reduction of these compounds was discovered later and revisited here with **3-32**.



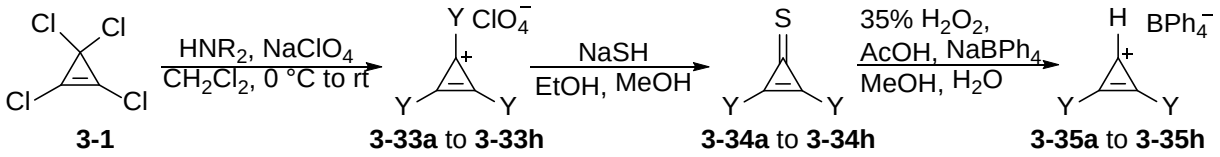
Scheme 3.11 Preparation and Reactions of Bis(amino)cycloprop-2-enethiones

With an effective methodology in hand, a range of bis(amino)cyclopropenium salts were produced. Performing tri-substitution upon tetrachlorocyclopropene was reproducibly high yielding (entries 1-5 and entry 7, **Table 3.1**) with the exception of the *N*-methylaniline (entry 6) and *tert*-butyl thiol (entry 8), both of which are substantially less nucleophilic than the other substrates. The reaction with *N*-methylaniline required reflux and extended reaction time in order to form a satisfactory amount of tris(amino)cyclopropenium product **3-33f**. In the cases of salts **3-33a** and **3-33e**, material was lost during aqueous workup of the perchlorate salts, thus a more organic soluble anion was used.

Yields at the thione-forming step varied substantially. This reaction was originally reported at room temperature for 20 hours, however the majority of tris(amino)cyclopropenium salts required elevated temperatures and extended reaction times to obtain modest yields. Exemplifying the influence of amine substituents, the conditions used to form a thione with tris(*N*-methylanilino)cyclopropenium chloride (entry **3-33f)** were milder than the other tris(amino)cyclopropenium salts. Tris(*N*-methylanilino)cyclopropenium chloride decomposed at elevated temperature, but gave a reasonable yield of **3-34f** when the reaction was performed at

room temperature. Despite these difficulties, one indisputable advantage of working with bis(amino)cycloprop-2-enethiones was that they could be purified via chromatography.

Table 3.1 Preparation of Bis(amino)cyclopropenium Salts **3-35a** to **3-35h**



3-1 **3-33a** to **3-33h** **3-34a** to **3-34h** **3-35a** to **3-35h**

entry	label	Y =	yield of **3-33** (%)	yield of **3-34** (%)	yield of **3-35** (%)
1	a	NMe_2	9, 64[a]	42	41
2	b	NEt_2	99	86	48, 61[c]
3	c	Pyrrolidino	91, >99[a]	42	35, 34[c]
4	d	Piperidino	90	57	48[c]
5	e	Morpholino	6, >99[a]	79	52
6	f	*N*-MePh	47[b]	69	39
7	g	NBn_2	>99[b]	53	59
8	h	S(*t*-Bu)	45, 59	<5	-

a) Tetraphenylborate salt isolated; b) chloride salt isolated; c) perchlorate salt isolated.

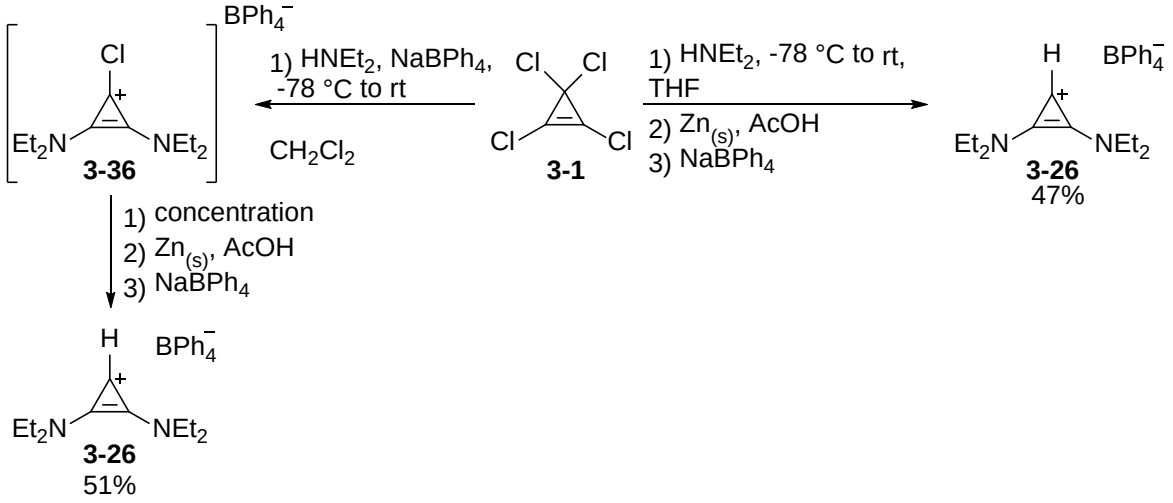
Conversion of bis(amino)cycloprop-2-enethiones to bis(amino)cyclopropenium salts was found to be quick and high yielding with minimal alteration from a known procedure for the preparation of triazolium salts.[188] Though yields at this stage were modest, the reactions were clean, affording easily crystallized cyclopropenium salts. Using this route, several previously inaccessible cyclopropenium salts (**3-35a**, **3-35c** to **3-35e, Table 3.1**) were successfully prepared. For comparison purposes bis(diethylamino)cyclopropenium tetraphenylborate was also prepared via this route. For bis(diethylamino)cyclopropenium tetraphenylborate this process was slightly better yielding but less efficient overall (41% over 3 steps, vs. 32%, one pot 2 steps).

It was more practical to prepare cyclopropenium salts with different counterions using this protocol because the counterion was added last, as an acid or salt, to relatively pure material. Bromide, perchlorate, tetrafluoroborate, hexafluorophosphate, and tetraphenylborate anions were explored. Except for tetraphenylborate, these bis(diethylamino)cyclopropenium salts were ionic liquids rather than solids. By-products from the peroxide reaction could be removed via aqueous wash and high vacuum, to give reasonably pure material without further purification.

3.6 Improved Preparation of Bis(diethylamino)-Cyclopropenium Tetraphenylborate

Looking for a cleaner, milder, reduction method chloro-bis(diethylamino)-cyclopropenium tetraphenylborate **3-36** was combined with elemental zinc in acetic acid. This reduction was discovered to be an extremely efficient and clean way of forming cyclopropenium salts (**Scheme 3.12**). Surprisingly, while there were no signs of degradation of the cyclopropenium ring under these conditions, a portion of tetraphenylborate anion was unaccounted for in the crude reaction mixture. Possibly one of the boron-carbon bonds was cleaved under these conditions to give benzene and a borane, which was removed upon workup. To determine the optimal approach the reaction was performed in two different ways. One reaction was done in using THF in one pot. The other reaction used dichloromethane but also included a solvent exchange, as dichloromethane could also react with zinc. The substitution in THF was less selective towards chloro-bis(diethylamino)cyclopropenium, but the reaction was successful and higher yielding than previous methods. Performing the reaction in dichloromethane and performing a solvent exchange was found to be the best yielding preparation of cyclopropenium **3-26** to date (51% yield). The only drawback to this protocol was

that ~20% more sodium tetraphenylborate was required to compensate for the amount lost following the zinc reduction.



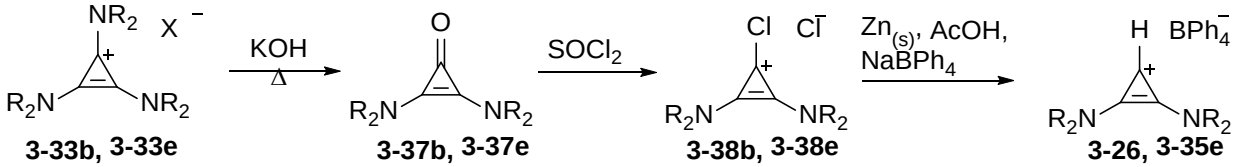
Scheme 3.12 Preparations of Cyclopropenium Salt (**3-26**) using Zinc as a Reducing Agent

3.7 Preparation of Bis(amino)cyclopropenium salts via Cyclopropenones

In 1991 Landau and Seitz reported that bis(amino)cyclopropenones could be converted to chloro-bis(amino)cyclopropenium salts with oxalyl chloride.[189,190] Bis(amino)cyclopropenones can be formed from tris(amino)cyclopropenium salts by reaction with hydroxide. To see if this was a more effective route to cyclopropenium salts, two cyclopropenium salts were prepared in this way (**Table 3.2**). Bis(morpholino)cyclopropenium tetraphenylborate **3-35e** (entry 1) was looked at because the first two steps were well precedented for this process, and bis(diethylamino)cyclopropenium **3-26** (entry 2) so it could be compared to other methods. Both cyclopropenones were prepared without difficulty (**3-37b**, **3-37e**) though the yield with cyclopropenone **3-37e** was not as high as reported. Thionyl chloride was used instead of oxalyl chloride and was found to be effective converting both cyclopropenones back to chloro-cyclopropenium salts which were reduced without isolation. Using the recently discovered zinc

reduction on **3-38e** produced salt **3-35e** in modest yield (over 2 steps). The reaction to form **3-26** was lower yielding. This method was lower yielding and longer than the thione route overall, but may be useful in the preparation of some bis(amino)cyclopropenium salts.

Table 3.2 Formation of Bis(amino)cyclopropenium Salts via Cyclopropenones



3-33b, 3-33e **3-37b, 3-37e** **3-38b, 3-38e** **3-26, 3-35e**

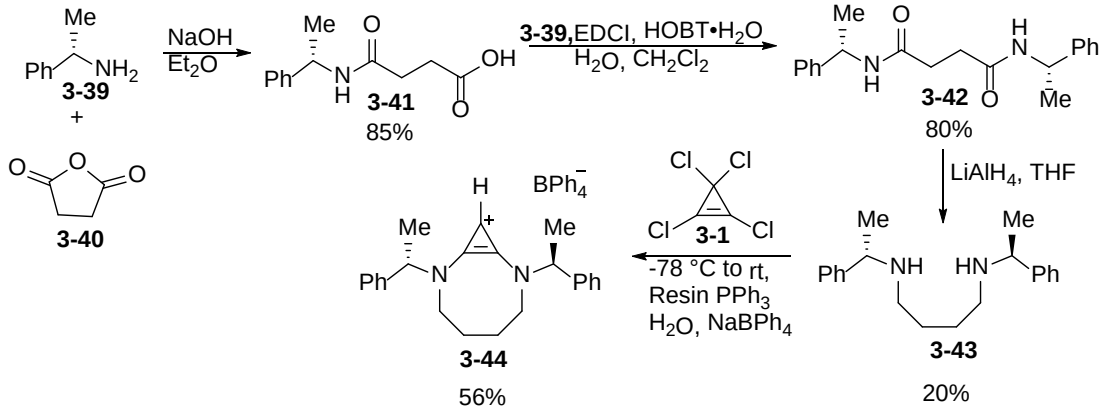
entry	amine NR_2	yield of **3-37** (%)	yield cyclopropenium (%)
1	Morpholino	39	62
2	NEt_2	14 (77)[a]	36

a) Literature yield in brackets.[191]

3.8 Preparation of Bis(amino)cyclopropenium Salts from Chiral Amines

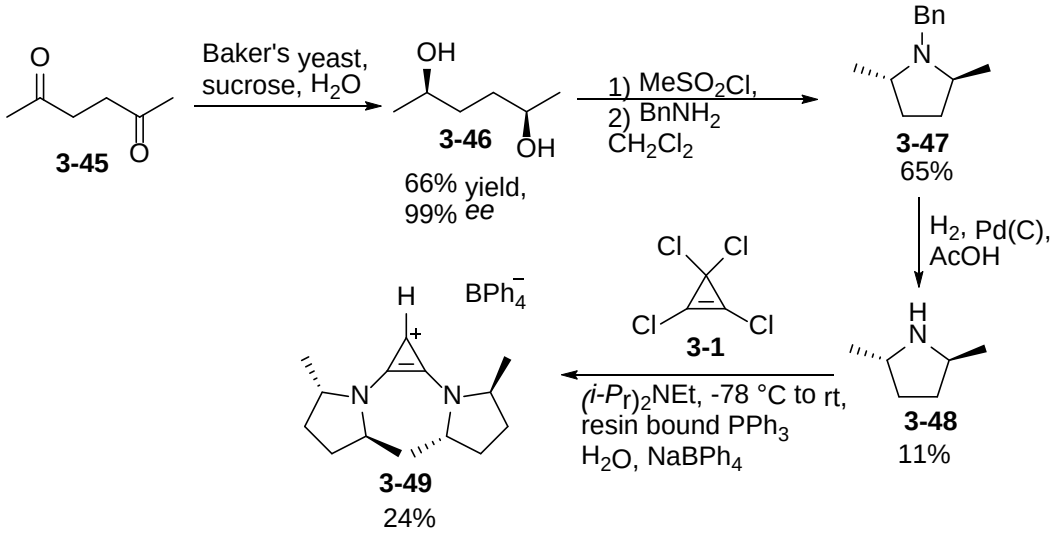
The preparation of chiral bis(amino)cyclopropenium salts from enantioenriched secondary amines was explored using the methods previously described. The first cyclopropenium salt targeted (**3-44**) possessed a fused membered ring. Restricted rotation about the NC(sp^2) bonds ensures the stereocenters are close to the reacting site, something which may have been an issue with the salt prepared by Tamm.[42] The diamine was prepared from commercial (S)-1-phenyl-ethylamine, via a known process.[192] The chloro-bis(amino)cyclopropenium compound was effectively reduced by triphenylphosphine in water, however this mixture could not be satisfactorily purified. When a resin-bound phosphine was used in place of triphenylphosphine it could be purified and the resulting crystals were suitable for X-ray diffraction. That analysis showed the substituents on both nitrogen atoms to be oriented in a near planar fashion (bond

angles 115.5-123.3 degrees), which validated computational predictions. In hindsight, a zinc reduction is almost certain to improve the yield of bis(amino)cyclopropenium salt **3-44**.



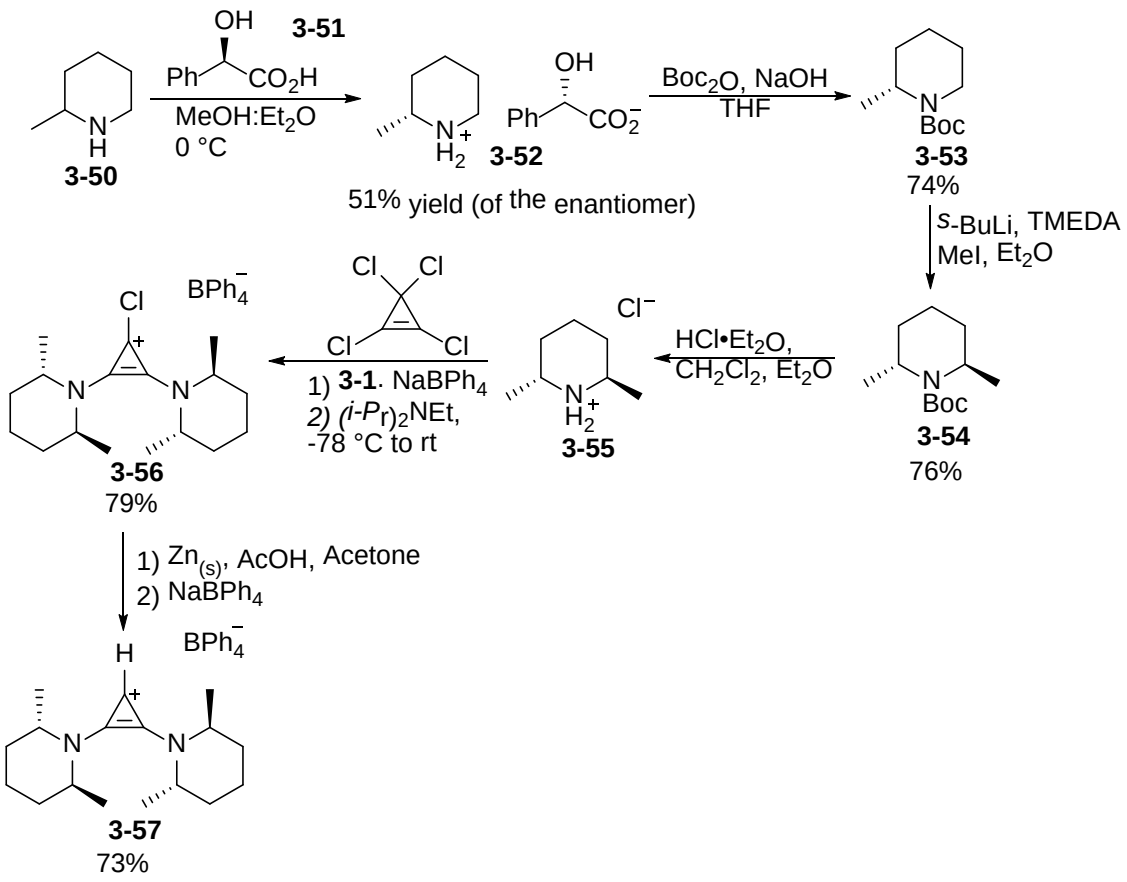
Scheme 3.13 Preparation of Bicyclic Cyclopropenium Salt **3-44**

A bis-(2,5-dimethylpyrrolidino)cyclopropenium salt was prepared using the known (*R,R*)-2,5-dimethylpyrrolidine (**Scheme 3.14**).[193] The enzymatic reduction and cyclization with benzylamine went as reported, but de-benzylation proved to be troublesome. Large amounts of this amine were lost to evaporation, as it was found to form an azeotrope with diethyl ether. Forming a cyclopropenium salt from this amine was effective, though the isolation was low yielding.



Scheme 3.14 Preparation of Bis(amino)cyclopropenium Salt **3-49**

While both **3-44** and **3-49** could be prepared, both syntheses delivered limited amounts of material and insights from their use in catalysis led to the preparation of cyclopropenium **3-57** (**Scheme 3.15**). The resolution of inexpensive 2-methyl piperidine and highly diastereoselective α-alkylation was reported by Aggarwal and found to be very effective.[194] As both enantiomers of mandelic acid are available, this route could provide access to either enantiomer of 2,6-dimethyl piperidine. Similarly to (*R,R*)-2,5-dimethylpyrrolidine, (*R,R*)-2,6-dimethylpiperidine was found to azeotrope with solvents, however its hydrochloride salt does not. Ethereal hydrochloric acid was found to be less effective at cleaving the Boc group than triflic acid, but offered better material throughput as the chloride could be isolated directly from the reaction mixture via concentration. Attempting to form cyclopropenium salt **3-57** from (*R,R*)-2,6-dimethylpiperidine instead gave pure chloro-bis(amino)cyclopropenium salt **3-56**. This material could not be stored for extended periods but its isolation allowed the reduction to be performed separately. Subjecting chloro-bis(amino)cyclopropenium salt **3-56** to phosphine reduction resulted in ~65% conversion to the desired cyclopropenium salt. Using the recently discovered zinc reduction instead on salt **3-56** afforded cyclopropenium salt **3-57** in 73% yield on gram scale.

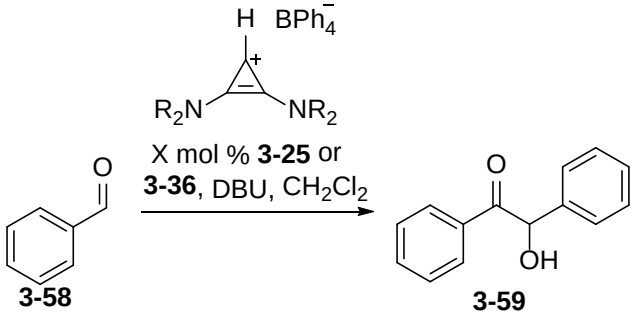


Scheme 3.15 Preparation of Bis(amino)cyclopropenium Salt **3-57**

3.9 Initial Investigations of *Umpolung* Reactivity

As the homo-benzoin reaction of benzaldehyde was the only umpolung reaction reported to be catalyzed by BACs in the literature, it was the first to be studied (**Table 3.3**).[42] The use of readily available cyclopropenium salt **3-25** gave low conversion (entry 1). As is the case for Tamm's catalyst, this salt features α-branching on the amino moieties resulting in a sterically hindered carbene. Cyclopropenium salt **3-26** was relatively more efficient, but the yield for this reaction was nevertheless quite low (entry 2). The use of a higher catalytic loading resulted in minimal improvement to the yield (entry 3). Thus the ability of BACs to induce the homo-benzoin reaction in benzaldehyde was verified, but its efficacy was poor.

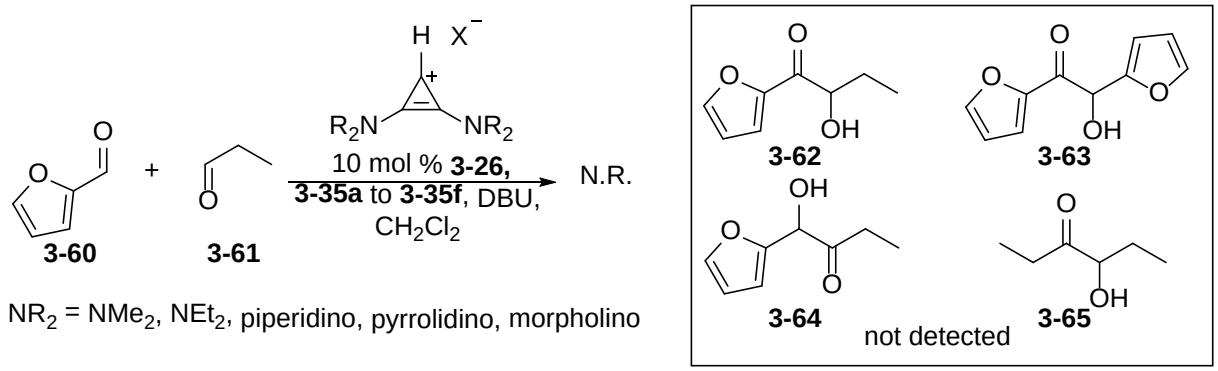
Table 3.3 Homo-Benzoin Reaction of Benzaldehyde



entry	R	Catalyst loading (mol %)	yield
1	*i*-Pr (**3-25**)	10	<5
2	Et (**3-26**)	10	16
3	Et (**3-26**)	20	21[a]

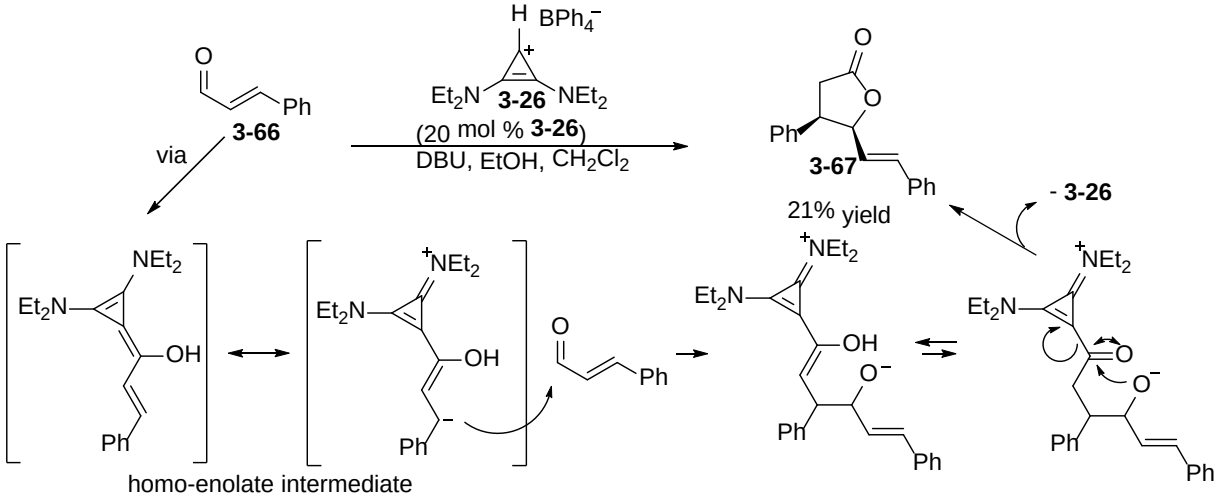
a) Solvent free.

Rather than attempt to improve upon the well studied homo-benzoin reaction of benzaldehyde, focus shifted towards detection of any efficient homo-benzoin or cross-benzoin reaction. As there are several NHC's known to effect the benzoin reaction (see **Chapter 1**), it is of interest whether this lack of benzoin reactivity is due to the electronic nature of the cyclopropenylidene core or the amino substituents. Thus a heteroaromatic aldehyde (furfural) and an aliphatic aldehyde (propanal) were reacted in the presence of various BACs looking for homo or cross-benzoin reactivity (**Scheme 3.16**). While bis(amino)cyclopropenylidenes which could be generated under these conditions (see **Chapter 4**) no benzoin products were detected. A subsequent set of reactions using the same catalysts with cinnamaldehyde and *p*-bromobenzaldehyde also failed to produce any benzoin products. Though it may seem problematic, there may be numerous advantages to a lack of benzoin reactivity in other *umpolung* reactions.



Scheme 3.16 BAC Catalyzed Cross-Benzoin Reactions

Reaction of cinnamaldehyde with EtBAC was found to yield one material of interest (**Scheme 3.17**). Lactone **3-67,** which is the result of cinnamaldehyde dimerization via a 'homo-enolate' intermediate, was produced in low yield. This product was determined to be the cis isomer through comparison of spectroscopic properties, as both isomers are known.[195] This was the first demonstration of a homoenolate reaction with any BAC; however homoenolate reactions with NHC's have been extensively studied.[196]



Scheme 3.17 BAC Catalyzed Homoenolate Reaction with Cinnamaldehyde

3.10 Conclusions and Future Work

Several novel bis(amino)cyclopropenium salts were prepared. Known methods for their preparation were not effective for several targets, due to over-substitution using less hindered amines. Low temperature reactions lead to selective di-substitution in the case of bis(amino)cyclopropenium salts **3-26**, **3-44**, **3-49** and **3-57**. Other bis(amino)cyclopropenium salts were prepared from tris(amino)cyclopropenium salts, via cycloprop-2-enethiones or cyclopropenones. While lengthier, these routes are of comparable complexity to the methods used to make NHC's. Zinc in acetic acid was discovered to be compatible with the cyclopropenium moiety and an effective reductant of chloro-bis(amino)cyclopropenium salts. Preliminary investigations on their organocatalytic activity were performed.

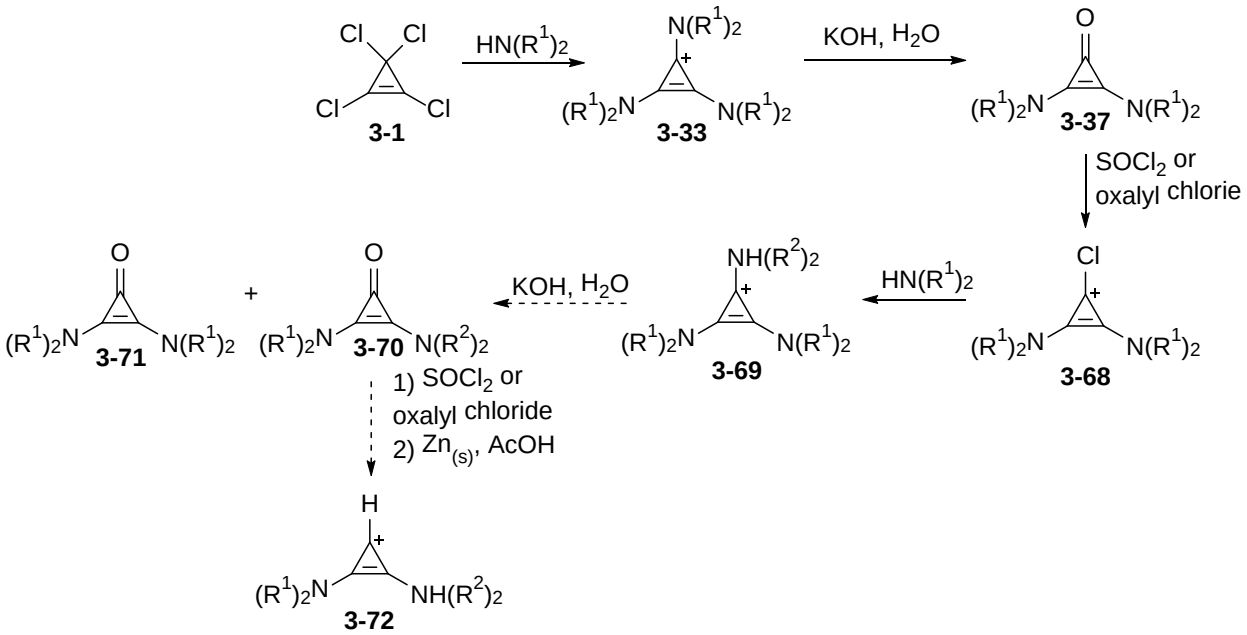
The accessibility of a large number of commercial/known chiral secondary amines and the straightforward way of assembling them make this scaffold ideal for producing chiral catalysts. The methods of cyclopropenium formation discussed above will be practical in the immediate future. However, as limits in accessing BAC catalysts can limit further discoveries, there remains room for improvement of these protocols.

A more active catalyst is desirable. It is hard to predict which substituents on the amino moieties best serve to the activate catalysts and this is best determined experimentally. Perhaps functionalities which serve as hydrogen bond donors or acceptors may prove beneficial in stabilizing transition states. Thus catalysts possessing ester, phenol or alcohol functionalities on the amino substituent could be prepared for this purpose.

When applicable, controlled di-substitution was the most efficient way of preparing bis(amino)cyclopropenium salts. The failed Lewis acid route with antimony was very efficient at directing di-substitution, though the resulting material could not be made into a

bis(amino)cyclopropenium salt. Other halophilic Lewis acids could be used instead. Tri(chloro)cyclopropenium tetrachloroaluminate is known to undergo electrophilic substitution with aromatic rings, and may react with silylamines in the desired manner, though this is unprecedented.[197,198] Boron trifluoride may also be a good candidate for this reaction. Tetrachloroaluminium may also be decomposed by exposure to water, to produce salts which could be manipulated more easily.

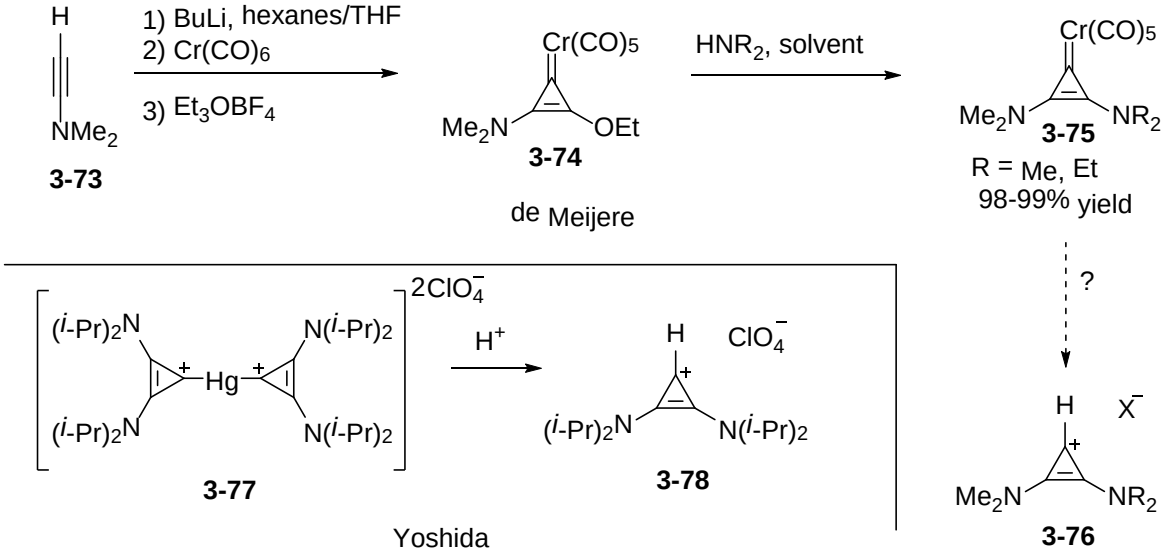
It is desirable to produce bis(amino)cyclopropenium salts with two different amino substituents. This can already be done on cyclic systems (such as pre-catalyst **3-44** if a different amine was used in the amide coupling), but is more challenging without a tether. Such catalysts could prove to be more effective than symmetrically substituted BACs. Many effective chiral catalysts block all but one quadrant of the substrate and it may be desirable to produce such a system on a BAC catalyst. Two strategies can be envisioned for the synthesis of non-symmetric bis(amino)cyclopropenium salt, either through stepwise modification using cyclopropenones (**Scheme 3.18**) or via templating with a transition metal.



Scheme 3.18 Preparation of Non-Symmetric Bis(amino)cyclopropenium Salts

The preparation of compounds such as **3-69** (**Scheme 3.18**) is known.[190] Partial hydrolysis under basic conditions is predicted to lead to a mixture of bis(amino)cyclopropenone **3-71** and non-symmetric **3-70**. Individually these steps are well precedented, though separating **3-70** from **3-71** may not be trivial. The disadvantages to this method would be its length, and anticipated low yield.

It may also be possible to make use of transition metals as templates for these reactions. De Meijere and coworkers prepared the chromium complexes **3-75** (**Scheme 3.19**), templating the carbene via an ynamine.[199] While there are currently no known methods to perform the protodemetallation of the cyclopropenylidene complex, acidic decomposition of mercury complex **3-77** to give a bis(amino)cyclopropenium salt was shown by Yoshida.[200] If a similar reaction is possible with compound **3-75**, **t**his route would be an efficient way to access a variety of un-symmetrically substituted bis(amino)cyclopropenylidenes.



Scheme 3.19 Preparation of Non-Symmetric Bis(amino)cyclopropenium Salts via Template

Chapter 4: BAC Catalyzed Stetter Reactions

4.1 Objectives

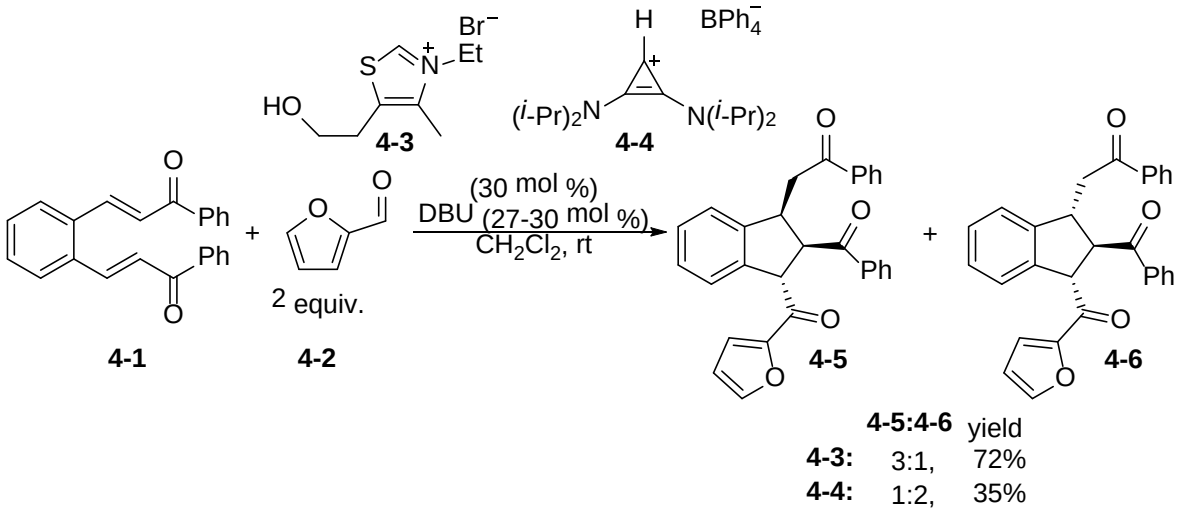
Since its initial report by Stetter and Schreckenberg the Stetter reaction (the catalytic conjugate addition of an acyl anion equivalent) has shown great potential as a carbon-carbon bond forming reaction. Stetter products, often 1,4-diketones which can be difficult to access otherwise, can be directly converted to heterocycles, cyclopentenones, or other useful materials in the synthesis of bioactive molecules.[95,96] There are several examples in the literature of Stetter reactions which are only effective with a limited range of substrates or catalysts. Enders and coworkers have demonstrated several intermolecular Stetter reactions on chalcone, or chalcone-like, acceptors with electron poor-aromatic and heteroaromatic aldehydes. However yields with electron rich aromatic aldehydes in these intermolecular Stetter reactions have been unsatisfactory thus far.[122] Several groups have sought to extend the scope of the Stetter reaction towards unexplored Michael acceptors or acceptors which were found unreactive previously. In this regard, β-alkyl enones could give rise to some of the most useful and versatile of Stetter products. Reactions with these substrates have been low yielding using thiazolium or cyanide catalysts and have seen little development despite being among the earliest examples of the Stetter reaction. Additionally the Stetter reaction can create one, or more, new stereocenters and yet enantioselectivity in these reactions is often modest or poor. Several complex non-commercial catalysts have been reported in recent years which are capable of inducing enantioselectivity in the Stetter reaction. However, the substrate scope for individual catalysts is often limited, and preparation of new chiral thiazolium or triazolium pre-catalysts is labor intensive. Thus a more broadly applicable, easily modified chiral scaffold was desirable.

Prior to this work bis(amino)cyclopropenylidenes were not known to be catalysts for the Stetter reaction, nor any reaction except the benzoin reaction using benzaldehyde. Thus it was difficult to predict at the outset if BACs would be effective catalysts for the Stetter reaction, and if so, what advantages they may confer over commonly used NHCs. The primary objective of this work was to examine whether BAC catalysts could generate synthetically attractive yields in Stetter reactions. This line of inquiry was successful. The objective then became to explore Stetter reactions which can be challenging with current NHCs, such as those using electron-rich aromatic aldehydes, or β-alkyl substituted enones, to see if there are any advantages to BAC catalysis. The last objective of this work was to explore the feasibility of enantioselective BAC catalysis in the Stetter Reaction.

4.2 Preliminary Findings

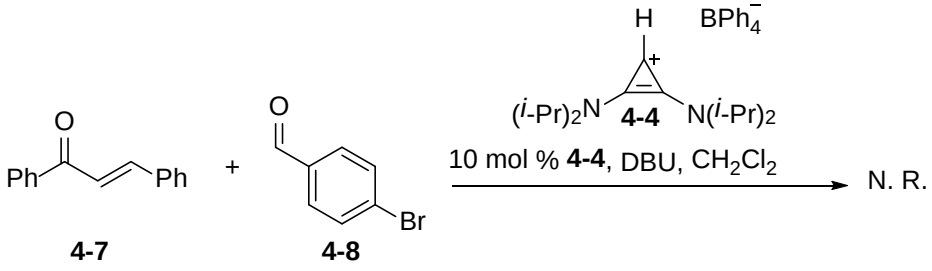
Gravel and coworkers screened several NHC catalysts as well as bis(di-isopropylamino)-cyclopropenylidene (*i*-PrBAC) while developing a diastereoselective synthesis of indanes via a domino Stetter-Michael reaction.[x,147] They found *i*-PrBAC produced some of the desired indane (**Scheme 4.1**).[201] Reaction conditions were well developed for this transformation, and the catalyst compared poorly against several NHCs in terms of yield, diastereoselectivity, and the number of side products. Despite the low yield, this was a positive indication of catalyst activity in Stetter processes.

[x] Sánchez-Larios, E.; *unpublished results.*



Scheme 4.1 Preliminary Findings in Stetter Reactivity

Subsequent explorations of *i*-PrBAC catalyzed Stetter reactions using a chalcone substrate were unsuccessful (**Scheme 4.2**).[xi] Chronologically, *i*-PrBAC was developed prior to Arduengo's discovery that sufficiently stabilized carbenes can persist without bulky "blocking groups."[12d] Thus it was hypothesized that the bulky isopropyl groups, intended to shield the carbene site from unwanted side reactions, could be unnecessary and may simply be making the active site less accessible to substrates. To test this hypothesis several BACs possessing less bulky amine substituents were screened in Stetter reactions.



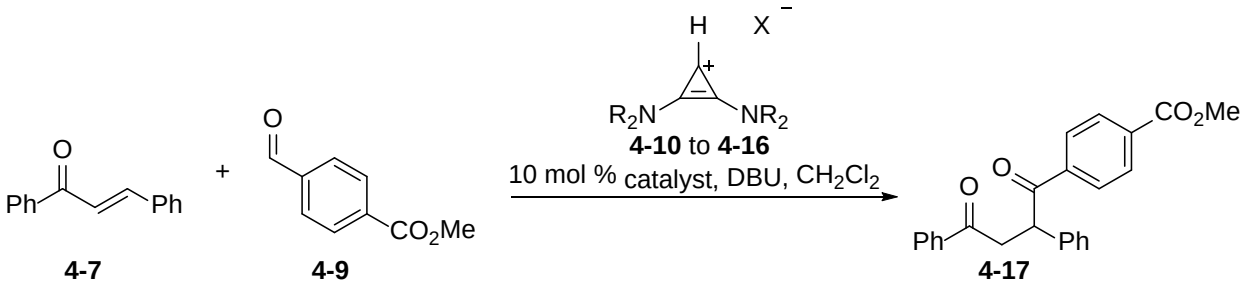
Scheme 4.2 Further Exploration of *i*-PrBAC

[xi] Gravel, M.; *unpublished results*

4.3 Development of a General Stetter Reaction

A number of bis(amino)cyclopropenium salts were prepared (see **Chapter 3** for details) and screened in the Stetter reaction (**Table 4.1**). The bis(amino)cyclopropenylidenes with dimethylamino (MeBAC) and diethylamino substituents (EtBAC) showed high conversion within the reaction time frame (entries 1-3) proving bulky "blocking" groups are not a requirement for catalytic activity. Surprisingly, bis(amino)cyclopropenylidenes with cyclic substituents (entries 4-6) gave modest conversions. As expected, *i*-PrBAC performed poorly, with only slight improvement through increased time and catalytic loading (entries 7, 8). An *N*-methyl-aniline derived catalyst (**4-16**) was found to be less active than the other catalysts and required a strong base for activation (entry 9). Significantly, none of these reactions had detectable amounts of benzoin side products, which was different from similar reactions with NHCs. EtBAC was chosen for further exploration, as EtBAC and MeBAC catalysts gave the highest yields and EtBAC was the most easily obtained. Two of the salts presented in this screening were perchlorate rather than tetraphenylborate salts. This was a consequence of their preparation, and the implications of this difference in will be addressed in **Section 4.7**.

Table 4.1 Screening BAC Catalysts for Stetter Reactivity

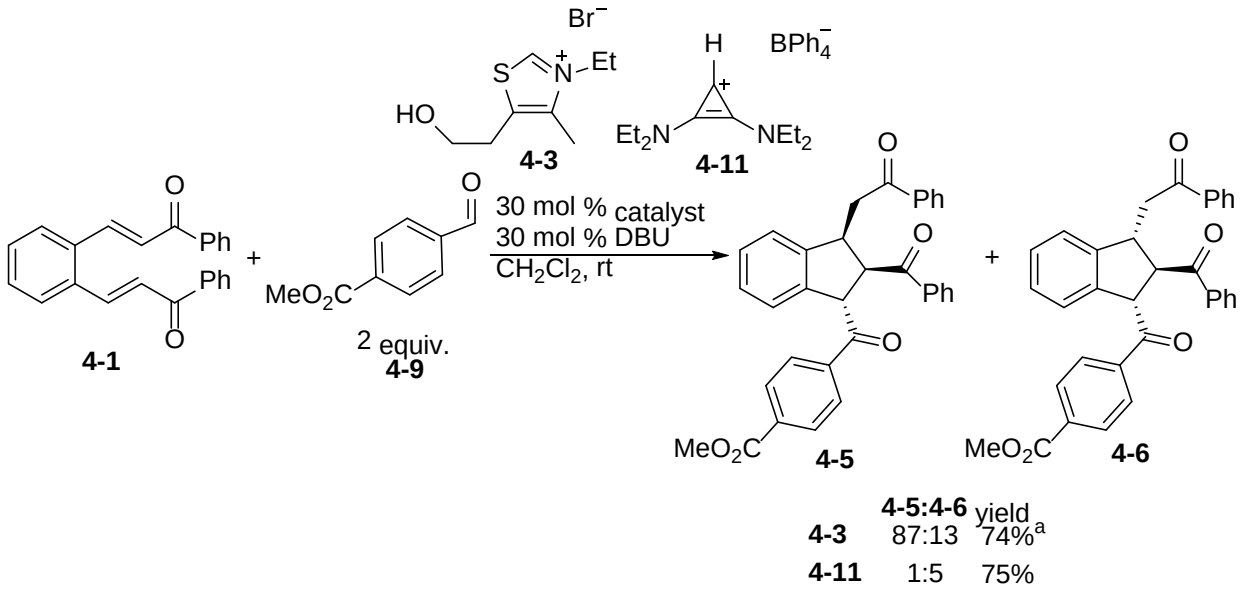


entry	catalyst	NR_2	X	time (hrs)	conversion (yield)[c] %
1	**4-10**	NMe_2	BPh_4	2	80
2	**4-11**	NEt_2	BPh_4	2	87
3	**4-11**	NEt_2	BPh_4	3	100 (98)
4	**4-12**	pyrrolidino	ClO_4	2	31
5	**4-13**	piperidino	ClO_4	2	14
6	**4-14**	morpholino	BPh_4	2	23
7	**4-15**	N(*i*-Pr)$_2$	BPh_4	3	14 (<10)
8	**4-15**	N(*i*-Pr)$_2$[a]	BPh_4	16	22 (21)
9	**4-16**	N(CH$_3$)Ph[b]	BPh_4	16	<5

a) Using 30 mol % catalyst loading; b) 10% conversion with KHMDS as base; c) Yield of isolated purified product.

Revisiting the Stetter-Michael reaction with EtBAC afforded comparable yield to a thiazolium catalyzed reaction (**Scheme 4.3**).[147] However, the ratio of products in this reaction favoured what was established to be the thermodynamically favored diastereoisomer by a greater ratio than *i*-PrBAC. Presumably the two diastereomers interconvert under the basic reactions conditions, and such base driven isomerization is known. Having validated the efficiency of this

catalyst, attention was turned towards establishing the range of aldehydes that are amenable to Stetter reactions with chalcone.



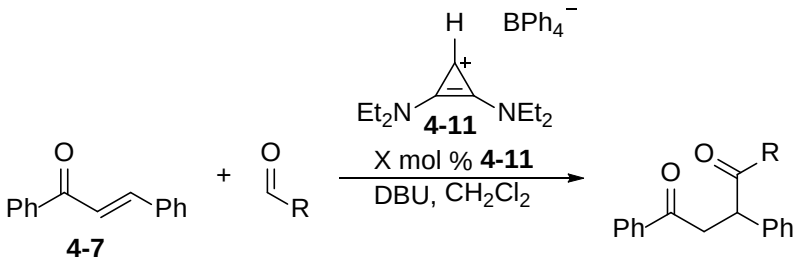
a) Sánchez-Larios, E.[147]

Scheme 4.3 Revisiting the Stetter-Michael Reaction

Surveying the different aldehydes (**Table 4.2**), reactions with aromatic aldehydes such as methyl-4-formyl benzoate (entry 3, **Table 4.1**) and *m*-anisaldehyde (entry 1, **Table 4.2**) were high yielding. So were reactions with a heteroaromatic aldehyde (furfural, entry 2). Reactions with challenging *ortho* substituted-aldehydes were low yielding (entry 3) or entirely non-productive (entry 4). *p*-Nitrobenzaldehyde (entry 5) failed to undergo the Stetter reaction, unsurprisingly as it has recently been found to engage in redox processes under similar conditions.[202] Yields of reactions with unactivated benzaldehyde (entry 6) or more electron rich aromatic aldehydes (entries 7, 8) were modest but compare favorably to those obtained using NHCs. This was the first example of *umpolung* organocatalysis using *p*-dimethylaminobenzaldehyde, or any *p*-amino-benzaldehyde derivative to date. Reactions with enals (entry 9) or aliphatic aldehydes (entry 10) did not generate significant amounts of Stetter

product. These outcomes (entry 9 and 10) are unfortunate in terms of reaction scope, as these can be valuable classes of substrates. Reactions with enals may be improvable with a more active catalyst as trace levels of Stetter product were detected in the reaction with cinnamaldehyde (entry 9). Reactions with a more electrophilic α-keto-aldehyde (entry 11) were also explored but did not give Stetter product.

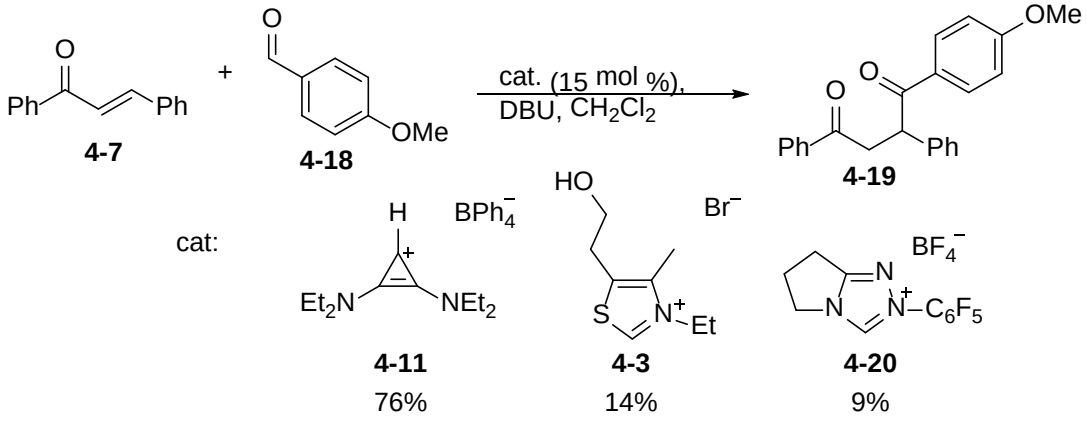
Table 4.2 Aldehyde Scope in the Stetter Reaction with Chalcone



entry	R =	catalyst loading (%)	yield (%)
1	*m*-$CH_3OC_6H_4$	10	72
2	2-furyl	10	99
3	*o*-FC_6H_4	20	21
4	*o*-ClC_6H_4	20	<5
5	*p*-$NO_2C_6H_4$	20	<5
6	Ph	20	65
7	*p*-$CH_3OC_6H_4$	15	(41)[a]
8	*p*-$N(CH_3)_2C_6H_4$	15	15
9	CHCHPh	20	(6)[a]
10	Et	10	<5[b]
11	COEt	15	<5[b,c]

a) Estimated conversion in parentheses; b) Cesium carbonate as base; c) THF as solvent.

As established in **Chapter 1** (**Sections 1.32, 1.33** and **1.36**), reactions with electron rich aromatic aldehydes can be low yielding with NHCs. Under modified reaction conditions (more catalyst, longer reaction time), the use of EtBAC resulted in a superior (76%) yield of the Stetter product compared to thiazolium **4-3** and triazolium **4-20** under identical conditions (14% and 9% respectively) (**Scheme 4.4**). This was the highest yielding formation of ketone **4-19** to date and demonstrates one potentially useful application of cyclopropenylidenes.



Scheme 4.4 Comparison to NHCs **4-3** and **4-20**

The intramolecular Stetter reaction was explored with compounds **4-21** and **4-22** (**Figure 4.1**). The negligible reaction observed with these substrates was consistent with that observed for other *ortho*-substituted aldehydes above.

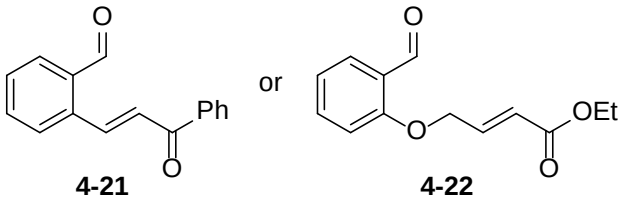
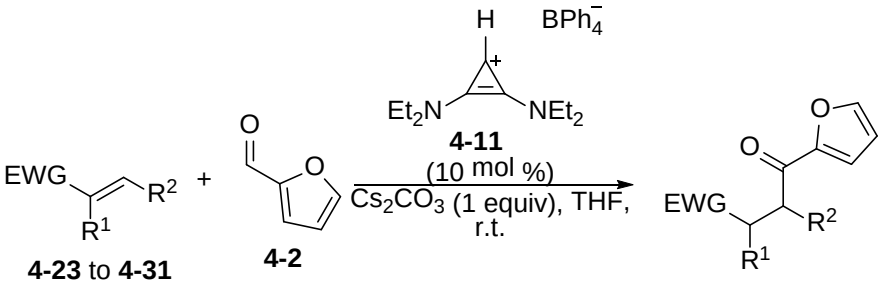


Figure 4.1 Intramolecular Stetter Substrates

With a good sense of the applicable aldehydes for the Stetter reaction, focus shifted to an exploration of the Michael acceptor component of the reaction. As BAC catalysis was

unprecedented with any Michael acceptor other than chalcone, substrates were chosen so that comparisons could be made to NHC catalyzed Stetter reactions.

Table 4.3 Acceptor Scope in the Stetter Reaction with Furfural



entry	acceptor	EWG	R^1	R^2	yield (%)
1	**4-7**	COPh	H	Ph	99[a]
2	**4-23**	COPh	H	*p*-$CO_2CH_3C_6H_4$	95
3	**4-24**	NO_2	H	Ph	<5
4	**4-25**	CO_2Et	CO_2Et	Et	<5
5	**4-26**	$COCO_2Et$	H	Ph	<5[b]
6	**4-27**	CO_2Me	Me	H	<5
7	**4-28**	COSEt	H	Ph	<5
8	**4-29**	COMe	H	Ph	8
9	**4-29**	COMe	H	Ph	31[c]
10	**4-30**	COPh	H	Et	34
11	**4-31**	2-pentenone			<5

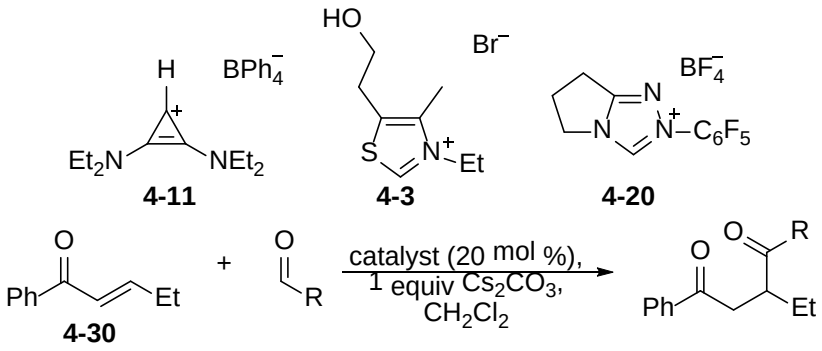
a) Using 10 mol % catalyst, DBU, CH_2Cl_2; b) Using 5 mol % catalyst, DBU, CH_2Cl_2; c) reaction run at 66 °C.

Investigating several acceptors for the intermolecular Stetter reaction (**Table 4.3**) a chalcone derivative **4-23** gave similar yield to chalcone (entry 1 and 2). A low conversion was

observed with nitro-alkenes (**4-24**, entry 3) such as those used by Rovis,[132] as well as the alkylidene malonate (**4-25**, entry 4) reported by Enders.[129] α-Keto esters (**4-26**, entry 5), as reported by Gravel and coworkers, were also unsuccessful.[59c] A low conversion was observed with ester **4-27** (entry 6) and thioester **4-28** (entry 7). Methyl ketone acceptor **4-29** (entry 8) gave a low yield (8%), which could be improved by changing reaction conditions (entry 9, 31%). Interestingly, a reaction with a phenyl alkyl enone **4-30** (entry 10) gave a modest yield (34%), which is comparable to the results of Stetter and coworkers with similar acceptors.[115] As the conditions of this reaction were much milder than those favoured by Stetter (refluxing ethanol) further exploration of this acceptor was merited. Following the success with acceptor **4-30**, 2-pentenone (**4-31**, entry 11) was also explored, but gave poor conversion.

It was found that EtBAC was more effective in catalyzing Stetter reactions with acceptor **4-30** than thiazolium or triazolium salts under identical conditions (**Table 4.4**, entries 1-3 and 4-6). These were the highest yielding Stetter reactions with β-alkyl enones to date (entries 1 and 4). Presumably the small size of the BAC catalyst relative to that of NHCs lowers the transition state energy for the sterically sensitive C-C bond forming step (when the Breslow intermediate adds to the Michael acceptor) and this is significant to the overall reaction rate. To extend the scope of the reaction further *p*-chlorobenzaldehyde and *m*-anisaldehyde were also explored (entries 7 and 8) but formation of side products (presumably via a dienolate intermediate) was competitive in these reactions. By-product formation was minimized by using a weaker non-nucleophilic base (cesium carbonate) and by keeping reaction times short. The shortened reaction time meant maximum conversion to Stetter product was likely not obtained. Further refinement of BAC catalyst designs may eventually overcome these issues.

Table 4.4 Stetter Reactions using Substrate **4-30**



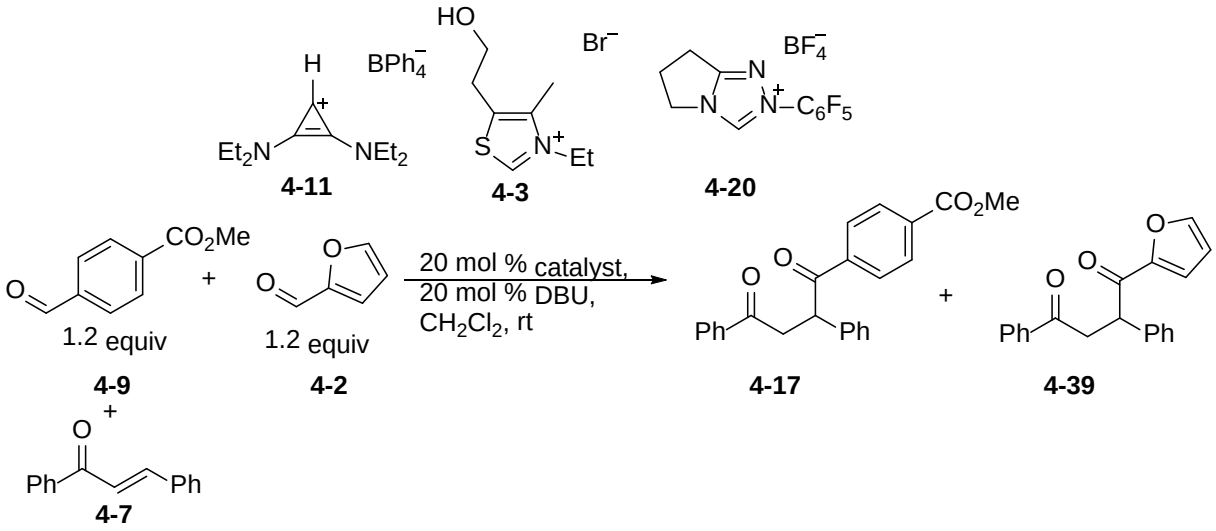
entry	R =	catalyst	reaction time	product	yield (%)
1	2-furyl	**4-11**	3.75 hrs[a]	**4-32**	49
2	2-furyl	**4-3**	3.75 hrs[a]	**4-32**	6
3	2-furyl	**4-20**	3.75 hrs[a]	**4-32**	20
4	*p*-$CO_2MeC_6H_4$	**4-11**	3 hrs	**4-33**	96
5	*p*-$CO_2MeC_6H_4$	**4-3**	3 hrs	**4-33**	38
6	*p*-$CO_2MeC_6H_4$	**4-20**	3 hrs	**4-33**	5
7	*p*-ClC_6H_4	**4-11**	18 hrs	**4-34**	12
8	*m*-$CH_3OC_6H_4$	**4-11**	18 hrs	**4-35**	n.d.[b]

a) performed solvent free (neat); b) Not determined due to the complexity of the reaction mixture.

4.4 Comparisons to Common NHCs

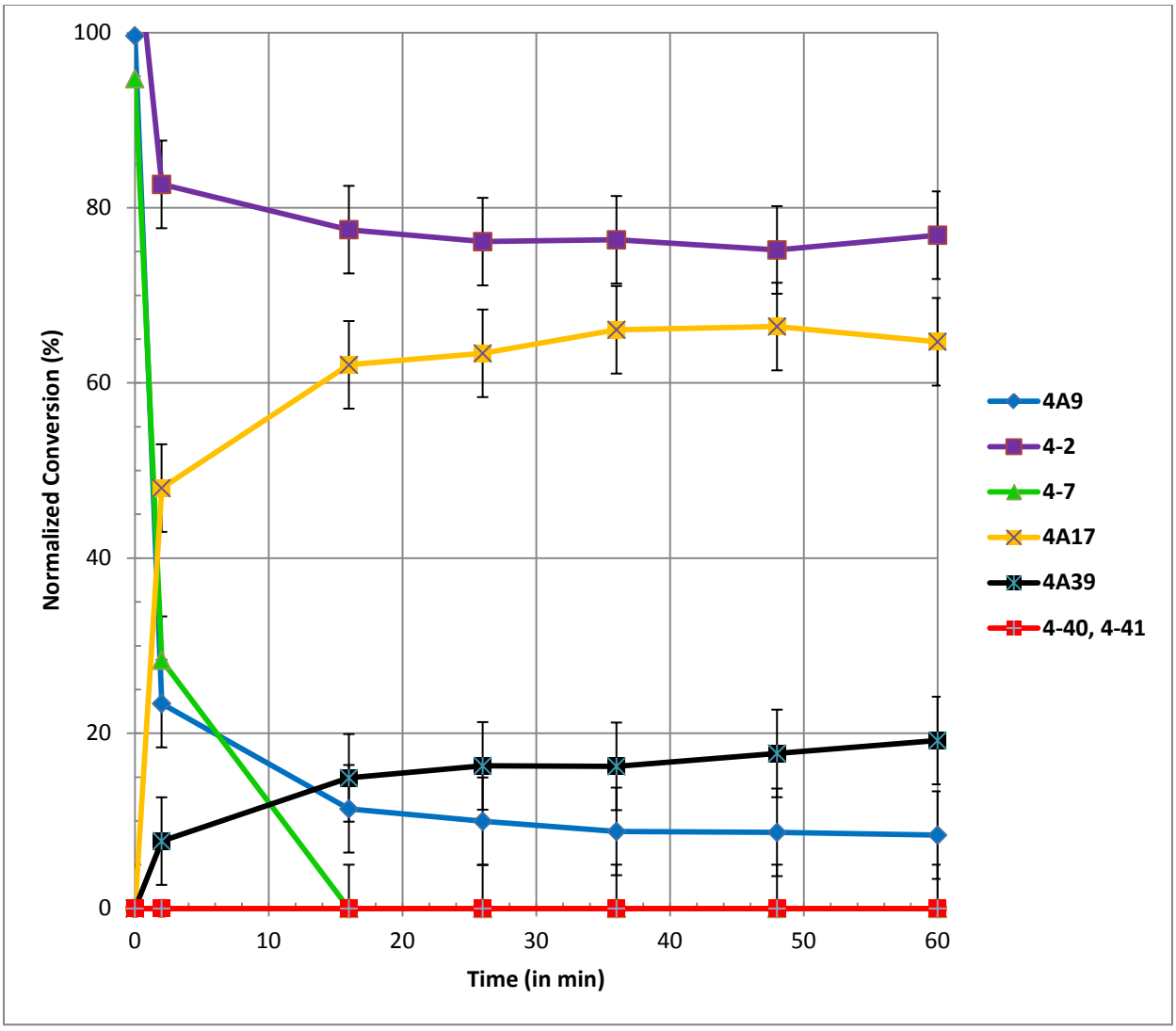
To further elucidate observed differences between methyl-4-formyl benzoate (**4-9**) and furfural (**4.2**), a set of competition reactions was carried out (**Table 4.5**). Under these conditions EtBAC produced a mixture of Stetter products which consisted mainly of product **4-17**. In contrast, thiazolium **4-3** and triazolium **4-20** produced mainly product **4-39**.

Table 4.5 Stetter Reactions with Aldehyde **4-2** and **4-9**



entry	catalyst	product ratio **4-17**:**4-39**	Combined yield (%)
1	**4-11**	5.6:1	99
2	**4-3**	1:1.7	80
3	**4-20**	1:7.3	85

To determine whether the observed product ratios were the result of kinetic or thermodynamic control, these reactions were repeated and followed by ^{1}H NMR (**Figures 4.2** to **4.4**) As all of the starting materials and products in this reaction have at least one distinct signal in the ^{1}H NMR, the relative amounts can be assessed as the reaction proceeds.



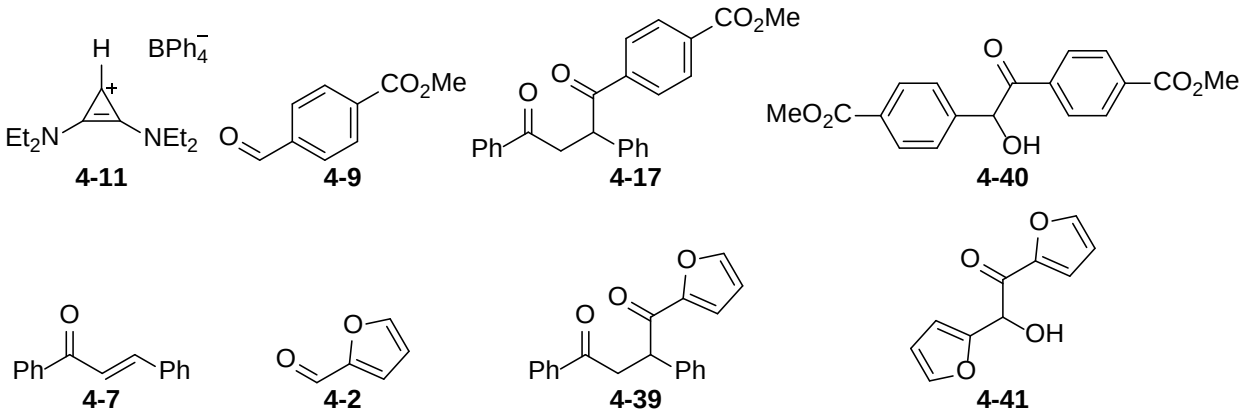


Figure 4.2 Monitoring of the Stetter Reaction Catalyzed by EtBAC

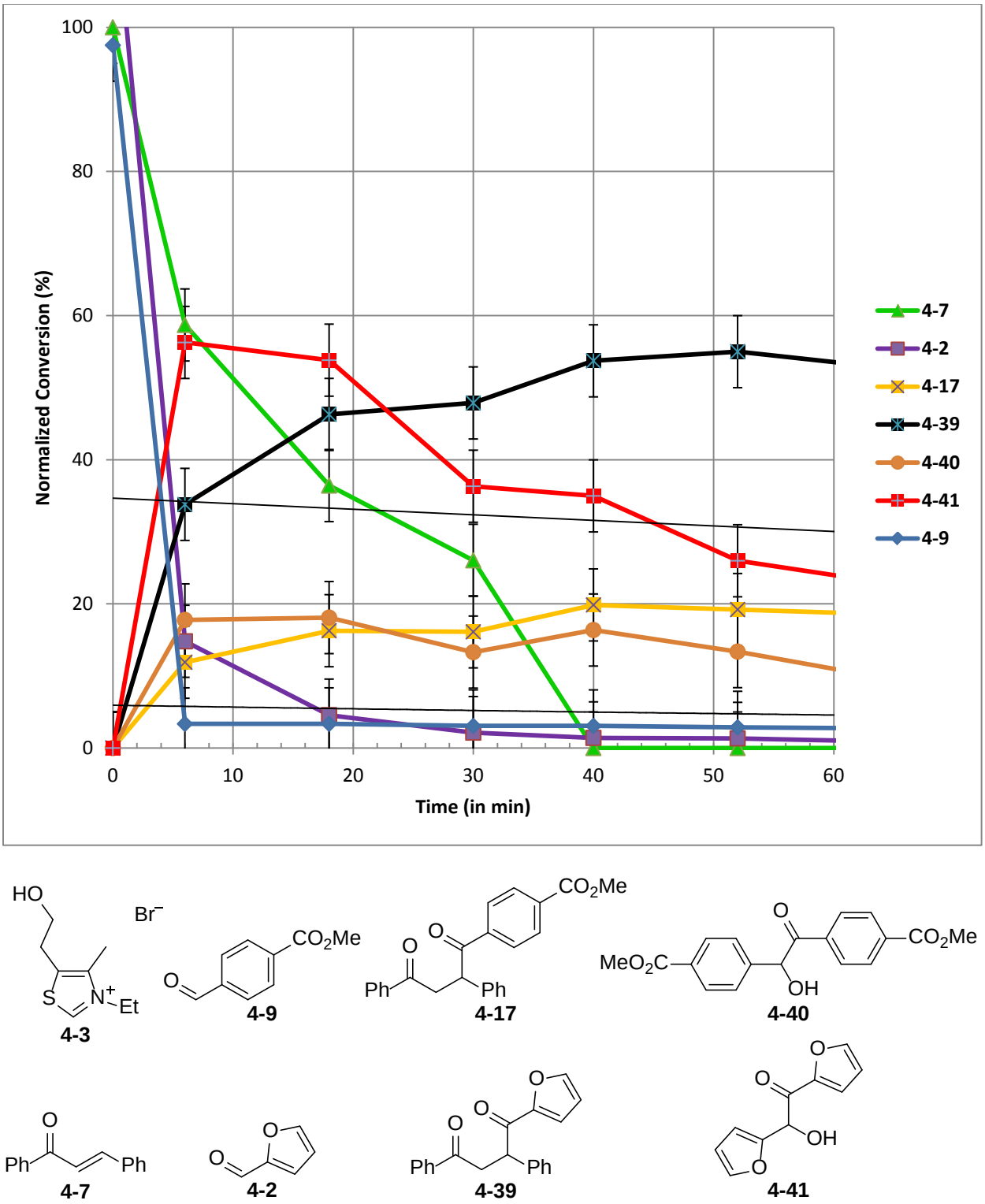


Figure 4.3 Monitoring of the Stetter Reaction Catalyzed by Thiazolium **4-3**

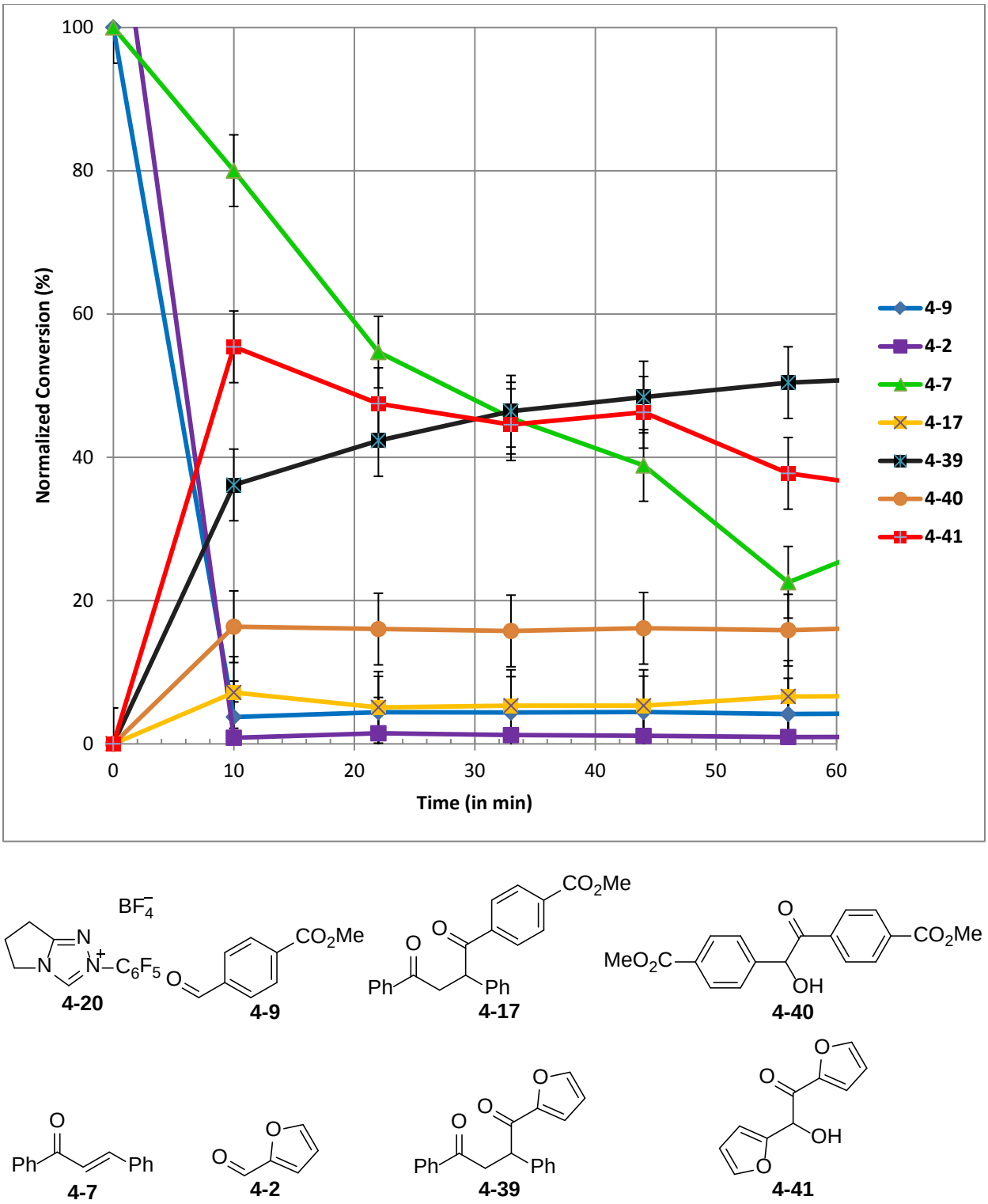
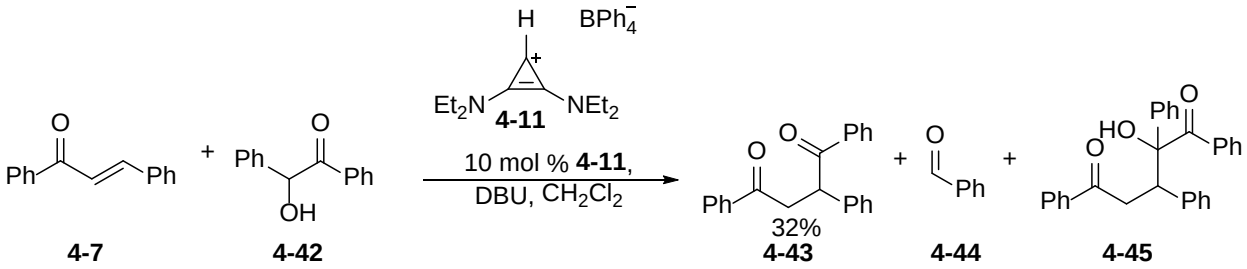


Figure 4.4 Monitoring of the Stetter Reaction Catalyzed by Triazolium **4-20**

In the reaction catalyzed by EtBAC (**Figure 4.2**), Stetter products arose from reaction with furfural as well as methyl-4-formyl benzoate. The relative amount of both products, once formed, did not change over time. At no point in this process were benzoin products detected. This contrasts the thiazolium and triazolium catalysts (**Figure 4.3** and **Figure 4.4** respectively), both of which showed substantial formation of benzoin products initially. In both cases there was a slow decrease in the amount of benzoin products present along with a corresponding increase in the amount of Stetter product formed. Both NHC catalysts primarily gave the furfural-derived Stetter product (**4-39**). Re-subjecting a 6:1 mixture of Stetter products (**4-39**:**4-17**) to EtBAC under reaction conditions (including one equivalent of aldehydes **4-2** and **4-9**) led to no change in the ratio of Stetter products, suggesting the Stetter reactions are irreversible under these conditions. As a furan ring is smaller than a phenyl ring, the substrate preference of both NHCs can be rationalized with a steric argument. The smaller EtBAC was presumably not as affected by the steric bulk of the reacting aldehyde, and thus reacts faster with the more electron-poor benzaldehyde derivative.

There are few reasonable explanations for the observation that benzoin products are not detected in situ with EtBAC. It could be EtBAC does not catalyze a benzoin reaction with furfural or methyl-4-formyl benzoate, but this was unlikely as a benzoin reaction did occur with EtBAC and benzaldehyde (**Section 3.9**). An early rise in benzoin product followed by a decrease could indicate a fast reversible benzoin reaction (relative to the Stetter reaction). This was observed in reactions with thiazolium **4-3** and to a lesser extent triazolium **4-20** but was not observed in reactions with EtBAC (**Figure 4.2** to **Figure 4.4**), so a fast reversible benzoin reaction was ruled out. To see if a slower retro-benzoin reaction was possible the homo-dimer of benzaldehyde **4-42** was combined with EtBAC and chalcone (**Scheme 4.5**). These conditions

generated a modest but indicative amount of Stetter product, indicating the benzoin reaction can be reversible with EtBAC. Benzaldehyde, which was not present in the reaction initially, was also detected along with Michael addition product **4-45**. Despite these positive indications, the low efficiency of this process makes it unlikely that a retro-benzoin process is significant in Stetter reactions. The most reasonable explanation remaining for the lack of observed benzoin side-products is that the Stetter reaction is significantly faster than the benzoin reaction when EtBAC is used as the catalyst.

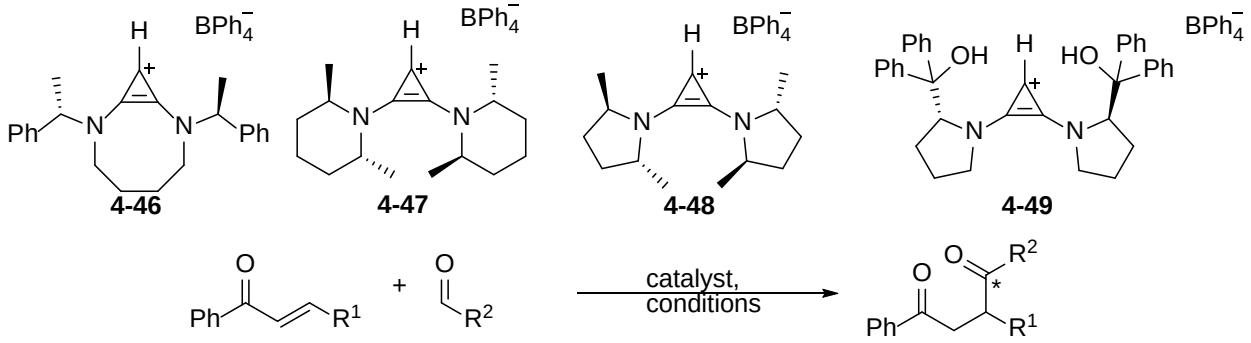


Scheme 4.5 Retro-Benzoin Stetter Reaction

4.5 Development of an Enantioselective Stetter Reaction

One of the objectives in exploring BAC catalysis was to investigate its ability to catalyze transformations enantioselectively. Tamm and coworkers were critical of the first chiral BAC, stating that the chiral amino substituents of that catalyst (pre-catalyst **11, Chapter 1**) were too conformationally labile to result in a good stereoinduction.[42] Consequently, novel pre-catalysts **4-46** to **4-49** were prepared (**Table 4.6**). Each was conformationally constrained in some way and possessed stereocenters in close proximity to the reacting site. To assess the potential of these catalysts, Stetter reactions were performed and the enantiomeric ratio of the products was subsequently determined.

Table 4.6 Enantioselective Stetter Reactions



entry	catalyst	R^1	R^2	conditions	yield (%)	*ee* (%)[a]
1	**4-46**	Ph	2-furyl	Cs_2CO_3, THF, 2 hrs	99	36
2	**4-46**	Ph	2-furyl	Cs_2CO_3, THF, 0 °C, 16 hrs	50	<10
3	**4-46**	Et	2-furyl	Cs_2CO_3, THF, 4 hrs	35	<5
4	**4-47**	Ph	2-furyl	Cs_2CO_3, CH_2Cl_2, 3 hrs	39	48
5	**4-48**	Ph	2-furyl	Cs_2CO_3, THF, 3 hrs	46	73
6	**4-49**[xii]	Ph	$CO_2MeC_6H_4$	DBU, CH_2Cl_2, 16 hrs	<5	-

a) Enantiomeric excess was determined by HPLC on a chiral stationary phase.

All chiral catalysts presented except for the one derived from **4-46** were found to be lower yielding and less reactive than EtBAC. In the chosen Stetter reaction pre-catalyst **4-46** afforded the highest yield and modest enantiomeric excess (entry 1). Cooling the reaction down was not beneficial (entry 2). When this same catalyst was applied to an alkyl Michael acceptor (entry 3), the yield was relatively good (an analogous reaction with EtBAC only gave 49% yield), but enantioselectivity with this acceptor was poor. Part of the purpose of the 8-membered backbone on catalyst **4-46** was to restrict rotation along the N-C_{ring} bond, directing the stereogenic elements close to the reacting site. However modelling studies found the lowest

[xii]The author thanks Sida Zhou for the preparation of catalyst **4-49**

energy transition states for this catalyst poorly discriminate between the two faces of the Breslow intermediate, which is not ideal.[xiii] If addition of the Breslow intermediate to the Michael acceptor is taken as the key enantioinduction step, high facial selectivity in this step becomes vital to achieving good enantioinduction. Reaction with the 2,6-dimethyl piperidine-derived catalyst (**4-47**, entry 4) was lower yielding (39%) but also more enantioselective (48% *ee*). The *ee* with the piperidino catalyst was relatively good despite the possibility of conformer interconversion of the methyl groups near the reacting site. Reaction with the 2,5-dimethylpyrrolidine derived catalyst (**4-48**) was slightly better yielding (46%) and much more enantioselective. This enantiomeric excess is higher than what has been reported for triazolium systems (73 vs. 56% *ee*) with the same substrate.[122] A proline derived catalyst (**4-49**) was also prepared possessing bulky substituents, but was found not to be catalytically active. Overall, the enatioselectivities of these chiral catalysts has been found to be competitive with the most advanced triazolium systems, and these catalysts are amenable to further refinements.

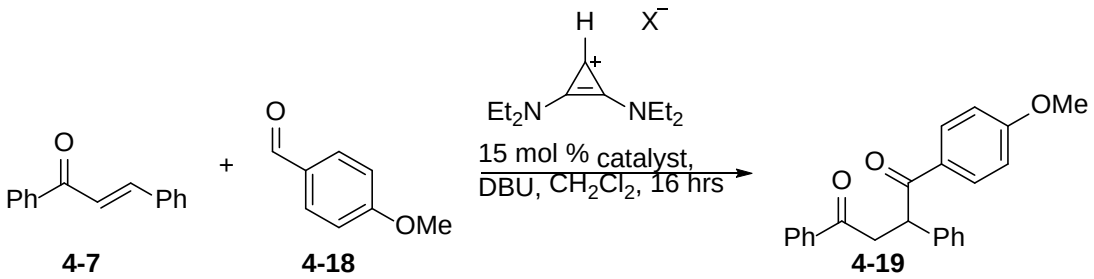
4.6 Counterion Effects

Until recently the counterion in NHCs was given very little consideration. In simplified mechanisms the counterion is uninvolved, except as a spectator ion. In practice it affects the solubility of the pre-catalyst species, and recent literature has suggested the counterion has a larger effect upon some reactions than previously thought.[203] Tetraphenylborate is not a common counterion; usually halide, perchlorate, or tetrafluoroborate salts are used. However the additional crystallinity of this salt was important in catalyst isolation. In **Table 4.1** above pre-catalysts **4-12** and **4-13** were prepared as perchlorate salts and assumed to behave similarly to

[xiii] Gravel, M.; *unpublished results*

their tetraphenylborate equivalent. In light of recent literature, this assumption was put to the test.

Table 4.7 Counteranion Screening for a Stetter Reaction



4-7 **4-18** **4-19**

entry	catalyst	X =	yield[a] (%)
1	**4-50**	Br	7
2	**4-51**	ClO_4	30
3	**4-52**	PF_6	25
4	**4-11**	BPh_4	39
5	**4-53**	BF_4[b]	11
6	**4-54**	BPh_4[c]	15

a) NMR yield as determined using bibenzyl as an internal standard; b) this catalyst could not be completely purified and was used in an impure state; c) BnBAC used instead of EtBAC.

Following an initial comparison between bis(pyrrolidino)cyclopropenium perchlorate (**4-12)** and its tetraphenylborate analogue, small amounts of bis(diethylamino)cyclopropenium were prepared as bromide, perchlorate, hexafluorophosphate and tetrafluoroborate salts. The pre-catalysts were screened to determine the extent of any counterion effects upon Stetter reactions (**Table 4.7**). Reactions using the tetraphenylborate salt were found to be better yielding than other bis(amino)cyclopropenium salts. Interestingly this experiment resulted in a range of NMR yields of ~30% with the same BAC catalyst (entries 1-5). Unfortunately, all but the

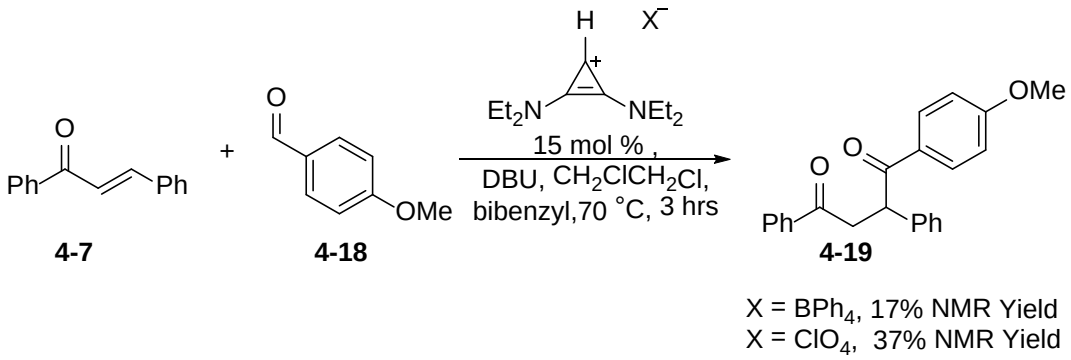
tetraphenylborate salt were colorless oils instead of crystalline solids. Thus there was an uncertainty in the amounts of catalysts used, as well as possibility of impurities interfering with the reaction. Nearly all the salts appeared pure by proton NMR, except for the tetrafluoroborate salt which could not be purified further. This experiment strongly suggests a counterion influence, though further study is necessary to remove uncertainty and measure the magnitude of this effect.

It was hoped that the more crystalline bis(dibenzylamino)cyclopropenylidenes (BnBAC, entry 6) would perform with similar efficiency to EtBAC, and this could serve as a template with which to compare the different anions more rigorously. Unfortunately this catalyst displayed reduced reactivity making it unsuitable for further screening.

Another effect of the tetraphenylborate anion was discovered during this line of inquiry. Several thiazolium and triazolium derived carbenes have reported catalytic activity at elevated temperatures over extended periods. One of the more puzzling aspects of EtBAC was that conversion was often found to be lower at elevated temperature reactions relative to room temperature reactions. This was hypothesized to be due to the strained cyclopropene motif being thermally unstable. Surprisingly, the absence of tetraphenylborate anion was found to improve reactivity at elevated temperatures.

A reaction was performed with chalcone **4-7** and *p*-anisaldehyde, to compare bis(diethylamino)cyclopropenium tetraphenylborate (**4-11**) against bis(diethylamino)-cyclopropenium perchlorate (**4-51)** at elevated temperature (**Scheme 4.6**). It was found that both Stetter reactions gave lower conversion compared to the room temperature reaction. However, the perchlorate salt was nearly twice as effective as the tetraphenylborate salt under these conditions. Excitingly this suggests other Stetter reactions may be more effective at elevated

temperatures using cyclopropenium salts with different anions. As poor conversion is currently the main limitation to many Stetter reactions, this effect merits further exploration.



Scheme 4.6 Stetter Reactions at Elevated Temperatures

4.7 Conclusions and Future Work

The application of BACs to the Stetter reaction was successful. The first BAC catalyzed Stetter reaction was reported; and these catalysts were found to be particularly effective at the intermolecular Stetter reaction with aromatic or heteroaromatic aldehydes. EtBAC was found to be superior to all other BAC catalysts prepared in the first generation. This catalyst gave high yielding Stetter reactions with an alkyl substituted acceptor, which is uncommon and valuable synthetically. This catalyst also gave good yields with electron rich aromatic aldehydes which are challenging for most NHCs. A small number of chiral BAC catalysts were applied to the Stetter reaction and preliminary findings suggest a high potential for further improvement both in yield and enantioinduction.

The primary future direction of this work is the construction of more reactive BAC catalysts, perhaps capable of inducing greater enantioselectivity, which will lead to further breakthroughs in this area. With more reactive catalysts yields are expected to improve in the

Stetter reaction. A more reactive catalyst could improve the number of substrates for which good yields are obtained thus improving the scope of the reaction. Additionally, the results with pre-catalysts **4-46** to **4-49** can be used for the design of catalysts capable of inducing greater enantioselectivity in reactions. Ways in which this could be accomplished will be discussed in **Chapter 6**.

Chapter 5: BAC Catalyzed Aza-Benzoin Reactions

5.1 Objective

The aza-benzoin reaction is an attractive transformation, capable of efficiently forming α-amino ketones. However, there remain many limitations to its widespread implementation in synthesis. Current methodologies utilize highly electrophilic substrates which may be unstable or form adducts with the catalyst.[204] Reactions with less electrophilic imines are often slow and low yielding.[205] Benzoin reactivity can be competitive. Bis(amino)cyclopropenylidenes have demonstrated high proficiency for Stetter reactions and a lack of proficiency in benzoin reactions. Though the origins of this substrate selectivity are unclear, it is hypothesized that bis(amino)cyclopropenylidenes could catalyze aza-benzoin reactions without the formation of benzoin side-products. This could potentially lead to improvements in substrate scope and yield compared to other methodologies. Additionally, establishing another type of reactivity serves to further demonstrate the potential of BACs as versatile carbene organocatalysts to the synthetic community.

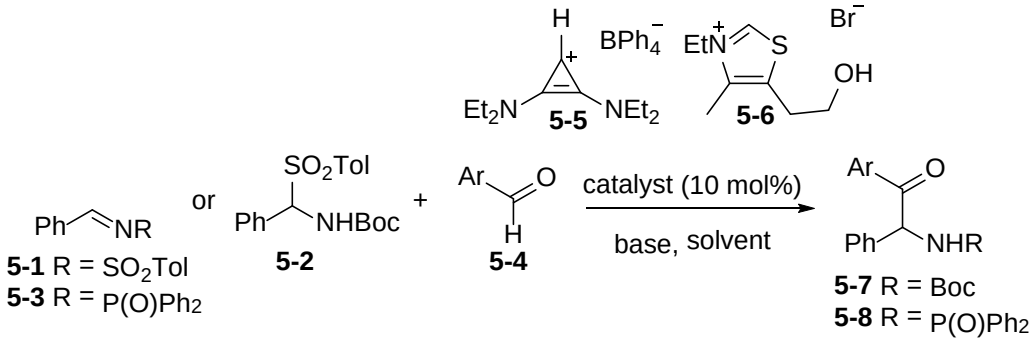
5.2 Selection of an Imine or Imine Equivalent

In order to establish a reaction using BACs the first step was to identify suitable imine substrates. Aza-benzoin reactivity has been demonstrated with *N*, *N*-dialkyl iminium salts as well as several aldimines and ketimines. In surveying the assortment of catalysts/imines reported for aza-benzoin reactions a degree of substrate catalyst matching becomes apparent. The initial search focused upon aldimines as they have the best literature precedence and additional challenges have been reported with ketimines or iminium salts as acyl acceptors. Aldimines

could be prepared by condensing aldehydes with amines, amides, phosphinamides, sulfonates or carbamates allowing for access to a range of imine substrates with varying degrees of electrophilicity arising from different *N*-substituents.

Despite a lack of literature precedent, ready supplies of *N*-tosyl-phenyl imine **5-1** led to it being screened for aza-benzoin reactivity (**Table 5.1**, entry 1). This reaction generated a small amount (~15%) of an unidentified substance, however these conditions were also found to decompose the imine substrate and imine **5-1** was set aside.

Table 5.1 Screening of Different *N*-Substituted Imines for Aza-Benzoin Reactions



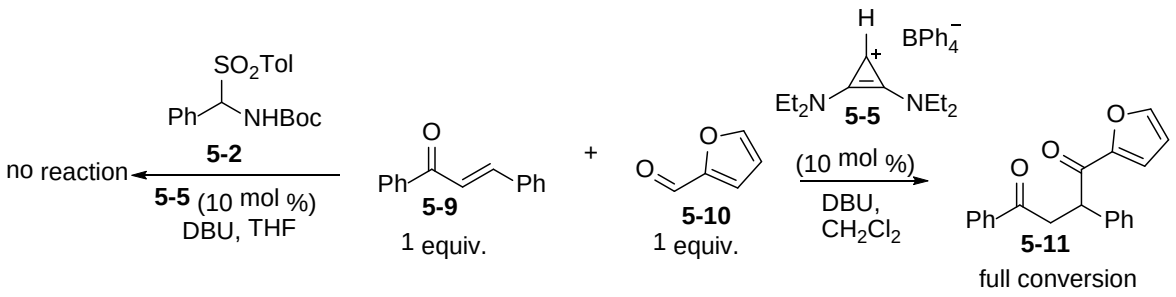
entry	substrate	Ar	catalyst	base	solvent	yield (%)
1	**5-1**	*p*-$CH_3O_2CC_6H_4$	**5-5**	Cs_2CO_3	THF	<5
2	**5-2**	2-furyl	**5-5**	DBU	CH_2Cl_2	<5
3	**5-2**	2-furyl	**5-5**	Cs_2CO_3	THF	<5
4	**5-2**	2-furyl	**5-6**	NEt_3	CH_2Cl_2	89
5	**5-3**	*p*-$CH_3O_2CC_6H_4$	**5-5**	K_2CO_3	CH_2Cl_2	(19)[a]

a) Conversion in brackets.

Phenylimino-*N*-*tert*-butyl-carbamate, a better precedented imine for aza-benzoin reactions, was explored next.[78,86] The related sulfinic acid adduct (**5-2**) was prepared in order to

act as a source of this imine (generated *in situ*). Unfortunately aza-benzoin reactions with imine **5-2** were unsuccessful using EtBAC as the catalyst (**Table 5.1**, entries 2, 3). To examine if the sulfinate group was interfering with the desired reactivity a thiazolium-catalyzed aza-benzoin reaction was performed using the same substrate (**Table 5.1**, entry 4). The thiazolium catalyzed reaction was found to be very efficient (89% yield of **5-7** where Ar = 2-furyl), suggesting interference from the sulfinate group was unlikely in the BAC catalyzed reaction. It is clear from this result that an imine being suitable for NHC catalyzed aza-benzoin reactions is no guarantee that it will react using a BAC catalyst.

There were two possible explanations for this lack of reactivity between EtBAC and the imine of **5-2**; either the imine was not electrophilic enough to react with the acyl anion generated from EtBAC, or the imine was too electrophilic and interacted with the carbene. In order to identify suitable imines going forward it was important to distinguish between these two possibilities. To do so, an experiment was devised wherein imine **5-2** was added to an otherwise high-yielding Stetter reaction (**Scheme 5.1**). If the problem arose from the imine being insufficiently electrophilic, the imine would be ignored in favor of the Stetter acceptor and the effect on the reaction should be slight. Alternatively, if the problem arose from the imine being too electrophilic a reaction with the catalyst could occur, inhibiting Stetter reactivity. When the reaction was performed Stetter products and aza-benzoin products were not detected suggesting the imine to be too electrophilic for the BAC catalyst. It is possible a carbene-imine adduct was formed, similar to the NHC adducts observed by Rovis and coworkers as well as Bode.[77,206]



Scheme 5.1 Exploration of *N*-Boc Imines with EtBAC

Mayr and coworkers have endeavored to quantify the relative electrophilicity and nucleophilicity of several classes of organic molecules, including imines.[207] Surveying their results, *N*-phosphinoyl imines stand out as less electrophilic than Boc or tosyl imines in reactions towards electrophiles (E = -15.95 vs -14.22 and -11.5 respectively).[xiv] The electrophilicity of *N*-phosphinoyl imines is reportedly close that of some enones, which can react with BAC-derived acyl anion equivalents in Stetter reactions (E = -17.3 to -18.8). Scheidt and coworkers have used *N*-phosphinoyl imines as substrates in aza-benzoin reactions. However these reactions reportedly required aldehyde surrogates (acyl silanes).[83,84] Prior to this work aza-benzoin reactivity between aldehydes and *N*-phosphinoyl imines had not been established.

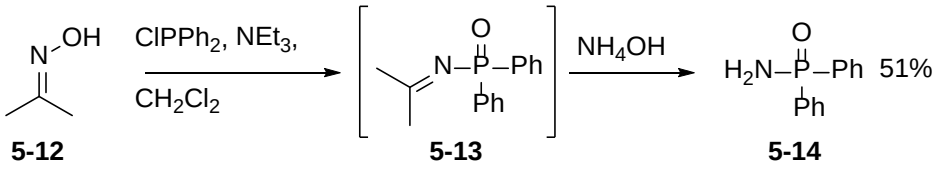
To probe this class of imines, an *N*-phosphinoyl imine was prepared using a method developed by Charette and coworkers.[208] When *N*-phosphinoyl imine **5-3** was combined with EtBAC and methyl-4-formyl benzoate under basic conditions, a small amount (19%) of aza-benzoin product was formed (**Table 5.1**, entry 5). A similar outcome was obtained from a reaction with the sulfinic acid adduct of **5-3** (**5-17a**). This marked the first time an aza-benzoin reaction has been catalyzed by a BAC. Importantly no by-products (including benzoin) or decomposition materials were detected, indicating a high potential to improve conversion by optimizing reaction conditions. Aldehyde surrogates were not necessary, suggesting substrate

[xiv] For a full explanation of the Electrophilicity parameter (E) see Mayr's article.[207]

selectivity arising from the BAC catalyst. On the basis of this success, several substrates were prepared and attention turned towards optimizing the reaction with *N*-phosphinoyl imines.

5.3 Substrate Preparation

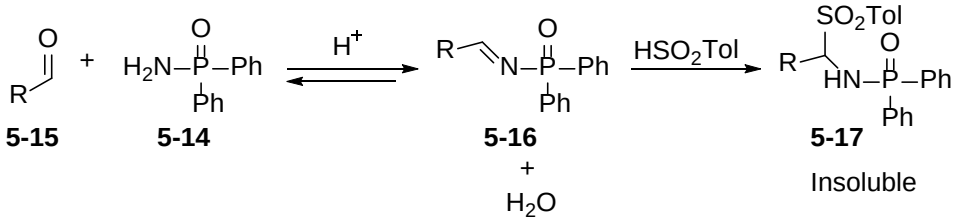
A critical but often underappreciated aspect of methodology development is the accessibility of substrates. If substrate preparation is challenging or requires several steps it detracts from the ultimate value of a methodology. To fully explore the scope of aza-benzoin reactions several *N*-phosphinoyl imines and sulfinic acid adducts were prepared. This functionality could arise from condensing an aldehyde with the amino group of a phosphinamide or by coupling an aldimine with chlorodiphenylphosphine. Diphenylphosphinamide was prepared by combining hydroxylamine **5-12** with chlorodiphenylphosphine (**Scheme 5.2**). While not the same as coupling to an *N*-hydroxy aldimine, it proceeds through a similar intermediate (**5-13**). This reaction was messy, low yielding, and generated toxic by-products. Thus when comparing alternatives, the aldehyde condensation method was selected. This condensation requires a driving force, and there were several ways this could be accomplished.



Scheme 5.2 Formation of Diphenylphosphinamide from Chlorodiphenylphosphine

The Charette group has developed an effective protocol using *p*-toluene sulfinic acid (**Scheme 5.3**). The acid not only catalyzed condensation to form the imines, it reacted with the resulting imine to form an adduct (**5-17)** which was insoluble in the reaction mixture. The low solubility of these adducts made characterization challenging and chromatographic purification impossible. As the reaction used excess toluene sulfinic acid, substrate purity was a concern. The

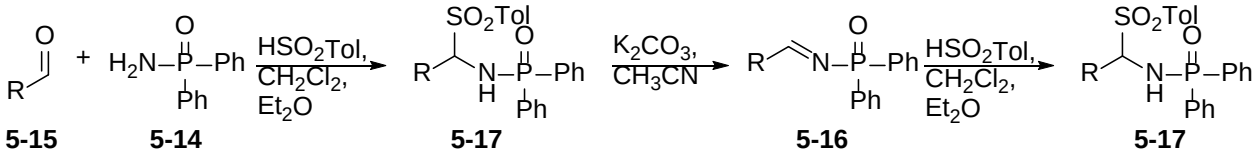
most straightforward way to ensure purity of this material was to liberate the imine which could be chromatographed and characterized. It was discovered that these imines were prone to hydrolysis, even by ambient humidity, making them less than optimal substrates. Imines which have been crystallized were more resistant to hydrolysis than finely powdered samples but a more long term solution was required. It was found that sulfinic acid adducts could be re-formed cleanly from the purified imines and these were storable for extended periods.



Scheme 5.3 Formation of *N*-Phosphinoyl Imines, and Sulfonyl Phosphinamides

This methodology was successfully used to prepare the substrates in **Table 5.2**. While successful in most cases (entries 1-6) the reaction did not work for derivatives of furfural or *o*-chlorobenzaldehyde (entries 7 and 8). This may be due to the sulfinic acid adduct being soluble in the reaction mixture, at least in the case of (*o*-chlorobenzaldehyde).

Table 5.2 *N*-Phosphinoyl Imine Preparation using Charette's Method



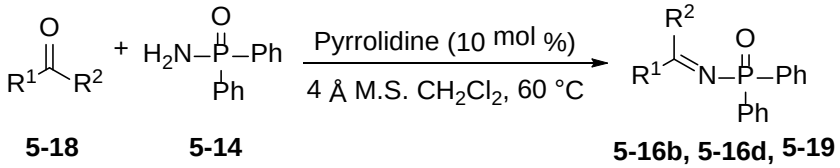
5-15 **5-14** **5-17** **5-16** **5-17**

entry	R =	number[a]	yield **5-17** (%)[b]	yield **5-16** (%)[b]	yield **5-17** (%)[b,c]
1	Ph	**a**	63	73-90	59-90
2	*p*-$C_6H_4CH_3$	**b**	77-87	78-89	50-92
3	*p*-C_6H_4Br	**c**	80	73	87
4	*p*-$C_6H_4OCH_3$	**d**	60	83	94
5	*m*-$C_6H_4OCH_3$	**e**	89	92	80
6	*m*-*p*-$C_6H_3(OCH_3)_2$	**f**	82	81	78
7	2-furyl	**g**	<5	-	-
8	*o*-C_6H_4Cl	**h**	<5	-	-
9	PhCH=CH	**i**	26	49	-
10	$(CH_2)_6CH_3$	**j**	52[d]	-	-

a) Such that entry 1 refers to compounds **5-17a** and **5-16a,** and entry 2 refers to **5-17b** and **5-16b** etc.; b) isolated yield. Where appropriate a range of yields are given; c) from imine **5-16a-j** respectively; d) purified via crystallization making additional steps unnecessary.

As this project was underway a methodology was reported by el Cid and coworkers, which used catalytic pyrrolidine to prepare sulfonyl imines as well as a few *N*-phosphinoyl imines (**Table 5.3**).[209] Pyrrolidine catalyzes the imine formation, by first forming a more reactive iminium, while molecular sieves drive the process by removing water. This more streamlined process was probed with limited success.

Table 5.3 *N*-Phosphinoyl Imine Preparation using el Cid's Method



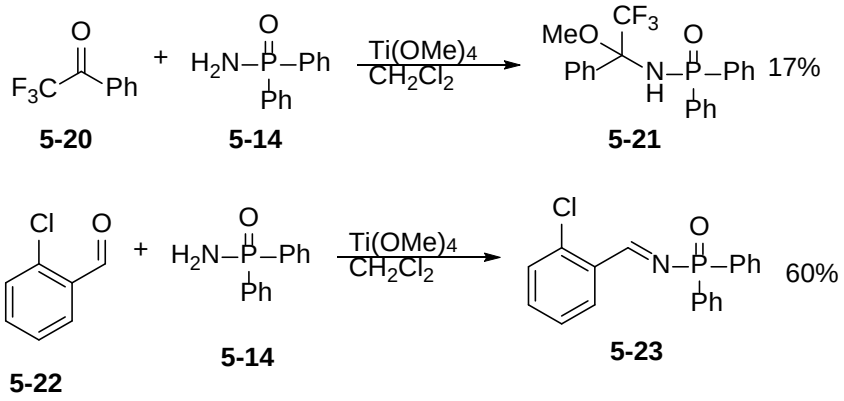
5-18 **5-14** **5-16b, 5-16d, 5-19**

entry	R^1 =	R^2 =	yield (%)[a]
1	$C_6H_4CH_3$	H	25-59
2	$C_6H_4OCH_3$	H	<45[b]
3	Ph	CF_3	<5

a) Yield reported as a range where appropriate; b) >90% pure.

The process gave a satisfactory yield of *p*-toluene *N*-phosphinoyl imine (entry 1). However *p*-methoxyphenyl *N*-phosphinoyl imine was formed in lower yield than other methods and its purification was more difficult as well (entry 2). Forming a sulfinic acid adduct with this material was low yielding compared to other methods (31%). Ketimines also could not be prepared using this methodology (entry 3).

The methodology of Jennings and Lovely was used to prepare imines which could not be accessed otherwise (**Scheme 5.4**).[210] Using stoichiometric titanium tetramethoxide allowed for formation of ketimine **5-21** as a methoxy hemiaminal and *o*-chlorophenyl *N*-phosphinoyl imine **5-23**. This methodology benefited from much shorter reaction times and generated substrates which were unobtainable by other means. With an effective route to all of the desired imine substrates established, attention turned towards the aza-benzoin reaction itself.

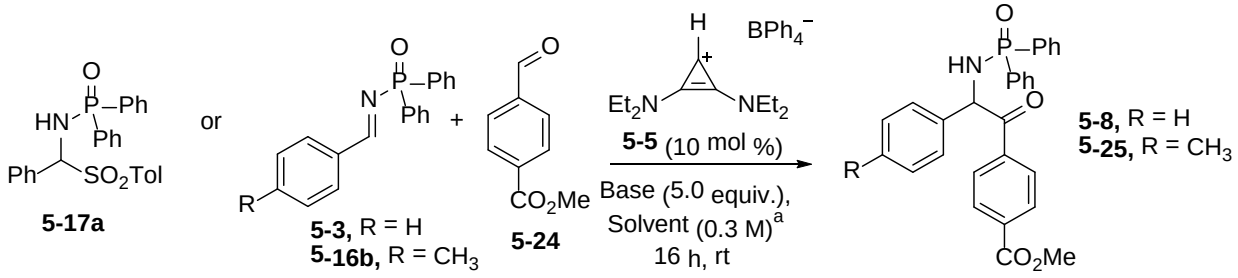


Scheme 5.4 Lewis Acid Mediated Preparation of Phosphinamides or Equivalents Thereof

5.3 Optimization of the BAC Catalyzed Aza-benzoin Reactions

A full parameter optimization was undertaken (**Table 5.4**) starting from conditions developed in the Stetter reaction (entries 1 and 2). Increasing reaction temperature, which can have a large effect upon conversion, was explored and was found to be detrimental to the reaction (entry 3), similar to what was observed in the Stetter reaction.

Table 5.4 Optimization of Aza-Benzoin Reaction with EtBAC



entry	imine	solvent	base	other changes[b]	conversion (%)
1	**5-17a**	CH_2Cl_2	K_2CO_3	-	26
2	**5-3**	CH_3CN	K_2CO_3	-	19
3	**5-17a**	CH_2Cl_2	K_2CO_3	100 °C	<10
4	**5-17a**	CH_2Cl_2	DBU	-	<5

Table 5.4 Optimization of Aza-Benzoin Reaction with EtBAC (Cont.)

5	**5-17a**	THF	Cs_2CO_3	-	<5
6	**5-17a**	Toluene	Cs_2CO_3	-	7
7	**5-17a**	CH_3CN	Cs_2CO_3	-	89 (55)[c]
8	**5-17a**	CH_2Cl_2	Cs_2CO_3	-	<5
9	**5-17a**	CH_2Cl_2	Cs_2CO_3	4Å mol. sieves	94
10	**5-17a**	CH_3CN	Cs_2CO_3	different catalyst[d]	34
11	**5-17a**	CH_3CN	Cs_2CO_3	1.0 M, 30 mg scale	100 (77)[c]
12	**5-17a**	CH_3CN	Cs_2CO_3	1.0 M	<5%
13	**5-17a**	CH_3CN	Cs_2CO_3	0.8 M	<5%
14	**5-17a**	CH_3CN	Cs_2CO_3	0.6 M	56
15	**5-17a**	CH_3CN	Cs_2CO_3	0.3 M	79
16	**5-17a**	CH_3CN	Cs_2CO_3	0.06 M	50
17	**5-17a**	CH_3CN	Cs_2CO_3	-	92[e]
18	**5-17a**	CH_3CN	Cs_2CO_3	25 equiv. H_2O	<5[e]
19	**5-17a**	CH_3CN	Cs_2CO_3	4Å mol. sieves	100 (76)[c,e]

a) Concentration with respect to imine; b) Changes from the above stated conditions such as different temperature, reaction concentration or an additional reagent; c) isolated yield in brackets; d) bis(diisopropylamino)cyclopropenium tetraphenylborate substituted for bis(diethylamino)cyclopropenium tetraphenylborate e) 20 mol% of catalyst used.

In reactions with BACs, as with NHC's, the carbene catalyst was formed from a pre-catalyst salt using a base. In aza-benzoin reactions with sulfinamides the base also generated the imine *in situ* by causing elimination of the sulfinate group. The conjugate acid of the base has been speculated to play additional roles in the reaction, such as acting as a proton shuttle in the

tautomerism to form Breslow intermediates. Thus the base was an important variable to optimize early, as it can have a significant effect on the reaction.

It was known from the results with the Stetter reaction that amine bases such as triethylamine or Hünig's base were too weak to generate significant concentration of carbene in solution from bis(amino)cyclopropenium salts. The first BAC catalyzed aza-benzoin reaction used potassium carbonate, a mild base, which worked in Stetter reactions previously (**Table 5.4**, entry 1, 2). The elimination of sulfinate groups to give imines has precedent with this base and it was mild enough that a large excess could be used without complication.[208] The next base explored, DBU, was established as a superior base to carbonates in the Stetter project. It gave a low conversion to aza-benzoin product (<5%) as well as a messy reaction (entry 4). This is consistent with the results of Scheidt, who stated that thiazolium derived catalysts gave low conversion with aldehydes in reactions that used DBU.[83,84] However, as Scheidt was able to use DBU to perform reactions with aldehyde surrogates (acyl silanes) the question of substrate compatibility arose. Use of a thiazolium salt in combination with DBU gave low conversion (23%) in an aza-benzoin reaction compared to potassium carbonate and the same thiazolium salt (65%) so substrate compatibility is likely an issue with DBU. Cesium carbonate was selected as the optimal base for aza-benzoin reactions because of its mild nature, and better solubility in organic solvents (compared to potassium carbonate).

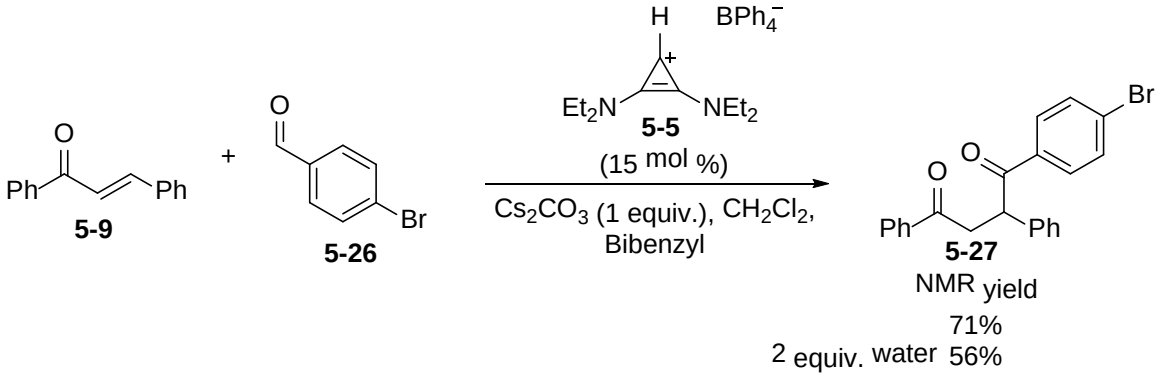
A variety of solvent were screened to see the effect of different solvents upon the reaction. THF (entry 5) and toluene (entry 6) afforded low conversion whereas acetonitrile (entry 7) resulted in full conversion to aza-benzoin product and a reasonable isolated yield (55%). Surprisingly dichloromethane (entry 8) failed to give any aza-benzoin product with cesium carbonate (see entry 9 below), and acetonitrile was chosen as the optimal solvent.

Increasing the concentration of the reaction mixture had a positive effect upon the reaction up to around 0.3 M (entries 10-16). Higher concentrations could be effective (entry 10) but the reaction mixture tended to solidify before full conversion was attained (entry 11). The yield was found to improve further by increasing the catalytic loading to 20 mol % (entry 17).

With optimal conditions established (20 mol% catalyst, cesium carbonate, 0.3 M acetonitrile) a more systemic issue of reproducibility emerged. Replicating the outcomes of BAC catalyzed aza-benzoin reactions proved difficult, with yield often being unaccountably low (not shown). Suspicion fell on the quality of the reagents or air contamination, but neither explanation proved satisfactory. Over the course of this work ambient humidity varied substantially, and it was hypothesized that incidental introduction of water could be at fault. To test this hypothesis, two identical aza-benzoin reactions were set up; and activated molecular sieves were added to one reaction while water was added to the other. The reaction where water was intentionally introduced gave low conversion to aza-benzoin product (entry 18) while the reactions run in the presence of dry molecular sieves gave full conversion and improved yield (entry 19). Subsequently, molecular sieves have been added to all aza-benzoin reactions and obtaining reproducible yields has not been an issue. Given how well the reaction with potassium carbonate in CH_2Cl_2 worked (entry 1), the outcome of the reaction using cesium carbonate in CH_2Cl_2 (entry 8) was suspect. When that reaction was re-run in the presence of molecular sieve excellent conversion was observed (94%, entry 9). It is likely that hydration of the cesium carbonate used introduced water into the original experiment.

To explore the possibility of a side reaction between water and the catalyst, water was added to a known Stetter reaction (**Scheme 5.5**). Conversion in this wet Stetter reaction was only slightly lower than in a reaction possessing no additional water (56% vs. 71%); suggesting it is

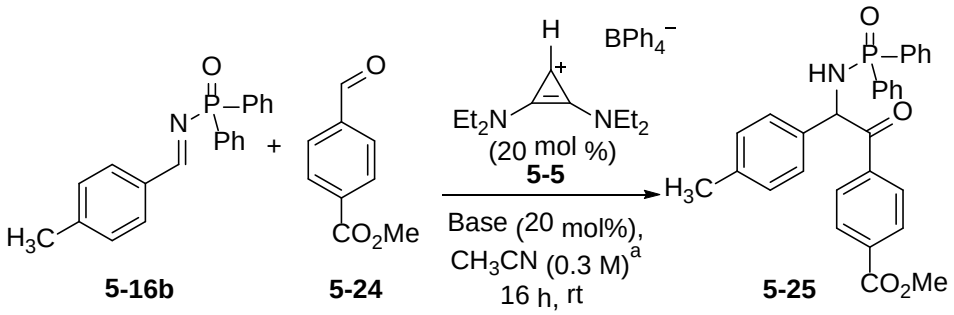
not as simple as a reaction between water and the catalyst. Aza-benzoin reactions could be run with EtBAC in the presence of diphenylphosphinamide (a hydrolysis by-product) without consequence. In these unsuccessful reactions a large amount of the reacting imine and aldehyde could be recovered, so substrate decomposition is likely not to blame. Thus, though some simple possibilities could be ruled out, the manner by which water interferes with otherwise high-yielding aza-benzoin reactions is unclear.



Scheme 5.5 Stetter Reactions with and without Water

Further experiments found sodium hydride, potassium *tert*-butoxide and catalytic cesium carbonate to be effective bases for the aza-benzoin reaction (**Table 5.5**, entries 1-3), provided an imine (**5-16b**) was used instead of the sulfinic acid adduct (**5-17a**). KHMDS was not effective as a base with the imine (**Table 5.5**, entry 4).

Table 5.5 Additional Base Screening for Aza-Benzoin Reactions with EtBAC



5-16b **5-24** **5-25**

entry	base	yield
1	Cs_2CO_3	83
2	KO*t*Bu	91
3	NaH	87
4	KHMDS	<5

With optimal solvent, base and conditions established (**Table 5.4**, entry 19) exploration of the scope of the reaction could commence.

5.4 Substrate Scope for the Aza-Benzoin Reaction

Following the optimization process an array of aldehydes and imines were screened to survey the effective scope of this BAC catalyzed aza-benzoin reaction (**Table 5.6**). The reaction was very effective with methyl-4-formyl benzoate (**5-24**) and phenyl sulfonyl phosphinamide (**5-17a**), with which the optimization was done (76%). The reaction between this imine and *p*-bromobenzaldehyde (**5-29)** was also high yielding (82%), but reactions with furfural (**5-30**) or benzaldehyde (**5-31**) were not high yielding (15, 13% respectively).

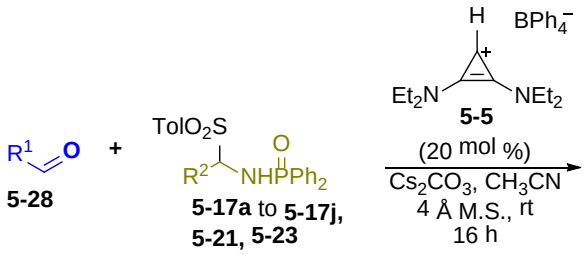
Compared to phenyl sulfonyl phosphinamide yields were generally higher with *p*-toluene sulfonyl phosphinamide **5-17b** which is more electron rich. Reactions with this imine and

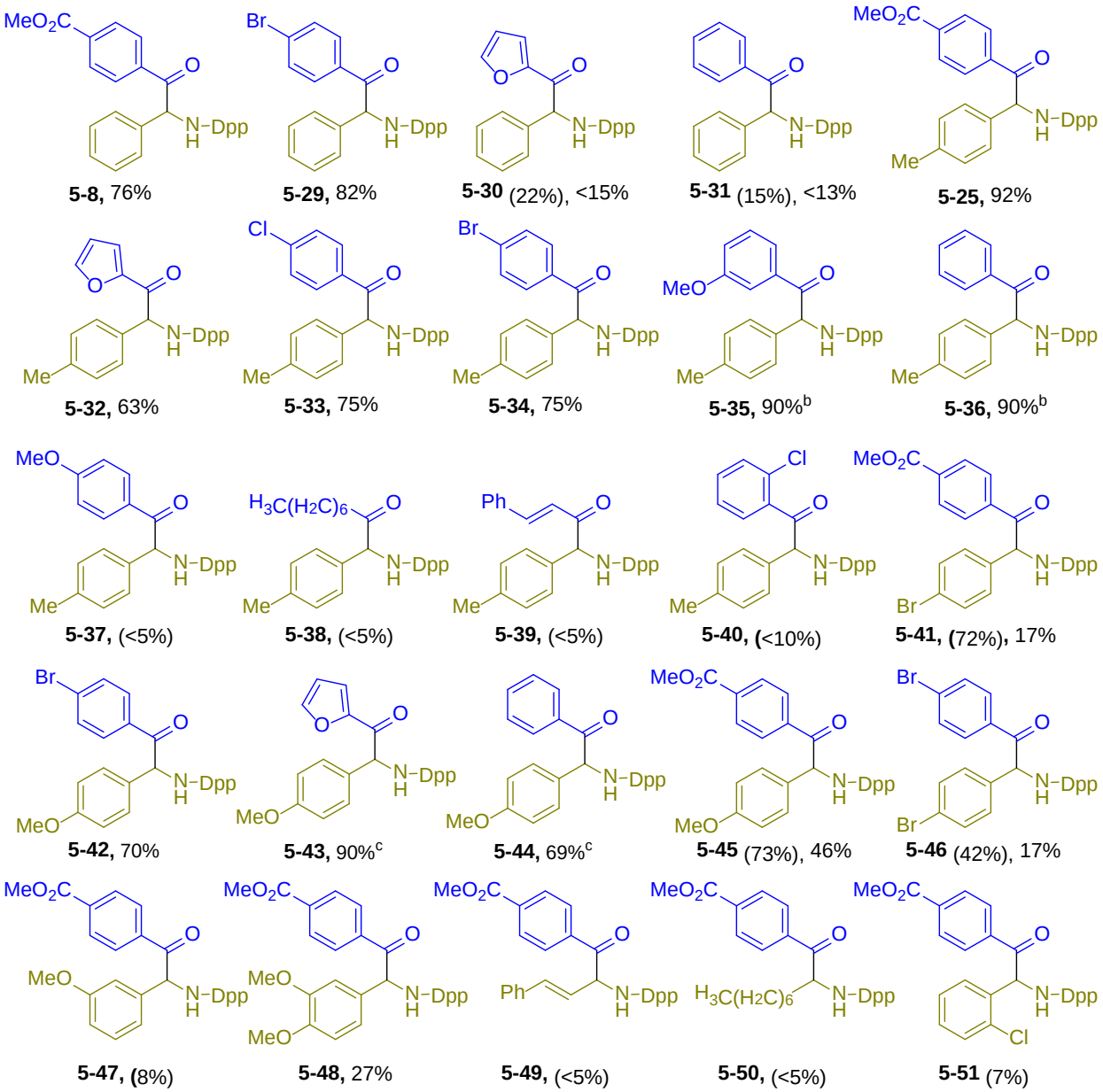
methyl-4-formyl benzoate (**5-25**), furfural (**5-32**), *p*-chlorobenzaldehyde (**5-33),** *p*-bromobenzaldehyde (**5-34**) and *m*-anisaldehyde (**5-35**) were all high yielding (92, 85, 75, 75, 90%). A good yield could even be obtained with benzaldehyde (90%) and this imine by using an excess of aldehyde (**5-36)**. Electron rich aromatic aldehydes such as *p*-methoxy anisaldehyde (**5-37)** did not work well in this reaction, nor did aliphatic aldehydes (**5-38)** or α-β-unsaturated aldehydes (**5-39)** (<5%). *Para*- or *meta*-substituted aromatic aldehydes could be high yielding but the yield was low (<10%) for the *o*-substituted aldehyde explored (*o*-chlorobenzaldehyde, **5-40**). This outcome is largely consistent with the results for the Stetter reaction, and provides good evidence that this aldehyde selectivity arises from BAC-aldehyde incompatibility, independent of the acceptor species.

Investigating another electron rich imine, *p*-methoxyphenyl sulfonyl phosphinamide (**5-17d**) afforded a good yield with p-bromo-benzaldehyde (**5-42)**, furfural (**5-43)** and benzaldehyde (**5-44)** using excess aldehyde (70, 90, 69%). A surprisingly low yield was obtained with obtained with this imine in combination with methyl-4-formyl benzoate (**5-45**) (46%).

A less electron rich imine, *p*–bromophenyl sulfonyl phosphinamide (**5-17c)** also gave good conversion to aza-benzoin product with methyl-4-formyl benzoate and *p*-bromobenzaldehyde (**5-41**) and (**5-46**) (72, 42% conversion), however these products were sensitive to chromatography and consequently only small amounts could be isolated (17, 17%).

Table 5.6 Substrate Scope for the Aza-Benzoin Reaction

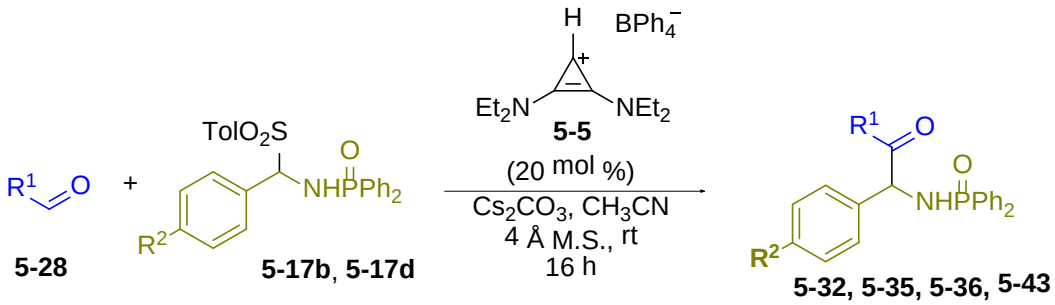




a) N-Dpp = $NPOPh_2$. All reactions performed on 0.15 mmol scale. Yields of isolated pure products. ^1H NMR conversion shown in parentheses where relevant; b) 5 equiv of aldehyde used; c) 3 equiv of aldehyde used.

The positioning of substituents on aromatic imines was explored with *o*-chlorophenyl *N*-phosphinoyl imine (**5-23**), *m*-methoxyphenyl sulfonyl phosphinamide (**5-17e**) and *m*-*p*-dimethoxyphenyl sulfonyl phosphinamide (**5-17f**). *o*-Chlorophenyl *N*-phosphinoyl imine (**5-23**) and *m*-methoxyphenyl sulfonyl phosphinamide **5-17e** both gave lower conversion than *m*-*p*-dimethoxyphenyl sulfonyl phosphinamide **5-17f**, (7% of **5-51**, 8% of **5-47**, 27% of **5-48**) though none of these reactions outcomes were satisfactory. Reactions with both methoxy substituted imines were overly viscous and required dilution. Further optimization may be required for these acceptors. α-β-Unsaturated imine (**5-17i**) as well as an aliphatic imine (**5-17j**) were also explored but found to be unreactive under these conditions (**5-49**, **5-50**).

Table 5.7 Aza-Benzoin Reactions using Excess Aldehyde



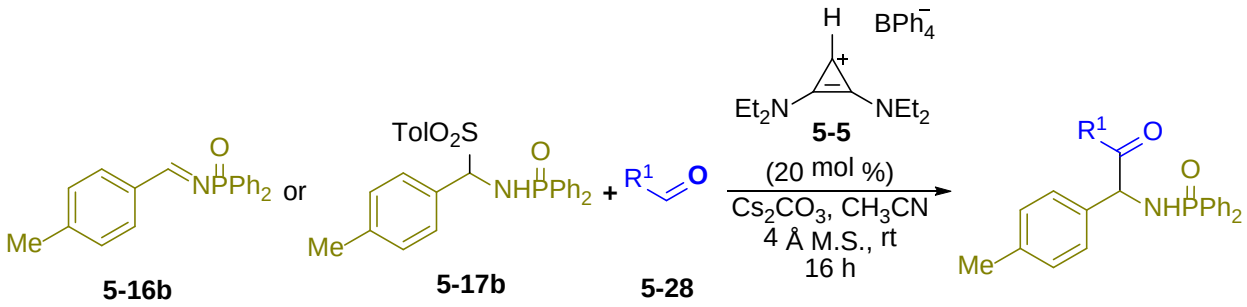
entry	R^1	R^2	# equiv aldehyde	yield (%)
1	2-furyl	CH_3	1.5	63
			5	85
2	*m*-$CH_3OC_6H_4$	CH_3	1.1	28
			5	90
3	Ph	CH_3	1.2	25
			5	90
4	2-furyl	OCH_3	1.5	33
			3	90

The majority of the reactions above were successful without using a large excess of aldehyde. In some instances an excess of aldehyde was found to substantially increase the yield, as is shown in **Table 5.7** (entries 1-4). Curiously the excess aldehyde was not consumed to provide this boost in yield, as one might expect, but was still present in the crude reaction mixture. This may serve as a general way to improve the yield in some aza-benzoin reactions, such as the reactions of phenyl *N*-phosphinoyl imine with furfural (**5-10)** or benzaldehyde.

5.5 Comparison between Phosphinamides and *N*-Phosphinoyl Imines

A concern in this methodology was the effect of using sulfinoyl phosphinamides instead of *N*-phosphinoyl imines (**Table 5.8**). For reactions with very reactive imines or iminium salts substrate inhibition is precedented. Rovis and coworkers have found a set of mild conditions wherein adduct formation is reversible.[77] Other groups have used syringe pump addition of the imine to prevent substrate inhibition. By extension slow generation of the reacting imine may be beneficial. However at low substrate concentrations undesired processes may proceed instead of the desired aza-benzoin reactions. EtBAC reacted effectively with both the imine and sulfinic acid derivative of *p*-toluene *N*-phosphinoyl imine (**5-16b**, **5-17b**). With furfural yield was better using the imine (entry 1, 63% vs. 96%), however for methyl-4-formyl benzoate (entry 2, 92% vs. 75%) it was worse. It can thus be concluded that substrate inhibition was not a significant concern between *N*-phosphinoyl imines and EtBAC.

Table 5.8 Comparison of Aza-Benzoin Reactions using Imines and Sulfinic Acid Adducts



5-16b **5-17b** **5-28** **5-5**

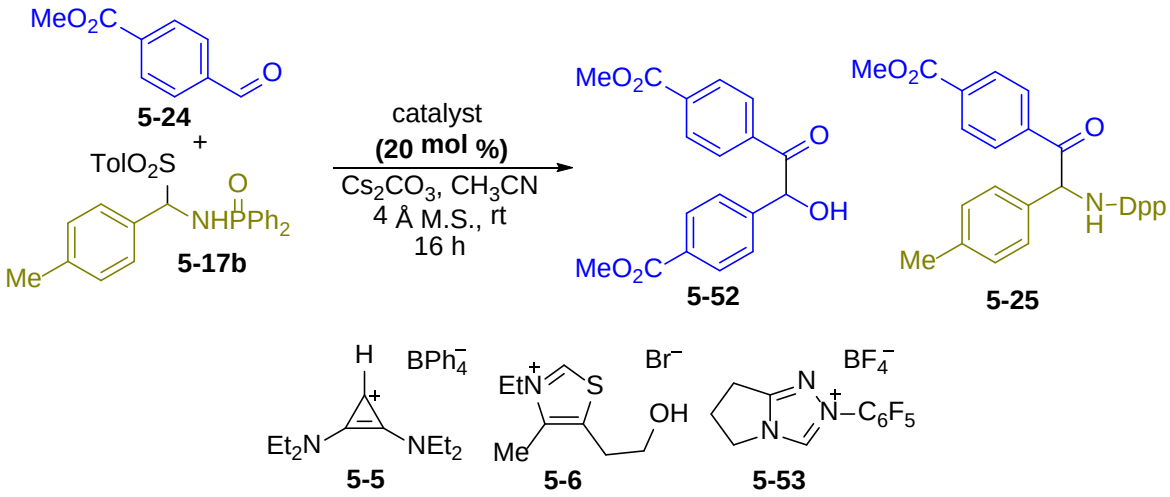
entry	R^1	product #	yield (from **5-17b**) %	yield (from **5-16b**) %
1	2-furyl	**5-32**	63	85, 96[a]
2	$C_6H_4CO_2Me$	**5-25**	92	75

a) On larger (0.3 mmol) scale.

5.6 Comparison to NHCs

In order to directly compare the efficiency of EtBAC against representative thiazolium and triazolium salts, a number of aza-benzoin reactions were performed in parallel with identical substrates (**Table 5.9**). Kinetics studies were also performed with bis(diethylamino)-cyclopropenium tetraphenylborate, thiazolium **5-6**, and triazolium **5-61**. Unfortunately following these air sensitive reactions by NMR spectroscopy proved challenging and there was a large amount of uncertainty in those results (not shown).

Table 5.9 Aza-Benzoin Comparison to NHCs via ^{1}H NMR



entry	pre-catalyst salt	conversion after 15 minutes[a] (%)		conversion after 4 hours[a] (%)	
		5-25	**5-52**	**5-25**	**5-52**
1	**5-53**	<5	>95	80 (9)[b]	20
2	**5-6**	<5	<5	>95 (62)[b]	<5
3	**5-5**	<5	<5	40	<5

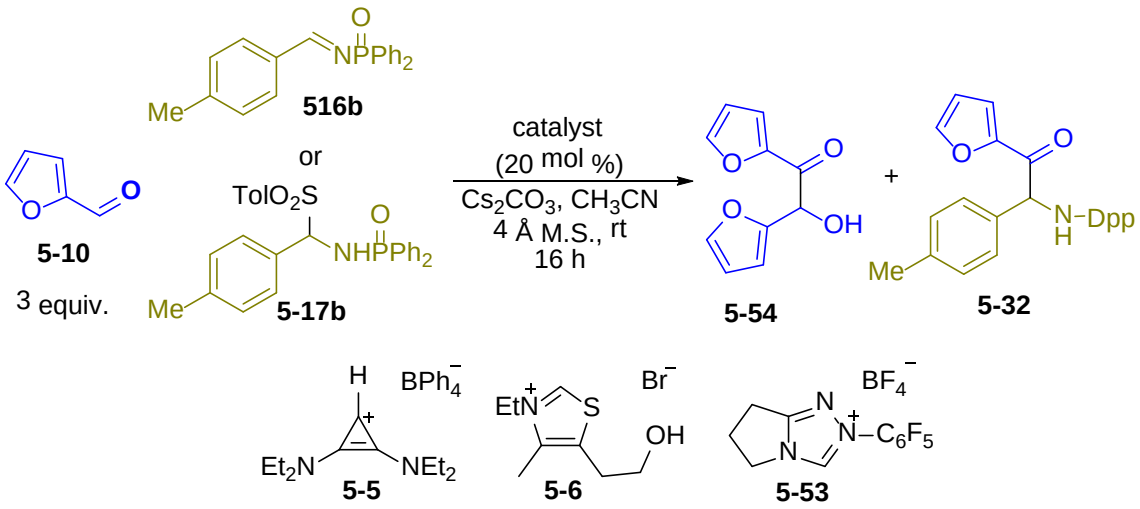
a) Based on the consumption of starting aldehyde as determined by ^{1}H NMR spectroscopy;

b) Isolated yield.

Similar to the more successful Stetter kinetic studies (**Chapter 4**), the triazolium salt was found to be very active initially and produces benzoin product **5-52** at the start of the reaction (entry 1). Following a retro-benzoin reaction some of the desired aza-benzoin product was formed, along with several other unidentified materials and resulting in an inflated conversion and low (9%) NMR yield. Thiazolium **5-6** appeared to form benzoin and aza-benzoin product at similar rates (not shown) but a facile retro-benzoin reaction led to the aza-benzoin product becoming the major product (entry 2) and it could be isolated in reasonable (62%) yield. Unlike

the NHC catalysts benzoin products were never produced in significant amounts with EtBAC (entry 3) and aza-benzoin product accumulated slowly over time.

Table 5.10 Aza-Benzoin NHC Competition Experiment



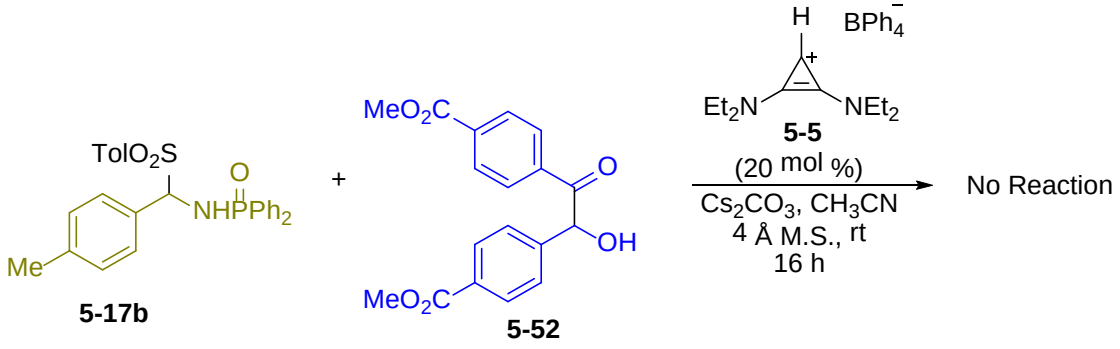
entry	pre-catalyst	from imine **5-16b** residual imine **5-16b** (%)[a]	residual **5-10** (%)[a]	benzoin **5-54** (%)[a]	aza-benzoin **5-32** (%)[a]	from **5-17b** aza-benzoin **5-32** (%)[b]
1	**5-5**	8	35	-	79	63
2	**5-6**	-	trace	67	91	63
3	**5-53**	-	-	47	70	23

a) Based on the consumption of starting materials by ^{1}H NMR spectroscopy using bibenzyl as internal standard; b) Isolated yield.

To determine if the presence of a sulfinate group was biasing the reaction in some way, a series of reactions were performed with furfural (**Table 5.10**). Outcomes of reactions with *p*–toluene sulfonyl phosphinamide **5-17b** were consistent with **Table 5.9** above. However reactions with the imine (**5-16b)** and 3 equivalents of furfural gave a different outcome. Under these

conditions EtBAC was found to effect high conversion to aza-benzoin product (entry 1). No benzoin products were detected and substantial amounts of furfural was present in the crude reaction mixture. Thiazolium catalysis also gave an efficient aza-benzoin reaction, however nearly all of the excess aldehyde was converted to benzoin product **5-54** (entry 2). Unlike the reaction with the sulfinic acid adduct, the reaction of triazolium in combination with imine (**5-16b**) produced significant amounts of aza-benzoin product (entry 3). Most of the remainder furfural was converted to the benzoin product, and a large number of impurities were present in the reaction.

Benzoin products were not detected in aza-benzoin reactions with EtBAC, but there was always the possibility of benzoin products being formed and quickly consumed by retro-benzoin reaction. To assess this possibility, benzoin product **5-52** was subjected to aza-benzoin reaction conditions where it could potentially act as an acyl anion equivalent (via retro-benzoin reaction). This reaction did not produce any aza-benzoin product or any aldehyde indicating a retro-benzoin reaction was likely not occurring under these conditions (**Scheme 5.6**). This experiment validates one of the predictions made at the start of this project, which is that benzoin side-products would not be formed in the course of aza-benzoin reactions with BAC catalysts.

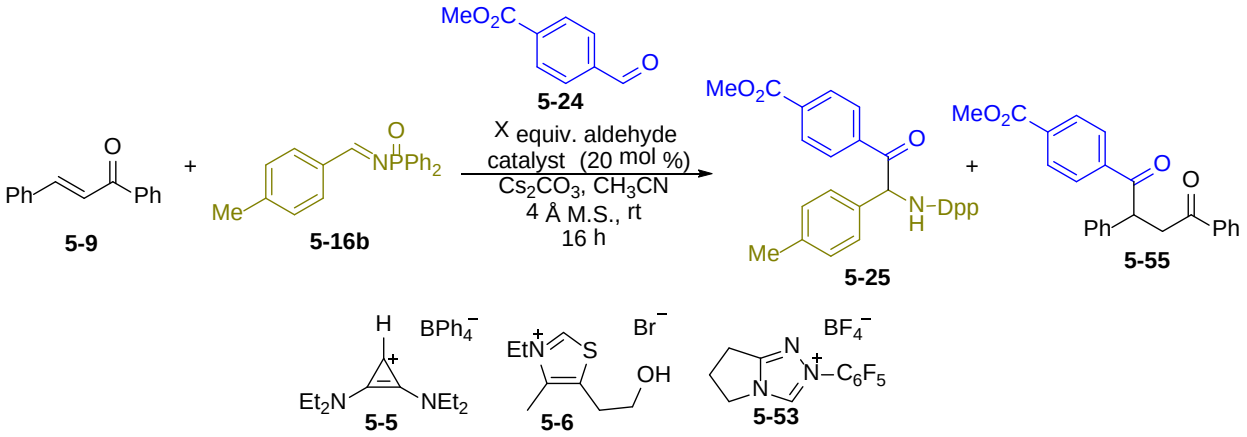


Scheme 5.6 Retro-Benzoin Aza-Benzoin Reaction

5.7 Aza-Benzoin/Stetter Competition

The electrophilicity of *N*-phosphinoyl imines in model reactions has been reported by Mayr as similar to that of chalcones.[207] The question arose as to how valid that comparison was in NHC catalyzed reactions. In Mayr's study, reactions were selected to minimize steric influences on reactivity so that any differences in kinetics would be purely due to differences in electrophilicity. However, steric factors have a large influence on the reactivity of Breslow intermediates in NHC catalysis.

Table 5.11 Stetter Aza-Benzoin Competition Experiment



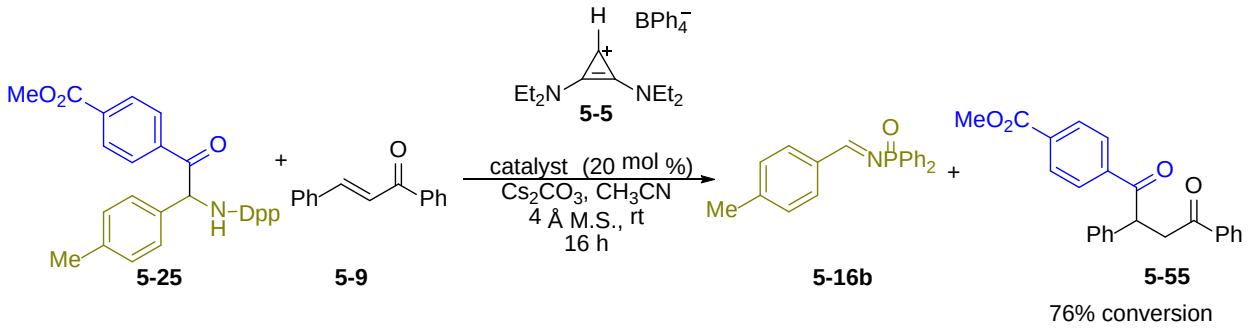
entry	catalyst	# equiv aldehyde	**5-25** : **5-55**[a]	yield of **5-25**[b] (%)	yield of **5-55**[b] (%)
1	**5-5**	1.5	1:2	-	-
2	**5-6**	1.5	1:0.5	-	-
3	**5-53**	1.5	1:0	-	-
4	**5-5**	1	1: 2.8	10	50
5	**5-6**	1	1: 0.13	18	4
6	**5-53**	1	1: 0	8	-

a) Determined from ^{1}H NMR integration of the crude reaction mixture; b) isolated yield only determined on reactions with 1 equivalent aldehyde.

A set of competition reactions were performed to establish the relative reactivity of *p*-toluene *N*-phosphinoyl imine **5-16b** and chalcone **5-9** towards Breslow type intermediates derived from EtBAC, thiazolium and triazolium salts. In these experiments limiting amounts of aldehyde were reacted with one equivalent of imine **5-16b** and one equivalent of chalcone (**Table 5.11**).

EtBAC produced more Stetter product than aza-benzoin product in this reaction (entry 1 and 4). In contrast, both the thiazolium and triazolium catalysts formed Breslow intermediates which reacted with *N*-phosphinoyl imine **5-16b** more readily than chalcone, as determined by the ratio of products as well as isolated yields (entries 2, 3 and 5, 6, **Table 5.11**). No Stetter product was generated using the triazolium salt. Studies were done to determine whether this preference was due to kinetic or thermodynamic control. When the reaction was followed over a period of time both products formed at a similar rate initially suggesting the Stetter product is thermodynamically favored.

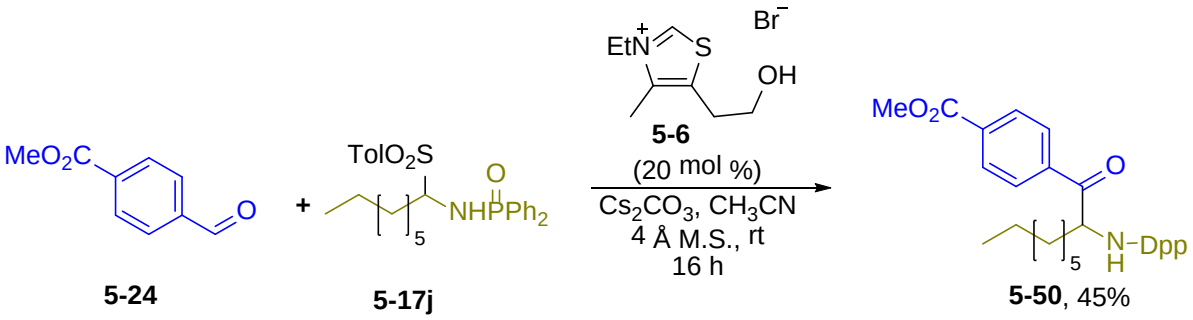
By subjecting an aza-benzoin product to reaction conditions with chalcone and without any aldehyde, a mixture formed which contained the Stetter product **5-55** and *p*-toluene *N*-phosphinoyl imine **5-16b** (**Scheme 5.7**). This process was very efficient with 76% of the α-amino ketone undergoing retro-aza-benzoin to form the Stetter product. This is conclusive proof of a retro-aza-benzoin-Stetter reaction.



Scheme 5.7 Retro-Aza-Benzoin Stetter Reaction

5.8 Aza-Benzoin Reactions with Aliphatic Imines

Aliphatic imines can be challenging substrates for the aza-benzoin reaction, as imine enamine tautomerism is possible and is favorable in many cases (i.e.: Boc imines). Aside from decreasing the amount of imine available to react with, undesired reactions may occur with enamine tautomers which may be irreversible and competitive with the desired transformation. Thus it was unsurprising that a reaction with octyl sulfonyl phosphinamide (**5-17j**, **Scheme 5.8**) to form **5-50** (**Table 5.6**) was unsuccessful. However following this line of inquiry it was discovered that thiazolium **5-6** could catalyze a modest yielding (45%) aza-benzoin reaction with octyl sulfonyl phosphinamide (**5-17j**) using the conditions reported previously for pre-catalyst **5-5** (**Table 5.4**, entry 19). This is substantial as it was the only successful aza-benzoin reaction reported to date with an aliphatic imine. Additionally, the crude reaction mixture appeared to consist of starting material and the aza-benzoin product, thus this reaction could be optimized further. Should the reaction be found to have a reasonable substrate scope, it could even give rise to a new synthetic method.

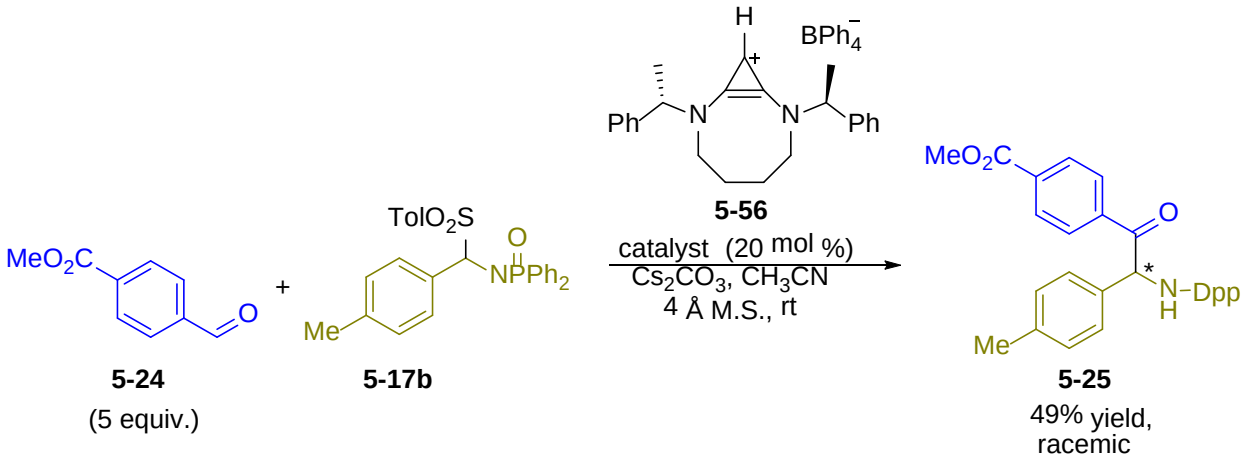


Scheme 5.8 Aza-Benzoin Reaction with an Aliphatic Substrate

5.9 Aza-Benzoin Reactions with Chiral Catalysts

One of the most attractive applications of the aza-benzoin reaction is the preparation of biologically relevant molecules. As this reaction gives rise to a new stereocenter, a means to direct the configuration at this center is desirable. Aza-benzoin reactions have been performed in an enantioselective manner by Miller and Mennen as well as Rovis and coworkers.[85,86] Having developed chiral BAC catalysts, efforts were made to induce stereoselectivity in the aza-benzoin reaction with *N*-phosphinoyl imines.

The use of catalyst **5-56** gave a low yield (16%) of the desired aza-benzoin product under the optimized reaction conditions developed for pre-catalyst **5-5** (**Table 5.4**, entry 19). Using 5 equivalents of methyl-4-formyl benzoate improved the yield somewhat (49%) (**Scheme 5.9**). This is unsurprising given the large difference in reactivity observed between isopropyl and ethyl amine substituents on the bis(amino)cyclopropenylidene core. Unfortunately it was determined by HPLC analysis on a chiral stationary phase that the product **5-25** formed as a racemic mixture.

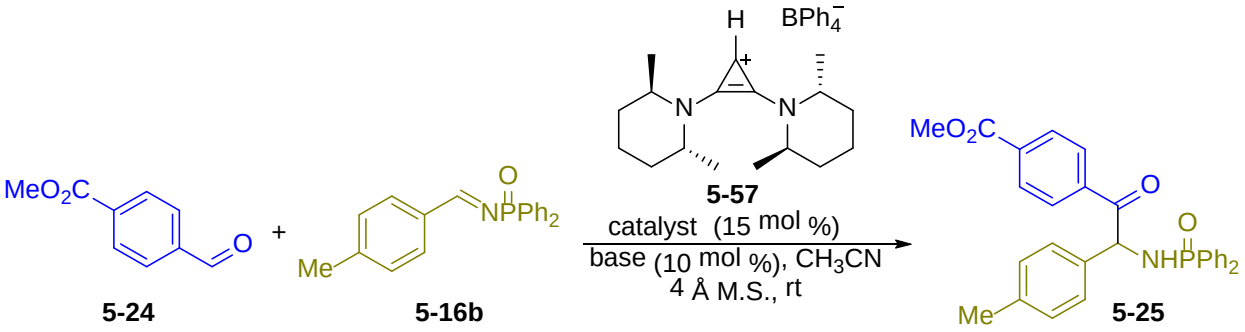


Scheme 5.9 Enantioselective Aza-Benzoin Reaction

It was unclear if the racemic nature of the product was due to a lack of selectivity from the catalyst, thermodynamic equilibration, or a base-induced epimerization of the newly formed stereocenter. Other aza-benzoin reactions are known to undergo post-reaction epimerization; the Rovis group reported cooling their reactions was necessary to limit epimerization.[86] If base induced epimerization was proceeding, reducing the base loading could improve enantioselectivity. Consequently a reaction was performed with *p*-tolyl-*N*-phosphinoyl imine **5-16b** and sub-stoichiometric amounts of cesium carbonate. EtBAC gave full conversion (**Table 5.5**, entry 1) under these conditions, however conversion with chiral catalyst **5-56** was low (<5%) and enantiomeric excess could not be determined.

Another chiral catalyst (**5-57**) was utilized as it afforded better enantioselectivity in the Stetter reaction (**Table 5.12**).

Table 5.12 Effect of Base in the Enantioselective Aza-Benzoin Reaction



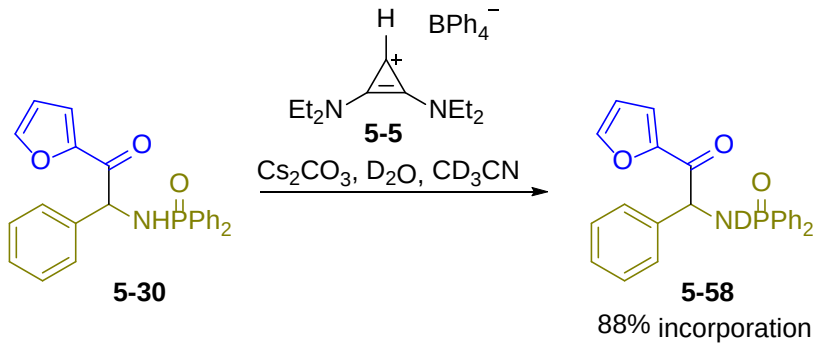
5-24 **5-16b** **5-25**

entry	base	conversion (%)[a]	enantiomeric excess
1	Cs_2CO_3	<5	-
2	NaH	<5	-
3	KO*t*-Bu	78 (28)[b]	<5%

a) Conversion determined by ^{1}H NMR analysis of the crude reaction mixture; b) isolated yield in parentheses.

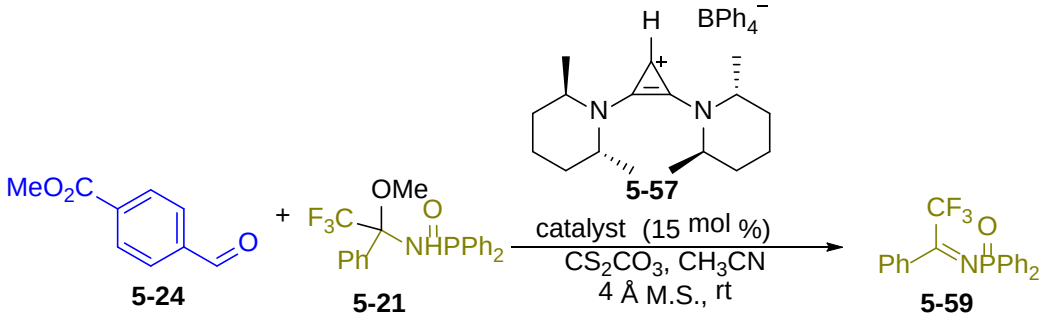
Reactions with substoichiometric cesium carbonate and sodium hydride both failed to give the aza-benzoin product (**Table 5.12**). The reaction with potassium *tert*-butoxide was modestly effective, though additional by-products were present. Its enantiomeric excess was found to be negligible by HPLC analysis on a chiral stationary phase.

To further explore the possibility of epimerization an aza-benzoin product (**5-30**) was subjected to excess cesium carbonate in D_2O along with EtBAC. The phosphinamide proton was found to undergo deuterium exchange while the site α to the carbonyl did not (**Scheme 5.10**). This result rules out the possibility of epimerization as being responsible for the racemic nature of the product under these reaction conditions.



Scheme 5.10 Deuterium Exchange Reaction

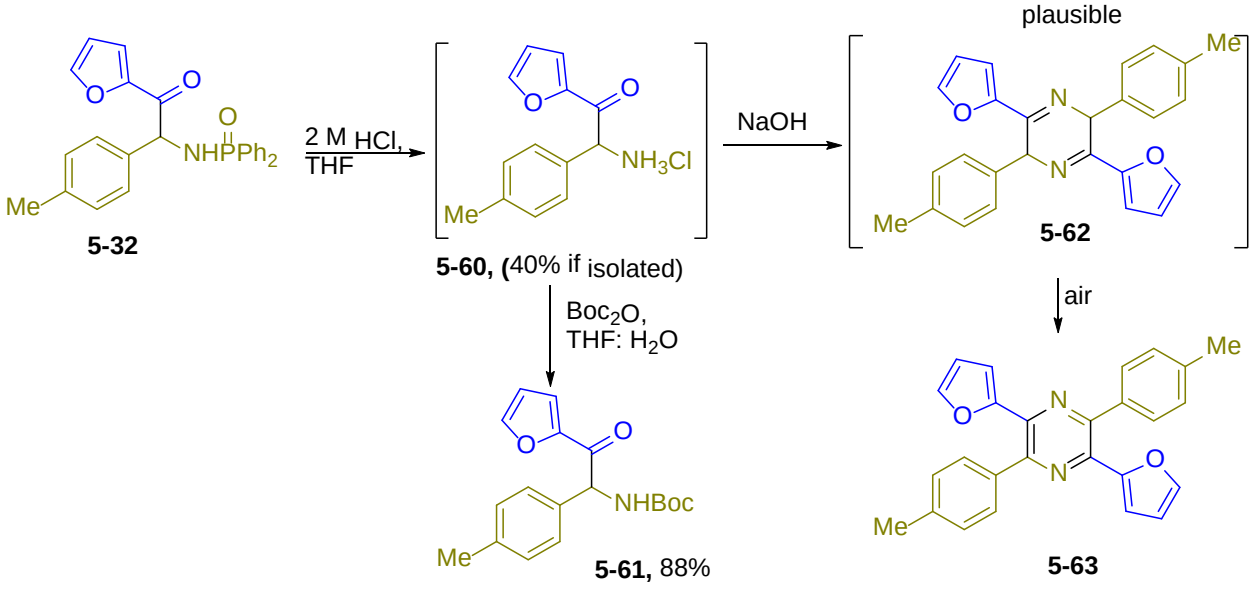
Subsequently an aza-benzoin reaction was attempted with highly electrophilic imine **5-21** (as a methanol adduct), however the only reaction that occurred was loss of methanol under reaction conditions (**Scheme 5.11**).



Scheme 5.11 Aza-Benzoin Reaction with a Masked Ketimine

5.10 Deprotection Reaction

Phosphinamides are less commonly used than carbamates or amides as protecting groups for amines. To demonstrate the utility of this methodology it was beneficial to show the product phosphinamide could easily be converted into other more commonly used functional groups. The nitrogen-phosphorous bond could be easy cleaved by exposing the α-keto phosphinamide to dilute aqueous acid, yielding the aminoketone as a hydrochloride salt (40%). Generating the free amine led to decomposition. Dimerization of aromatic α-amino ketones to form hydropyrazines, such as **5-62**, which oxidize to pyrazines (**5-63)**, is well precedented and may explain the low yield for the deprotection.[211] If the hydrochloride salt was not isolated and protected as a *t*-butyl carbamate *in situ*, Boc-protected α-amino ketone **5-61** could be isolated in excellent yield (88%, **Scheme 5.12**). This satisfactorily demonstrates the synthetic usefulness of the aza-benzoin products obtained with this method, as manipulation of compounds possessing a *t*-butyl carbamate group is well known.



Scheme 5.12 Deprotection of α-Keto Phosphinamides

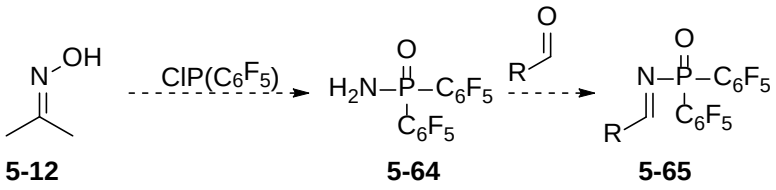
5.11 Conclusions and Future Work

Bis(amino)cyclopropenylidenes were shown to be useful catalysts in the aza-benzoin reaction. Once the reaction was optimized it was found to give excellent yields with a modest substrate scope. Aromatic and heteroaromatic aldehydes, as well as a number of different *N*-phosphinoyl imines or sulfinic acid adducts can be used. Furthermore it has been shown that the reactivity of BACs was substantially different from representative NHCs under identical conditions. Benzoin side-products are not produced in substantial quantities with BACs and this may have advantages in future applications. Chiral BAC catalysts show moderate reactivity, though further development is required to achieve good enantioselectivity with these systems. Achieving enantioselectivity is an important future direction to this work as nearly all of the current benchmark NHC's for enantioselective catalysis are triazolium salts. This work found appreciable material loss from reactions which used triazolium **5-53** in the form of by-products, and there is no obvious way to avoid this outcome. For this reason BAC catalysts may eventually prove a suitable replacement for performing these reactions enantioselectively.

Looking forward, the effective substrate scope of this reaction is limited in a number of ways. Aliphatic or α-β-unsaturated aldehydes are not tolerated in this BAC-catalyzed reaction, and reactions with some imines were low yielding. In a number of instances excess aldehyde was required to push the reaction to completion. In the presence of more reactive substrates or catalysts it may be possible to generate α-amino ketones from a much wider range of substrates in synthetically useful yields, perhaps in an enantioselective manner.

Changing the nitrogen activating/protecting group is a feasible way to improve substrate scope. Replacing the diphenylphosphinamide moiety with a sulfonamide group could be expected to increase the electrophilicity of the imine. However given the lack of reactivity with

sulfonamide **5-1** above, this change will require subsequent modulation and may involve a complete re-optimization of reaction conditions. Sulfonamides also introduce a new challenge as they can be difficult to cleave. A more reasonable alternative is to make a more electrophilic *N*-phosphinoyl imine (**Scheme 5.13**). This could be done by placing electron withdrawing groups on the phenyl rings connected to the phosphorous center. Synthetically, this could be accomplished in a straightforward manner; chloro-di(pentafluorophenyl)phosphine is commercially available and could undergo analogous transformations to those of chlorodiphenylphosphine to prepare substrate **5-65**. This new set of substrates may open the reaction up towards aldehydes and imines which are not currently compatible with this methodology.



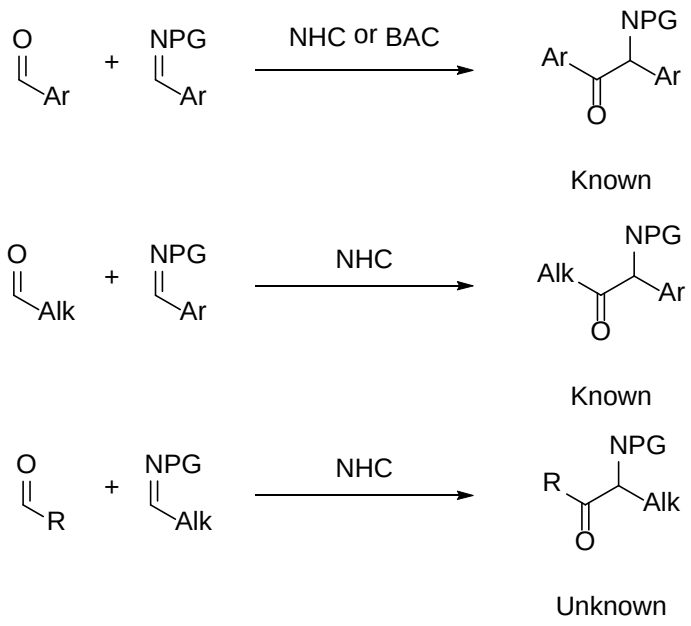
5-12 **5-64** **5-65**

Scheme 5.13 Synthesis of Functionalized Phosphinamides

Improvement may also be achievable through further modification of the BAC scaffold. As the BAC design process extends to all *umpolung* organocatalysis, how these modifications may be accomplished can be found elsewhere in this document (See **Chapter 6**).

The aza-benzoin reaction, to date, has only been reported with imines which lack α-protons such as aromatic imines, or formimines (**Scheme 5.14**). An aza-benzoin reaction with aliphatic aldimines or ketimines was unknown except for the single instance reported above (**Scheme 5.8**), and this represented an exciting opportunity for future work. Enamine formation is problematic with imines possessing strong electron withdrawing groups. But the combination of *N*-phosphinoyl imine group and inorganic bases appears to limit undesired enamine reactivity

allowing for a successful reaction with an aliphatic imine (45% yield of **5-50**) using a thiazolium salt. Significantly, the remainder of the crude reaction mixture appears to consist of starting material implying the yield can be improved. The preparation of *N*-phosphinoyl imine substrates is well established from this and other works. Thiazolium salts are known to operate at high temperatures and can form acyl anion equivalents with numerous aliphatic and aromatic aldehydes, so the reaction could have a broad scope. It is speculated that a competitive benzoin reaction may occur, however conditions can likely be developed which would exploit the known reversibility of this process. This process may even one day be accomplished with a high degree enantioselectivity. A survey of the literature finds a large number of biologically relevant α-amino ketones which possess aliphatic side chains, making development in this area of great interest to the synthetic community.[160]



Scheme 5.14 Current Substrate Limitations in the Aza-Benzoin Reaction

Chapter 6: General Discussion

The objective of this work was to extend the scope and capabilities of carbene catalyzed bond forming reactions. To pursue this goal, analogues of well known triazolium catalysts were prepared and a highly chemoselective approach to generating α-hydroxy ketones via the cross-benzoin reaction resulted. Bis(amino)cyclopropenylidenes, a scaffold nearly unexplored in organocatalysis, were found to be proficient catalysts in both the Stetter and aza-benzoin reactions. Though the exploration of reactions with BACs is far from complete, reactivity has already been found that was different from and occasionally superior to that of NHC's.

Comparing dissimilar carbenes is one of the biggest challenges inherent in carbene organocatalysis. Metrics such as pKa of the carbene carbon, chemical shifts, bond angles, and steric parameters can be useful for comparison, but fall short in predicting outcomes between different heterocyclic or carbocyclic carbenes. Additionally, there are applications some types of carbenes are better suited for than others. Thus, while comparison between similar carbenes can be done using relatively few "benchmark" reactions, comparing BACs to NHCs is no simple task. Direct comparisons can be made of reactions run in parallel with different catalysts. Such comparisons provided limited information, but taken as a whole were found to be self consistent and enabled a better understanding of catalysis using bis(amino)cyclopropenylidenes.

In the homo-benzoin and cross-benzoin reactions BACs are clearly inferior to thiazolium and triazolium derived NHC's. In the cross-benzoin reaction EtBAC showed negligible conversion coupling an aliphatic and aromatic aldehyde. While the chemoselectivity was not always ideal, all triazolium catalysts demonstrated at least modest conversion in cross-benzoin reactions (**Table 2.1**). BACs did not efficiently catalyze the formation of homo-benzoin products; in an aza-benzoin reaction 3 equivalents of aldehyde were used and the surplus aldehyde could be recovered. There were no indications of benzoin reactivity while a high-

yielding aza-benzoin reaction occurred (**Table 5.10**). Bis(amino)cyclopropenium salts, can thus be ranked inferior to thiazolium salts and triazolium salts, in benzoin applications.

In aza-benzoin reactions the situation was more complex. Aza-benzoin reactions have been reported where carbenes derived from thiazolium, and triazolium salts give rise to competing benzoin reactions or catalyst-imine adducts. The BAC-catalyzed aza-benzoin reactions using *N*-phosphinoyl imines were found to be reversible, and several of these reactions were high yielding. BACs outperformed triazolium and thiazolium derived NHC's with these substrates, though they were not compatible with more popular imine substrates.[79,86] Ultimately the scope of this reaction was limited to aromatic *N*-phosphinoyl imines and aromatic or heteroaromatic aldehydes. While this method is complementary to other methods, reactions using thiazolium salts appear to possess fewer substrate limitations. In reactions where the aldehyde is not valuable, NHC methods have an advantage. In situations where benzoin products complicate matters, BAC catalysis may be superior. There is no clear way to improve the scope of the BAC-catalyzed aza-benzoin reaction, unless more active BACs are prepared, as described below.

When a limited amount of aldehyde was reacted with a *N*-phosphinoyl imine and chalcone in a competition reaction, the Stetter reaction pathway dominated reactivity with BAC catalysts. In challenging Stetter reactions BACs outperform other catalysts. Reactions with β-alkyl substituted Michael acceptors could be done with cyanide, and in some instances thiazolium salts, but EtBAC demonstrated the highest yielding Stetter reactions with these substrates to date.[110,109] Electron-rich aromatic aldehydes were also better tolerated with EtBAC compared to thiazolium and triazolium derived carbenes. Most interestingly, a chiral BAC catalyst could be constructed in few steps and reactions performed with one such catalyst gave

rise to enantioselectivity exceeding that achieved with chiral triazolium catalysts. Much work has gone into the development of different BAC catalysts, hopefully easing access to more complex novel BAC catalysts. It is with more effective BAC catalysts capable of generating greater enantioselectivity that further advances in this area will be achieved.

Despite the accomplishment described in the previous chapters, there remain challenges to overcome in *umpolung* reactions with BACs. While enantioselectivity has been shown in the Stetter reaction it could not be achieved in the aza-benzoin reaction. Evidence supports a facile retro-aza-benzoin reaction, with competitive racemization of the product. The substrate scope of aldehydes in both the Stetter and aza-benzoin reactions are currently limited to aromatic and some heteroaromatic aldehydes. This substrate limitation appears specific to BAC catalysts. The scope for Michael acceptors and imine acceptors, though good, has room for improvement in terms of functional group tolerance.

At the start of this work very little was known about the suitability of BACs as organocatalysts. Following this study, directions for innovation in this system become apparent and three specific goals come to the forefront: preparing BACs with improved catalytic activity (both in terms of higher turnover rate, and activity with more substrates), studying the relevant reaction intermediates and preparing a wider variety of chiral catalysts.

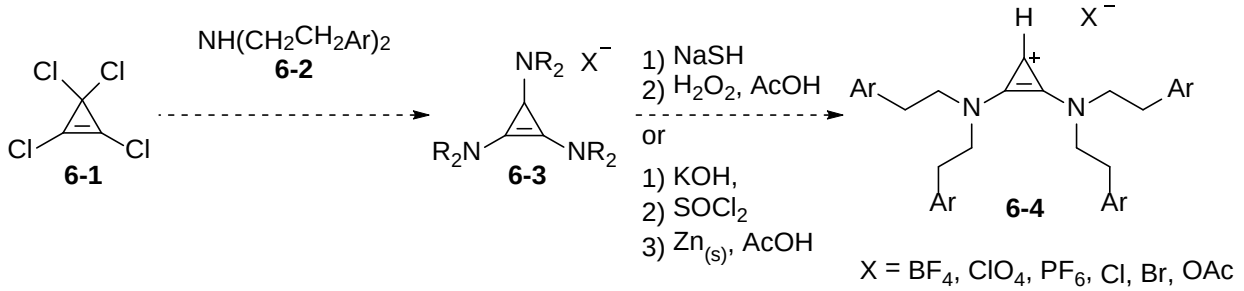
Examples have recently emerged where a triazolium salt's counterion was found to drastically influence catalytic activity.[212] Bis(diethylamino)cyclopropenium perchlorate was found to be more effective than bis(diethylamino)cyclopropenium tetraphenylborate in catalyzing Stetter reactions at elevated temperature. At the start of this work the tetraphenylborate anion was essential to material isolation. It improved the crystallinity of the bis(amino)cyclopropenium salts, and shifts the C_{ring}-H proton NMR signal into the 4-5 ppm

region, allowing for unambiguous identification in complex mixtures. With most NHCs heating improves catalyst efficiency, however with bis(diethylamino)cyclopropenium tetraphenylborate heating was detrimental to reactivity. The atypical thermal behaviour of EtBAC could be due, in part, to the anion. Perchlorate was likely not the most active, or safest, choice for reactions at elevated temperature; bis(diethylamino)cyclopropenium perchlorate was merely the best available salt to use. This opens up exciting possibilities for more active catalysts, tolerant to a wider range of reaction conditions, by using bis(amino)cyclopropenium salts with different counterions.

A screening of counterions was attempted but difficulties were encountered early on. Much of the crystallinity of these salts comes from the anion, and desirable cyclopropenium salts such as bis(diethylamino)cyclopropenium tetrafluoroborate or bis(diethylamino)cyclopropenium bromide were not crystalline and could not be satisfactorily purified. To address this issue and study the effects of different counterions in detail requires a new bis(amino)cyclopropenium salt possessing more of the intermolecular forces which give rise to crystallinity located on the cation. This was the intention behind the preparation of bis-(*N*-dibenzylamino)cyclopropenium salt which possessed improved crystallinity and solubility in organic solvents. However, the benzyl groups noticeably affected conversion in Stetter reactions. Presumably this is for steric reasons. Therefore a new catalyst is proposed with longer alkyl chains possessing phenyl or other aryl substituents. An ethyl tether between the phenyl substituent and the amino group could be expected to have less of an impact on catalytic activity while still improving crystallinity.

This catalyst could most easily be prepared from the corresponding amine, probably via a thione or cyclopropenone intermediate (**Scheme 6.1**). The amines can be accessed via reductive amination of hydrocinnamaldehyde derivatives if they are not commercially available. While

Y = H would be a good starting point having β-aryl groups introduces a new synthetic handle into these species.

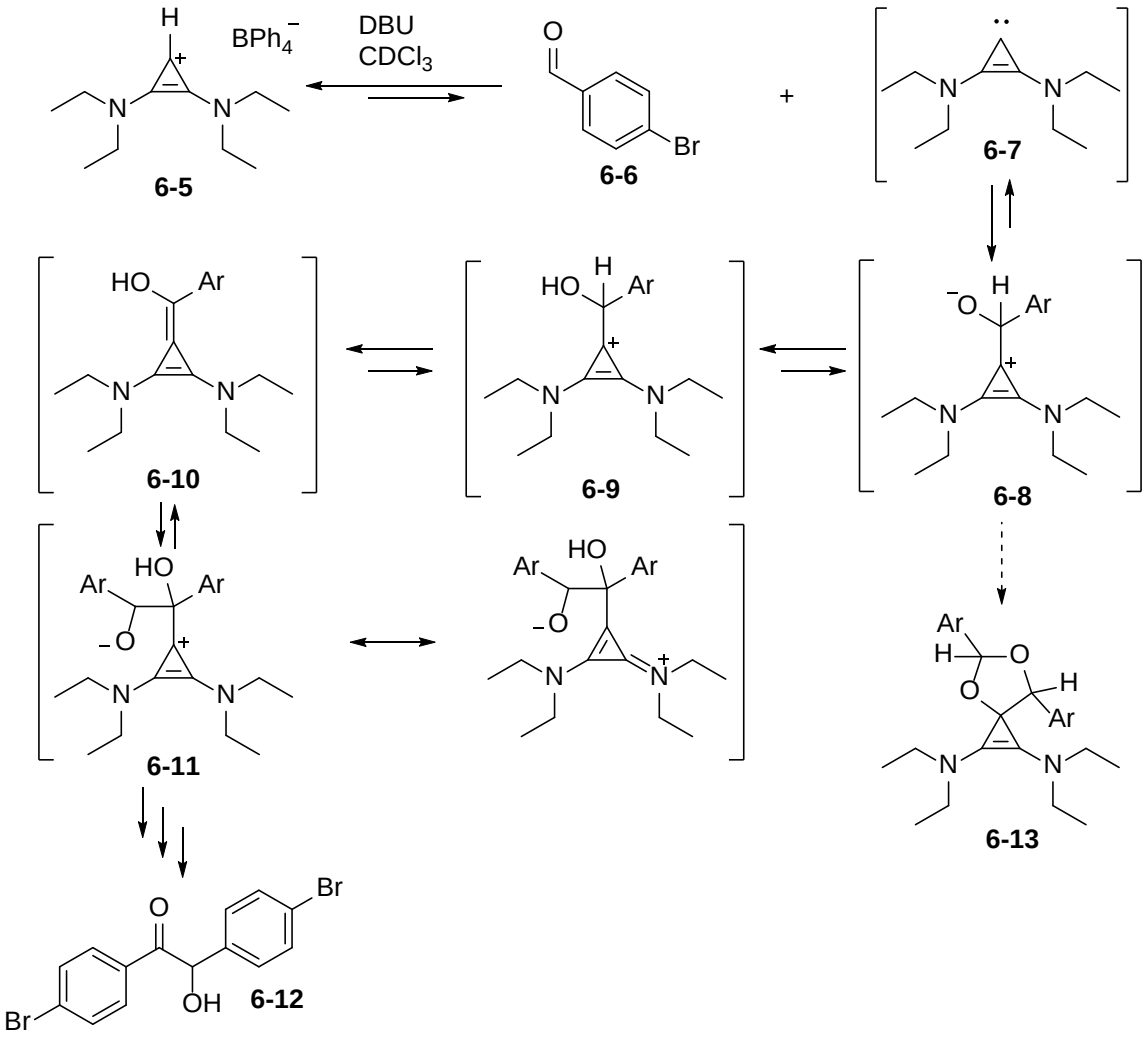


Scheme 6.1 Proposal for Bis(amino)cyclopropenium Salts Possessing Different Anions

One of the fundamental issues in carbene organocatalysis is catalyst lifetime. One reason a reaction can be low yielding is that the rate of decomposition of the active catalytic species is similar to the rate of the desired reaction. Attempting to improve catalyst lifetimes can be challenging, however there are many ways known to accelerate reaction rate. In addition to substrate concentration and temperature, additives are known to accelerate Stetter reactions. Catechol, as an additive, has been found to accelerate the turnover limiting step in some Stetter reactions.[133] Given the general robustness of BACs in Stetter and aza-benzoin chemistry, the yield and scope of these reactions could potentially be improved through the use of additives such as catechol. The potential for BAC catalyzed reactions with beneficial additives merits further exploration.

These efforts will be greatly aided if reaction intermediates could be isolated and studied in detail. While a few Breslow analogues have been isolated recently, analogous BAC-aldehyde adducts have not been isolated.[159] Considering the BAC catalyzed benzoin reaction,

computations suggest Breslow intermediate **6-10** (**Scheme 6.2**) to be an energetic resting state, and thus it may be possible to detect or even isolate.[xv]



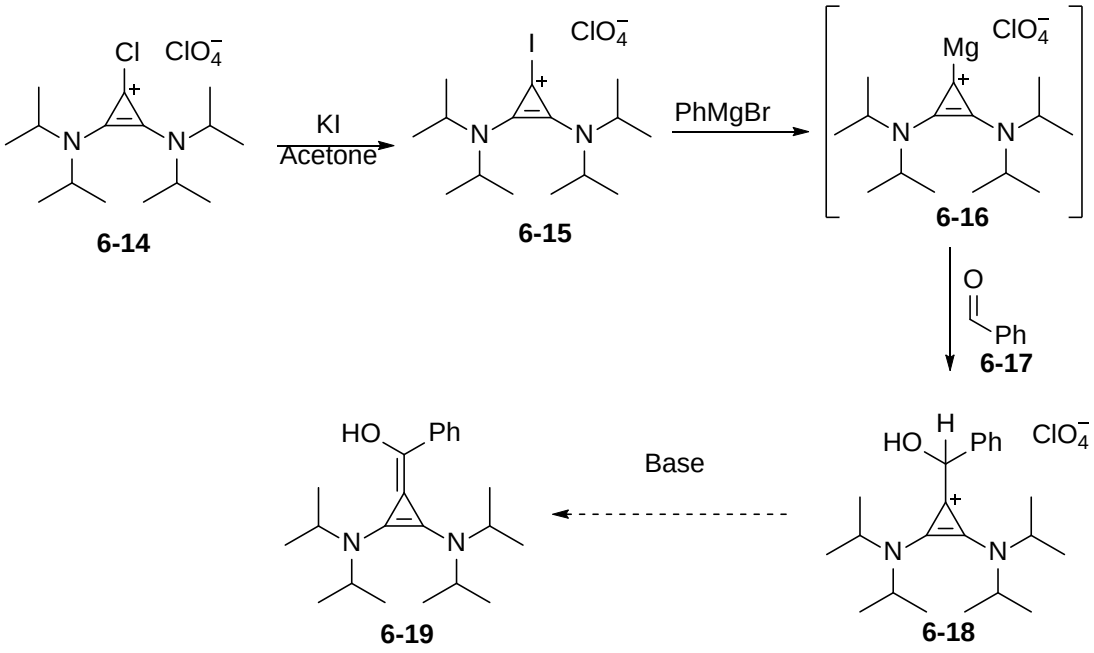
Scheme 6.2 Mechanistic Pathway of Homo-Benzoin Reaction Using BACs

Attempts to detect this intermediate spectroscopically lead to a series of singlets between 6 and 5 ppm in ^{1}H NMR, which are not characteristic of any particular species. One of these signals may be due to a small amount of benzoin product generated in situ (**6-12**). The rest of these signals could be due to the intermediates depicted in **Scheme 6.2**. This mixture was

[xv]When Ar = $C_6H_4CO_2Me$; Gravel, M.; *unpublished results*

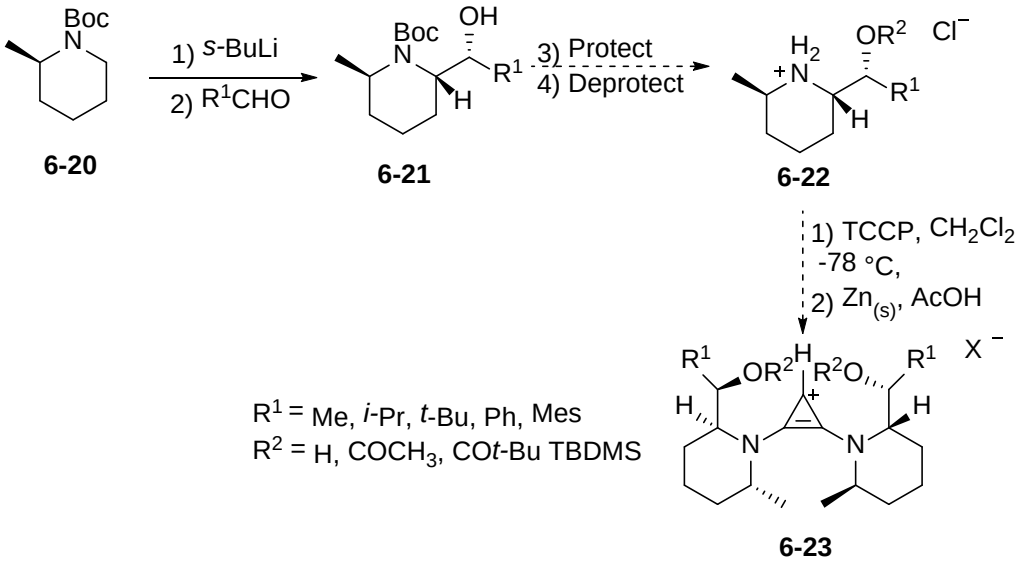
submitted to mass spectrometry and molecular ions with masses consistent with **6-8** to **6-10** were detected. The challenge in this case is in unambiguously detecting intermediate **6-10** and isolating it from the reaction matrix. These attempts have been unsuccessful to date.

A different way to access the Breslow intermediate may be available which circumvents these difficulties (**Scheme 6.3**). Yoshida and coworkers reported forming organomagnesium complex **6-17**, which when quenched with benzaldehyde generated adduct **6-18**.[213] There are few experimental details in this work but *i*-PrBAC can be used as an organocatalysts which makes the corresponding Breslow intermediate relevant, though not optimal. Conceivably, that Breslow intermediate could be formed by subjecting **6-18** to an appropriate base. By removing many side-products and interfering species from the reaction pathway this could lead to a detectable, or even isolable Breslow intermediate, which could in turn provide useful insights into designing better BAC catalysts.



Scheme 6.3 Grignard Route to Breslow Analogue

As a part of this work chiral BACs were prepared, and used successfully in the Stetter reaction (**Section 4.5**). While these results are promising, there is still much room for improvement in terms of activity and enantioselectivity in enantioselective catalysis with BACs. In this regard, the preparation of the 2,6-dimethylpiperidine catalyst introduced an interesting possibility. In this preparation a highly diastereoselective α-lithiation was achieved followed by addition of an alkyl iodide. It is known that lithiated intermediates can also add diastereoselectively to aldehydes.[214] Thus this reaction can easily serve as a starting point for a series of chiral catalysts possessing different functional groups (**Scheme 6.4**).

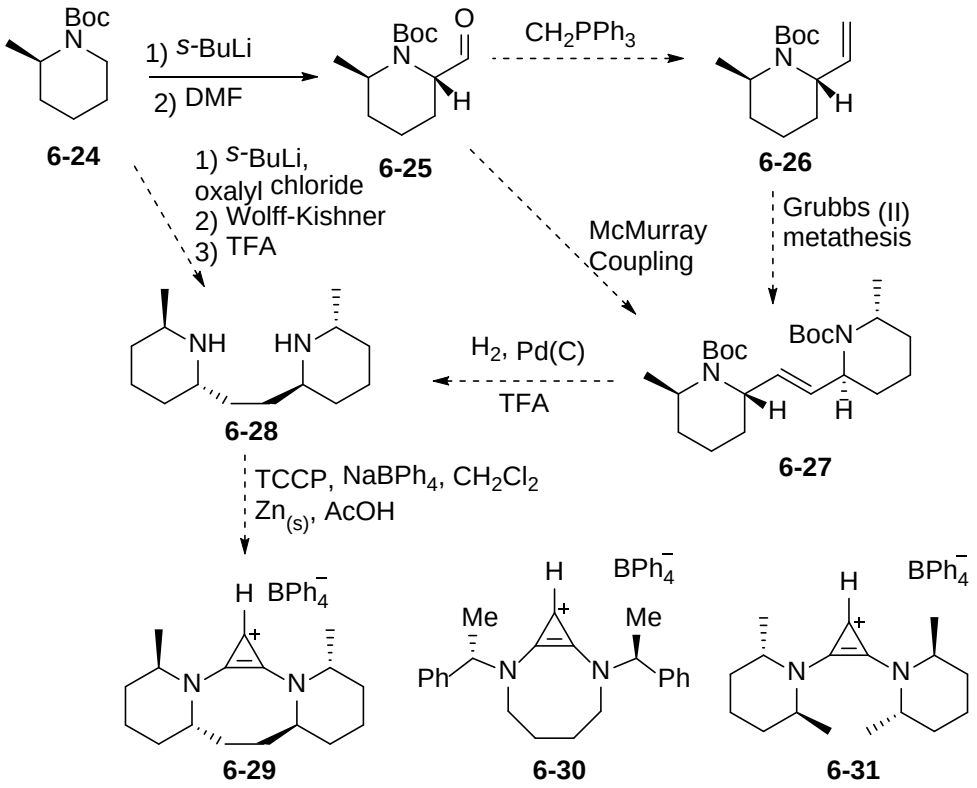


6-20 **6-21** **6-22** **6-23**

Scheme 6.4 Proposed Preparation of Chiral Bis(amino)cyclopropenium Salts

It may also prove possible to access a tethered catalyst such as **6-29** (**Scheme 6.5**). This would combine the rigidity of **6-30** with the higher enantioinduction of **6-31**, to potentially provide a catalyst capable of generating greater enantioselectivity. This catalyst could be prepared from amine **6-28** using olefin metathesis, followed by hydrogenation. Alternatively formylation followed by McMurray coupling may also be a valid route to amine **6-28** from *N*-

Boc-2-methylpiperidine. As more is learned about applying BACs to organocatalysis other widely available chiral secondary amines may serve as effective chiral moieties as part of a BAC scaffold.



Scheme 6.5 Proposed Preparation of Chiral Bicyclic Bis(amino)cyclopropenium Salts

In conclusion, the exploration of bis(amino)cyclopropenylidenes in *umpolung* reactions has been extremely successful. These catalysts have been successfully applied to the Stetter and aza-benzoin reactions, and this has lead to the discovery of new and useful reactivity. This newfound reactivity is not merely a curiosity, but has been found to be practical for many of the situations outlined above. These catalysts are in many ways complimentary to NHCs. Having a viable alternative to NHCs may prove invaluable for some applications going forward. This work will continue.

Chapter 7: Experimental

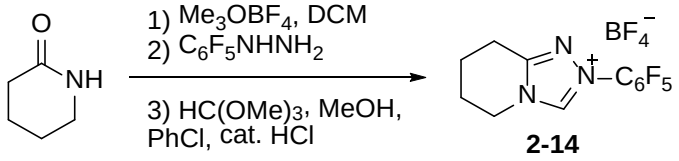
7.1 General Methods

Thin layer chromatography (TLC) was performed on Merck Silica Gel 60 F_{254} and was visualized with UV light, PMA or permanganate stain. For the Stetter and aza-benzoin work (**Chapter 4** and **Chapter 5**) silica gel SI 60 (40-63 μm) was purchased from Silicycle Chemical Division and was used for column chromatography. For cross-benzoin work (**Chapter 2**) silica gel SI 60 (40-63 μm) purchased from EMD was used for column chromatography as the products were found unstable to Silicycle silica. NMR spectra were recorded in $CDCl_3$ solution at 500 or 600 MHz for ^{1}H and 125 or 150 MHz for ^{13}C. The residual solvent protons (^{1}H) or the solvent carbon (^{13}C) were used as internal standards for chemical shifts. For reactions requiring internal standard bibenzyl was used. High-resolution mass spectra (HRMS) were obtained on a double focusing high-resolution spectrometer. Electrospray ionization was performed on a Qstar XL MS/MS system. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic and or intense peaks are reported. All samples were prepared as a film on a KBr disk or pellet using dry KBr (IR grade) for IR analysis. Melting points were measured on a melting point apparatus and are uncorrected. Anhydrous solvents were dried using a Braun Solvent Purification System and are stored under nitrogen (or argon) over 3 Å molecular sieves. Moisture content was analyzed by a Karl Fischer Coulometer 20D and at no time exceeded 25 ppm (60 ppm for CH_3CN) prior to use. Enantiomeric excess was assessed by an Agilent Technologies 1200 series chiral HPLC. Solid commercially available aldehydes were used directly with no further purification and all aldehydes which are liquid at room temperature were distilled prior to use. Commercial chalcone was recrystallized from ethanol before use. All reactions were carried out under an inert atmosphere unless stated

otherwise. Inert atmosphere was established via purging-filling 3 times using a double vacuum manifold and the inert gas was either UHP nitrogen or 4.8 argon. Bis(diisopropylamino)cyclopropenylidene was synthesized according to the procedure of Bertrand.[32] The procedures, spectra and full characterization data for several of the novel compounds described within this thesis are also available electronically.[215]

7.2 Experimental Details for Chapter 2

2-(Perfluorophenyl)-5, 6, 7, 8-tetrahydro-[1,2,4] triazolo[4,3-a]pyridin-2-ium tetrafluoroborate (2-14)

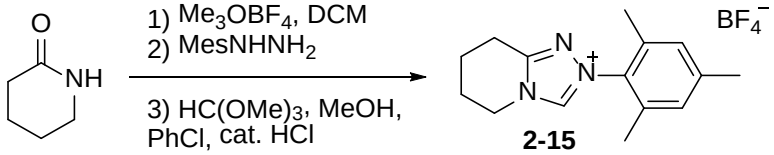


2-14

Trimethyloxonium tetrafluoroborate (5.99 g, 40.5 mmol) was added to a round bottomed flask which was placed under inert atmosphere. CH_2Cl_2 (40 mL) was added and after a short mixing period δ-valerolactam (3.96 g, 40.0 mmol) was added as a solution in CH_2Cl_2 (20 mL) at room temperature. The solution was diluted with CH_2Cl_2 to a final concentration of 0.5 M and stirred for 5 hours at room temperature. Pentafluorophenyl hydrazine (8.02 g, 40.5 mmol) (Alfa Aesar, purified by sublimation before use) was added in one portion and stirring continued for 72 hours. The solvent was evaporated *in vacuo* and co-evaporated with chlorobenzene to dryness. Chlorobenzene (8 mL) was added along with MeOH (16 mL) and trimethyl orthoformate (20 mL, 183 mmol) was added along with 4 drops of concentrated hydrochloric acid. The mixture was refluxed open air with fresh trimethyl orthoformate being added in (10 mL, 92 mmol) portions as necessary, and methanol being evaporated *in vacuo* from the mixture as needed. Conditions for the batch reported: 90 °C reflux for 2 days, solvent evaporated, fresh trimethyl

orthoformate, 120 °C reflux for 1 day, trimethyl orthoformate, 120 °C reflux for 1 day, solvent evaporated, fresh trimethyl orthoformate, 130 °C reflux for 1 day, solvent evaporated, fresh trimethyl orthoformate, 130 °C reflux for 1 day. The solvent was evaporated *in vacuo* to give the crude product as a viscous oil which was triturated with ethyl acetate to give the crude product as a beige solid. The solid was purified by recrystallization from hot ethyl acetate and diethyl ether to yield the product as a colorless crystalline material, 5.43 g (36% yield). **mp.** (°C) 222-223; ^{1}H NMR (500 MHz, acetone) δ 10.29 (br s, 1H), 4.71 (t, J = 5.5 Hz, 2H), 3.29 (t, J = 6.5 Hz, 2H), 2.80-2.26 (m, 2H), 2.23-2.19 (m, 2H); ^{13}C NMR (125 MHz, acetone) δ 156.2, 146.7, 144.6 (C-F, dtt, $^{1}J_{CF}$ = 251 Hz, $^{2}J_{CF}$ = 12.5 Hz, $^{3}J_{CF}$ = 4.4 Hz), 144.2 (C-F, dddd, $^{1}J_{CF}$= 256 Hz, $^{2}J_{CF}$= 13.4 Hz, $^{3}J_{CF}$= 3.8, 3.6 Hz), 139.3 (C-F, ddddd, $^{1}J_{CF}$= 249 Hz, $^{2}J_{CF}$= 13.8, 13.1, $^{3}J_{CF}$= 6.5, 2.6 Hz), 112.4 (C-F, app. t, $^{2}J_{CF}$= 13.6 Hz) , 47.8, 22.0, 21.6, 19.3; FTIR (KBr thin film) ν_{max} (cm^{-1}): 3137, 2967, 1596, 1526, 1075; HRMS (ESI^{+}) m/z calculated for $C_{12}H_9N_3F_5^{+}$ [M]$^{+}$: 290.0711; found: 290.0715.

2-(2,4,6-Trimethylphenyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyridin-2-ium tetrafluoroborate (2-15)

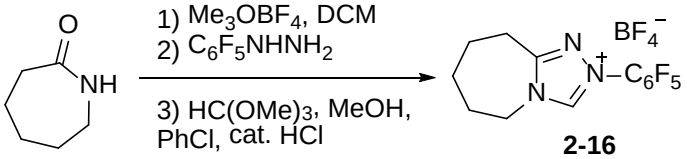


2-15

Trimethyloxonium tetrafluoroborate (492 mg, 3.33 mmol) was added to a round bottomed flask which was placed under inert atmosphere. CH_2Cl_2 (5 mL) was added and after a short mixing period δ-valerolactam (330 mg, 3.33 mmol) was added as a solution in CH_2Cl_2 (5 mL) at room temperature. The solution was diluted with CH_2Cl_2 to a final concentration of 0.5 M and stirred for 2 hours at room temperature. 2,4,6-Trimethylphenyl hydrazine (500 mg, 3.33

mmol) was added to the reaction in CH_2Cl_2 (4 mL) and methanol (0.5 mL) and stirred for 12 hours.[xvi] The solvent was evaporated *in vacuo* and co-evaporated with chlorobenzene to dryness. Chlorobenzene (2 mL) was added along with trimethyl orthoformate (4 mL, 37 mmol) and 0.3 mL of 2.0 M hydrogen chloride (in diethyl ether). The mixture was refluxed open to air for 11 hours at 130 °C and the solvent was evaporated *in vacuo.* Fresh trimethyl orthoformate was added (4 mL, 37 mmol) and the mixture was refluxed at 130 °C for 30 hours. The solvent was evaporated *in vacuo* to give the crude product as a viscous oil which was purified by column chromatography to give a brown solid. The solid was further purified by recrystallization from ethyl acetate and diethyl ether to give the pure product as crystalline tan needles, 151 mg (14% yield). R_f = 0.33 (5% MeOH/CH_2Cl_2); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 9.52 (br s, 1H), 6.82 (s, 2H), 4.55 (s, 2H), 3.08 (s, 2H), 2.35 (s, 3H), 2.20-2.05 (br s, 4H) 1.90 (s, 6H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 153.4, 143.6, 141.9, 135.3, 131.4, 129.8, 46.4, 21.6, 21.4, 21.3, 18.9, 17.4; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3130, 2962, 1580, 1450, 1058; **HRMS** (ESI^+) m/z calculated for $C_{15}H_{20}N_3^+$ $[M]^+$: 242.1651; found: 242.1657.

2-(Perfluorophenyl)-6,7,8,9-tetrahydro-5H-[1,2,4]triazolo[4, 3-a]azepin-2-ium tetrafluoroborate (2-16)



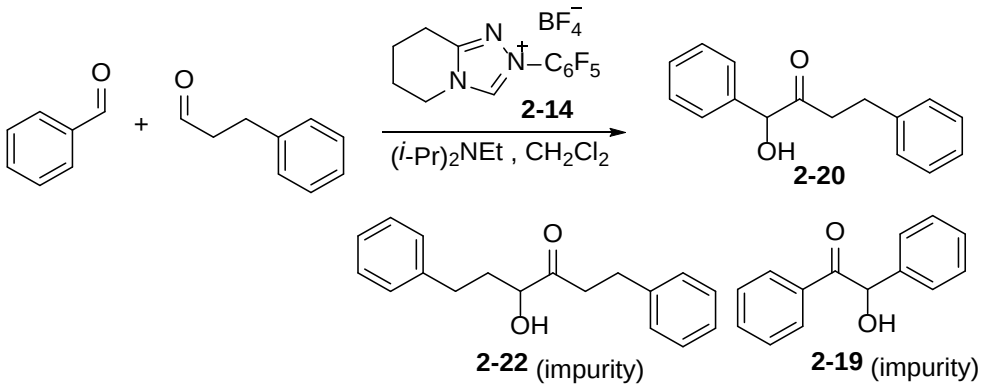
2-16

Trimethyloxonium tetrafluoroborate (747 mg, 5.05 mmol) was added to a round bottomed flask which was placed under inert atmosphere. CH_2Cl_2 (10 mL) was added and after a

[xvi] 2, 4, 6-Trimethylphenyl hydrazine was obtained by neutralization of its hydrochloride salt using a separatory funnel with 1N NaOH and diethyl ether. The ether layer was dried over sodium sulfate and the solvent was evaporated *in vacuo* to give the hydrazine as a red oil which was used directly.

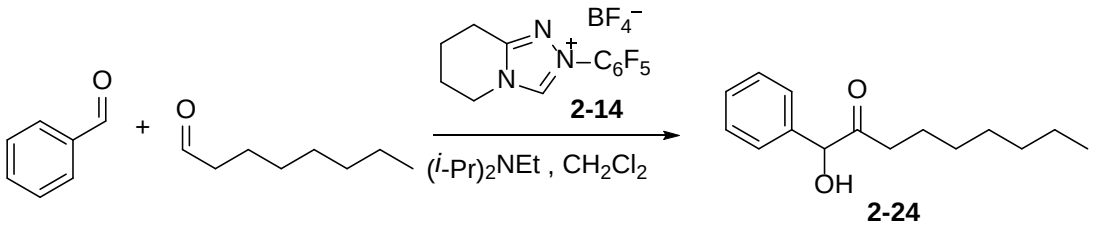
short mixing period caprolactam (571 mg, 5.05 mmol) was added as a solution in CH_2Cl_2 (10 mL) at room temperature. The solution was diluted with CH_2Cl_2 to a final concentration of 0.5 M and stirred for 3 hours at room temperature. Pentafluorophenyl hydrazine (1.00 g, 5.05 mmol) (Alfa Aesar, purified by sublimation before use) was added in one portion and stirring continued for 12 hours. The solvent was evaporated *in vacuo* and co-evaporated with chlorobenzene to dryness. Chlorobenzene (5 mL) was added along with MeOH (3 mL) and trimethyl orthoformate (4.4 mL, 40 mmol) was added along with 4 drops of concentrated hydrochloric acid. The mixture was refluxed at 130 °C open air with fresh trimethyl orthoformate being added in varying amounts as necessary, and methanol being evaporated *in vacuo* from the mixture as needed. Conditions for this batch: 6 hour reflux, trimethyl orthoformate (5.0 mL, 46 mmol) added, 12 hours reflux, solvent evaporated, trimethyl orthoformate (7 mL, 64 mmol) added, 10 hour reflux, trimethyl orthoformate (2 mL, 18 mmol) added, 12 hour reflux, solvent evaporated, trimethyl orthoformate (4 mL, 37 mmol) added, 6 hours reflux. The solvent was evaporated *in vacuo* to give the crude product as a viscous oil. The oil was purified by recrystallization from chloroform: diethyl ether to give a beige solid. The beige solid was recrystallized from toluene to yield the product as a white fluffy solid, 443 mg (22% yield). **^{1}H NMR** (500 MHz, $CHCl_3$) δ 10.05 (br s, 1H), 4.13 (s, 2H), 3.17 (s, 2H), 2.20-1.95 (br s, 4H), 1.86 (s, 2H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 159.7, 147.0, 143.7 (C-F, m, $^{1}J_{CF}$ = 259 Hz), 143.0 (C-F, m, $^{1}J_{CF}$= 262 Hz), 138.3 (C-F, m, $^{1}J_{CF}$= 260 Hz), 111.0 (C-F, m), 50.6, 29.6, 27.3, 26.1, 24.5 Additional carbon fluorine couplings were apparent but not resolved; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2986, 2905, 1688, 1580, 1190, 1178, 1080, 912, 902, 827; **HRMS** (ESI^+) m/z calculated for $C_{13}H_{11}N_3F_5^+$ $[M]^+$: 304.0867; found: 304.0877.

1-Hydroxy-1, 4-diphenylbutan-2-one (2-20)



The triazolium salt **2-14** (9 mg, 0.02 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (99 μL, 0.75 mmol), benzaldehyde 50 μL, 0.50 mmol) and CH_2Cl_2 (0.50 mL) were added. Lastly $(i\text{-Pr})_2NEt$ was added (87 μL, 0.50 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 30 minutes, then quenched by washing with 2 M HCl, and drying over Na_2SO_4. The crude reaction mixture was immediately purified by column chromatography (8% EtOAc/Hex, then 20% EtOAc/Hex) to yield 117.9 mg of the cross-benzoin product **2-20** contaminated with 13% of the homo-benzoin product from hydrocinnamaldehyde **2-22** and 2.6% of benzoin **2-19** which subsequent purification could not remove. The mixture was a white solid. This gives a computed yield of 84%. R_f = 0.22 (8% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.43-7.36 (m, 3H), 7.36-7.29 (m, 2H), 7.29-7.24 (m, 2H), 7.24-7.18 (m, 1H), 7.08 (d, *J* = 7.2 Hz, 2H), 5.07 (d, *J* = 3.9 Hz, 1H), 4.43 (d, *J* = 3.2 Hz, 1H), 2.96-2.88 (m, 1H), 2.86-2.78 (m, 1H), 2.78-2.64 (m, 2H); All spectra are consistent with those previously reported.[216]

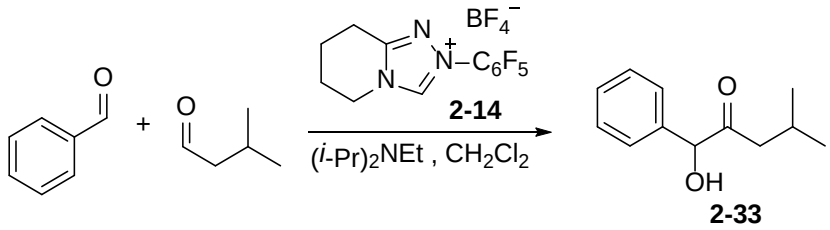
1-Hydroxy-1-phenylnonan-2-one (2-24)



2-24

The triazolium salt **2-14** (6.7 mg, 0.017 mmol) and internal standard bibenzyl (32 mg, 0.18 mmol) were added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Benzaldehyde (38 μL, 0.37 mmol), octanal (88 μL, 0.56 mmol) and CH_2Cl_2 (0.36 mL) were added. Lastly (i-Pr)$_2$NEt was added (63μL, 0.36 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 1 hour, then quenched with acetic acid (100 μL). The crude reaction mixture was immediately purified by column chromatography (12% EtOAc/Hex) to yield 78 mg (88% yield) of the cross-benzoin product **2-24** as a colorless oil. R_f = 0.3 (12% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.53-7.27 (m, 5H), 5.07 (s, 1H), 4.37 (s, 1H), 2.32 (ddq, J = 17.0, 7.0, 7.0 Hz, 2H), 1.58-1.42 (m, 2H), 1.25-1.20 (m, 2H), 1.20-1.10 (m, 6H), 0.85 (t, J = 7.5Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 209.9, 138.3, 129.2, 128.9, 127.6, 79.9, 38.0, 31.7, 29.1 29.0, 23.9, 22.7, 14.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3463, 2928, 2856, 1714, 1454, 700; All spectra are consistent with those previously reported.[217]

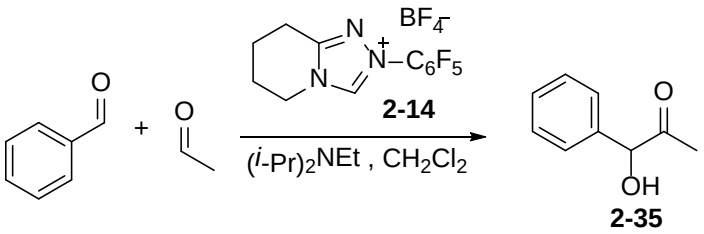
1-Hydroxy-4-methyl-1-phenylpentan-2-one (2-33)



2-33

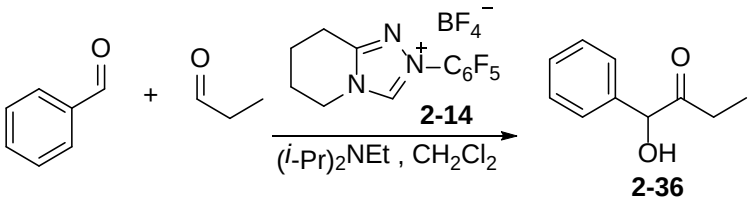
The triazolium salt **2-14** (6.7 mg, 0.017 mmol) and internal standard bibenzyl (32 mg, 0.18 mmol) were added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Benzaldehyde (38 μL, 0.37 mmol), isovaleraldehyde (58 μL, 0.54 mmol) and CH_2Cl_2 (0.36 mL) were added. Lastly $(i\text{-Pr})_2NEt$ was added (63 μL, 0.36 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 2 hour 20 min, then quenched with acetic acid (100 μL). The crude reaction mixture was immediately purified by column chromatography (10% EtOAc/Hex + 3% NEt_3) to yield 52 mg (71% yield) of the cross-benzoin product **2-33** as a pale yellow oil. R_f = 0.3 (12% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.40-7.28 (m, 5H), 5.04 (d, *J* = 4.0 Hz, 1H), 4.39 (d, *J* = 4.4 Hz, 1H), 2.27 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.18 (dd, *J* = 11.5, 5.0 Hz, 1H), 2.10 (ddq, *J* = 6.7, 6.7, 6.7 Hz, 1H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 209.3, 138.1, 129.1, 128.9, 127.7, 80.2, 46.9, 24.8, 22.6, 22.4; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3461, 2958, 1713, 1036, 760, 700; **HRMS** (EI^+) m/z calculated for $C_{12}H_{16}O_2$ $[M]^+$: 192.1150; found: 192.1139.

1-Hydroxy-1-phenylpropan-2-one (2-35)



The triazolium salt **2-14** (6.7 mg, 0.017 mmol) and internal standard bibenzyl (32 mg, 0.18 mmol) were added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Benzaldehyde (38 μL, 0.37 mmol), acetaldehyde (60 μL, 1.36 mmol) and CH_2Cl_2 (0.3 mL) were added. Lastly (i-Pr)$_2$NEt was added (63 μL, 0.36 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 1 hour, then quenched with acetic acid (100 μL). The crude reaction mixture was immediately purified by column chromatography (20% EtOAc/Hex + 1% NEt_3) to yield 42 mg (73% yield) of the cross-benzoin product as a colorless oil. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.40-7.31 (m, 5H), 5.09 (s, 1H), 4.60-4.10 (br. s, 1H), 2.08 (s, 3H); All spectra are consistent with those previously reported.[218]

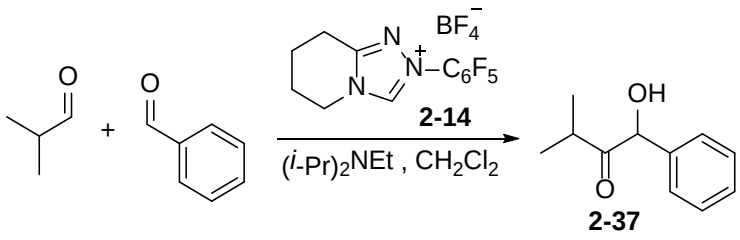
1-Hydroxy-1-phenylbutan-2-one (2-36)



The triazolium salt **2-14** (5 mg, 0.014 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Benzaldehyde (27 μL, 0.27 mmol), propanal (30 μL, 0.41 mmol) and CH_2Cl_2 (0.27 mL) were added. Lastly (i-Pr)$_2$NEt was added (46μL, 0.27 mmol) and the septum was then quickly exchanged for a cold

finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 2 hours, then quenched and washed with 1N HCl, and dried over Na_2SO_4. The material was passed through silica (EtOAc) to afford 42.5 mg of product **2-36** (theoretical yield 44.3 mg) contaminated with 3% benzoin and 5% homo-benzoin of propanal. Based on their respective molar masses this gives a computed yield of 89%. Further purification lead to significant isomerization/decomposition. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.42-7.32 (m, 5H), 5.11 (s, 1H), 4.42 (br s, 1H), 2.37 (dq, *J*=17.8, 7.4 Hz, 2H), 1.02 (t, *J* =7.3 Hz, 3H); All spectra are consistent with those previously reported.[219]

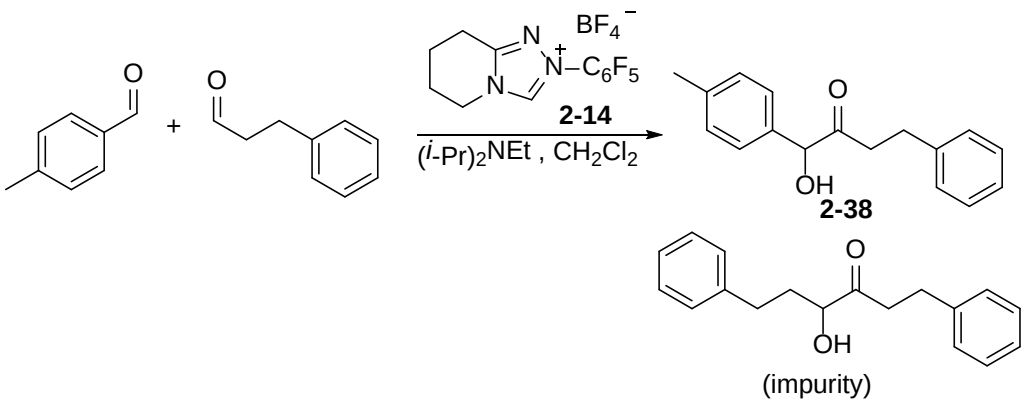
1-Hydroxy-3-methyl-1-phenylbutan-2-one (2-37)



The triazolium salt **2-14** (9 mg, 0.02 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Benzaldehyde (50 μL, 0.49 mmol), isobutyraldehyde 228 μL, 2.5 mmol) and CH_2Cl_2 (0.50 mL) were added. Lastly (*i*-Pr)$_2$NEt was added (87 μL, 0.50 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 16 hours, then quenched by washing with 2 M HCl, and drying over Na_2SO_4. The crude reaction mixture was immediately purified by column chromatography (10% EtOAc/Hex) to yield 59.8 mg (68% yield) of the cross-benzoin product **2-37** as a colorless oil. R_f = 0.25 (10% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.50-7.31 (m, 5H), 5.22 (d, *J* = 4.2 Hz, 1H), 4.38

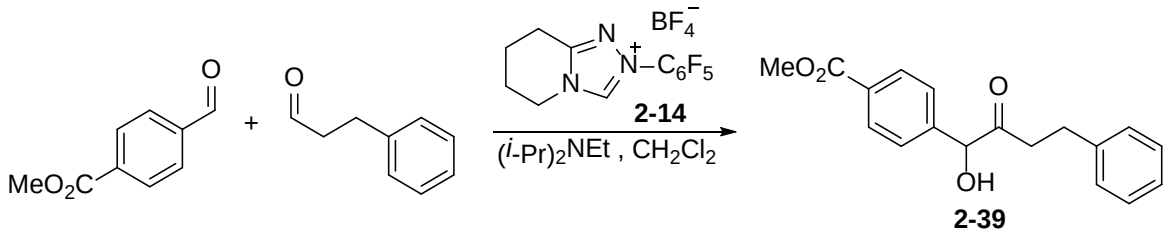
(d, J = 4.4 Hz, 1H), 2.70 (septet, J = 6.9 Hz, 1H), 1.14 (d, J = 7.1 Hz 3H), 0.84 (d, J = 6.7 Hz, 3H); All spectra are consistent with those previously reported.

1-Hydroxy-4-phenyl-1-(*p*-tolyl)butan-2-one (38)



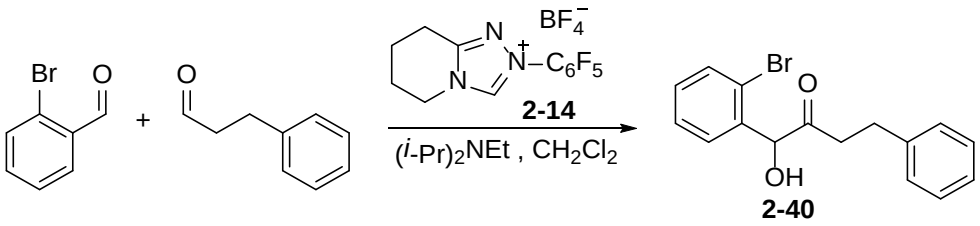
The triazolium salt **2-14** (9 mg, 0.02 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (99 μL, 0.75 mmol), *p*-tolualdehyde 59 μL, 0.50 mmol) and CH_2Cl_2 (0.50 mL) were added. Lastly $(i\text{-Pr})_2NEt$ was added (87 μL, 0.50 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 2 hours, then quenched by washing with 2 M HCl, and drying over Na_2SO_4. The crude reaction mixture was immediately purified by column chromatography (10% EtOAc/Hex) to yield 132.4 mg of the cross-benzoin product **2-38** contaminated with 14% of the homo-benzoin of hydrocinnamaldehyde which subsequent purification could not remove. This gives a computed yield of 91%. R_f = 0.25 (10% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.25-7.18 (m, 2H), 7.20-7.14 (m, 5H), 7.05 (d, J = 7.0 Hz, 2H), 5.00 (d, J = 4.3 Hz, 1H), 4.26 (d, J = 4.3 Hz, 1H), 2.95-2.85 (m, 1H), 2.82-2.74 (m, 1H), 2.74-2.59 (m, 2H), 2.62 (s, 3H); All spectra are consistent with those previously reported.

Methyl 4-(1-hydroxy-2-oxo-4-phenylbutyl)benzoate (2-39)



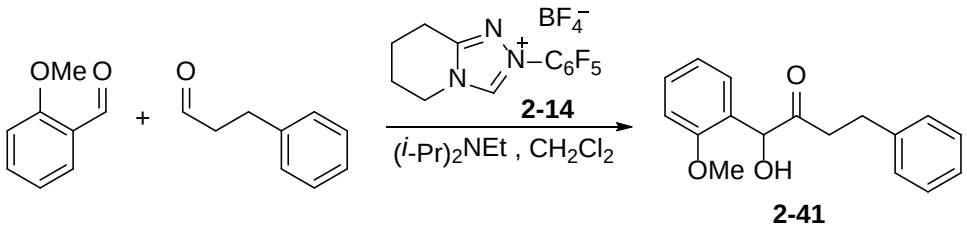
The triazolium salt **2-14** (6.7 mg, 0.017 mmol), methyl-4-formylbenzoate (58 mg, 0.35 mmol) and internal standard bibenzyl (32 mg, 0.18 mmol) were added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (69 μL, 0.52 mmol), and CH_2Cl_2 (0.35 mL) were added. Lastly (i-Pr)$_2$NEt was added (61 μL, 0.35 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 3 hours, then quenched with acetic acid (100 μL). The crude reaction mixture was immediately purified by column chromatography (25% EtOAc/Hex) to yield 64 mg (61% yield) of the cross-benzoin product **2-39** as a pale yellow oil. R_f = 0.3 (25% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.01 (d, J = 7.7 Hz, 2H), 7.35 (d, J = 7.7 Hz, 2H), 7.22-7.14 (m, 3H), 7.01 (d, J = 7.5 Hz, 2H), 5.08 (s, 1H), 4.41 (s, 1H), 3.91 (s, 3H), 2.90-2.84, (m, 1H), 2.84-2.75 (m, 1H), 2.75-2.66 (m, 1H), 2.66-2.58 (m, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 207.9, 166.7, 142.8, 140.1, 130.6, 130.3, 128.7, 128.3, 127.5, 126.5, 79.7, 52.4, 39.6, 29.7; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3460, 3028, 2952, 1720, 1610, 1282, 1113, 752, 700; **HRMS** (EI^+) m/z calculated for sodium adduct $C_{18}H_{18}O_4Na$ $[M]^+$: 321.1097; found: 321.1104.

1-(2-Bromophenyl)-1-hydroxy-4-phenylbutan-2-one (2-40)



The triazolium salt **2-14** (9 mg, 0.02 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (99 μL, 0.75 mmol), *o*-bromobenzaldehyde 58 μL, 0.50 mmol) and CH_2Cl_2 (0.50 mL) were added. Lastly $(i\text{-Pr})_2NEt$ was added (87 μL, 0.50 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 2 hours, then quenched by washing with 2 M HCl, and drying over Na_2SO_4. The crude reaction mixture was immediately purified by column chromatography (10% EtOAc/Hex) to yield 140.8 mg (89% yield) of the cross-benzoin product **2-40** as a colorless oil, which solidified to a white solid upon standing. R_f = 0.25 (10% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.30-7.22 (m, 3H), 7.22-7.16 (m, 3H), 7.09 (d, *J* = 7.3 Hz, 2H), 5.59 (d, *J* = 4.1 Hz, 1H), 4.45 (d, *J* = 4.2 Hz, 1H), 2.98-290 (m, 1H), 2.90-2.80 (m, 2H), 2.72-2.64 (m, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 208.0, 140.2, 137.4, 133.5, 130.3, 129.3, 128.6, 128.3, 128.2. 126.4, 123.9, 78.5, 39.7, 29.7; All spectra are consistent with those previously reported.

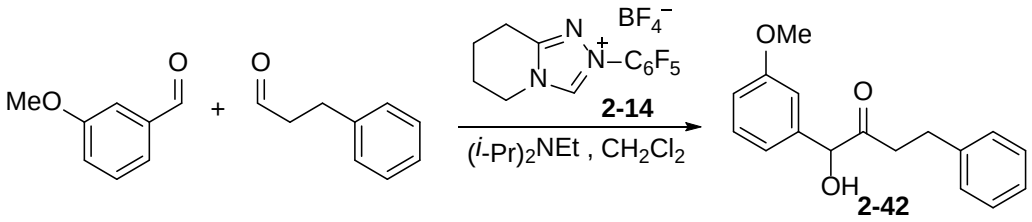
1-Hydroxy-1-(2-methoxyphenyl)-4-phenylbutan-2-one (2-41)



2-41

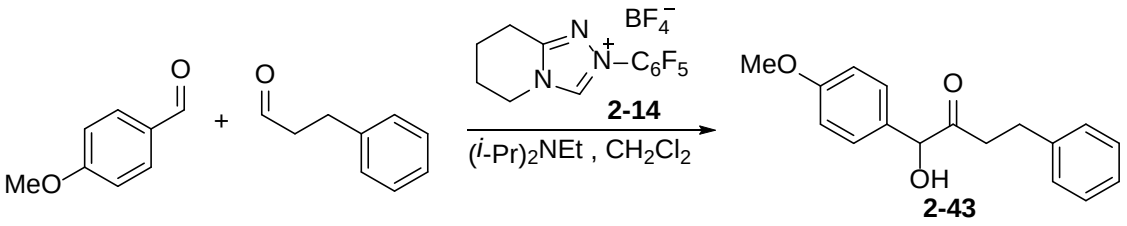
The triazolium salt **2-14** (6.7 mg, 0.017 mmol) and internal standard bibenzyl (32 mg, 0.18 mmol) were added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (69 μL, 0.52 mmol), *o*-methoxybenzaldehyde 48 mg, 0.35 mmol) and CH_2Cl_2 (0.35 mL) were added. Lastly (i-Pr)$_2$NEt was added (61 μL, 0.35 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 3 hours, then quenched with acetic acid (100 μL). The crude reaction mixture was immediately purified by column chromatography (15% EtOAc/Hex) to yield 95 mg (99% yield) of the cross-benzoin product **2-41** as a pale yellow oil. R_f = 0.3 (15% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.31 (dt, *J*= 8.5, 1.5 Hz, 1H), 7.28-7.15 (m, 4H), 7.08 (d, *J* = 7.0 Hz , 2H), 6.95 (t, *J* = 7.5 Hz , 1H), 6.88 (d, *J* = 8.5 Hz , 1H), 5.33 (d, *J* = 3.5 Hz , 1H), 4.21 (d, *J* = 7.0 Hz , 1H), 3.79 (s, 3H), 2.94 (ddd, *J* = 14.5, 9.0, 6.5 Hz, 1H), 2.82 (ddd, *J* = 14.5, 9.0, 6.5 Hz, 1H), 2.71 (ddd, *J* = 17.0, 8.5, 6.5 Hz, 1H), 2.63 (ddd, *J* = 17.3, 9.0, 6.1, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 209.0, 157.0, 140.7, 130.1, 129.4, 128.6, 128.4, 126.6, 126.3, 121.3, 111.3, 75.3, 55.6, 39.3, 29.9; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3469, 3027, 2938, 2839, 1714, 1600, 1492, 1248, 1050, 755, 700; **HRMS** (EI^+) m/z calculated for $C_{17}H_{18}O_3$ $[M]^+$: 270.1256; found: 270.1247.

1-Hydroxy-1-(3-methoxyphenyl)-4-phenylbutan-2-one (2-42)



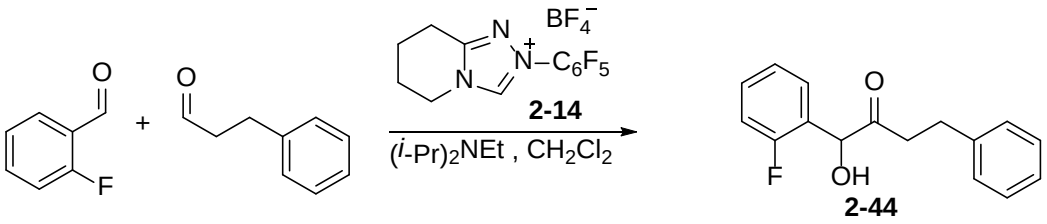
The triazolium salt **2-14** (5.2 mg, 0.014 mmol) and internal standard bibenzyl (27 mg, 0.15 mmol) were added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (59 μL, 0.45 mmol), *m*-methoxybenzaldehyde 36 μL, 0.29 mmol) and CH_2Cl_2 (0.29 mL) were added. Lastly (i-Pr)$_2$NEt was added (51 μL, 0.29 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 3 hours, then quenched with acetic acid (100 μL). The crude reaction mixture was immediately purified by column chromatography (20% EtOAc/Hex + 3% NEt_3) to yield 65 mg (82% yield) of the cross-benzoin product **2-42** as a pale yellow oil. R_f = 0.3 (20% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.27-7.21 (m, 3H), 7.20-7.18 (m, 1H), 7.04 (d, J = 7.0 Hz, 2H), 6.88 (dd, J = 8.5, 2.5 Hz, 2H), 6.80 (t, J = 1.6 Hz, 1H), 5.01 (s, 1H), 4.40-4.20 (br. s, 1H), 3.78 (s, 3H), 2.94-2.86 (m, 1H), 2.84-2.75 (m, 1H), 2.73-2.60 (m, 2H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 208.6, 160.2, 140.3, 139.5, 130.2, 128.7, 128.3, 126.5, 120.0, 114.6, 112.7, 79.9, 55.4, 39.5, 29.8; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3462, 3027, 2937, 1714, 1600, 1488, 1453, 1260, 1156, 1047, 784, 749, 699; **HRMS** (EI^+) m/z calculated for $C_{17}H_{18}O_3$ $[M]^+$: 270.1256; found: 270.1256.

1-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (2-43)



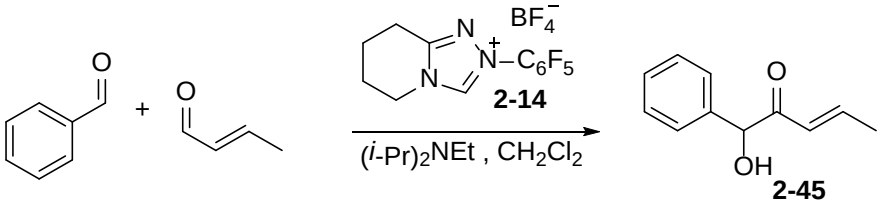
The triazolium salt **2-14** (6.7 mg, 0.018 mmol) and internal standard bibenzyl (32 mg, 0.15 mmol) were added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (69 μL, 0.52 mmol), *p*-methoxybenzaldehyde (43 μL, 0.35 mmol) and CH_2Cl_2 (0.35 mL) were added. Lastly $(i\text{-Pr})_2NEt$ was added (61 μL, 0.35 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 3 hours, then quenched with acetic acid (100 μL). The crude reaction mixture was immediately purified by column chromatography (20% EtOAc/Hex) to yield 95 mg (99% yield) of the cross-benzoin product **2-43** as a pale yellow oil. R_f = 0.3 (20% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.24 (t, *J* = 7.5 Hz, 2H), 7.21-7.15 (m, 3H), 7.03 (d, *J* = 7.0 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.99 (s, 1H), 4.34-4.26 (br. s, 1H), 3.80 (s, 3H), 2.88 (ddd, *J* = 14.5, 8.6, 7.0 Hz, 1H), 2.84-2.76 (m, 1H), 2.74-2.60 (m, 2H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 209.0, 160.0, 140.4, 130.0, 128.8, 128.6, 128.3, 126.4, 114.6, 79.5, 55.4, 39.6, 29.8; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3463, 3028, 2934, 2837, 1713, 1609, 1585, 1511, 1454, 1251, 1175, 1031, 835, 750, 700 **HRMS** (EI^+) m/z calculated for $C17H_{18}O_3$ $[M]^+$: 2701256; found: 270.1256.

1-Hydroxy-1-(4-methoxyphenyl)-4-phenylbutan-2-one (2-44)



The triazolium salt **2-14** (6.7 mg, 0.018 mmol) and internal standard bibenzyl (32 mg, 0.15 mmol) were added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (69 μL, 0.52 mmol), *o*-fluorobenzaldehyde (36 μL, 0.35 mmol) and CH_2Cl_2 (0.35 mL) were added. Lastly $(i\text{-Pr})_2NEt$ was added (61 μL, 0.35 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 3 hours, then quenched with acetic acid (100 μL). The crude reaction mixture was immediately purified by column chromatography and pTLC (15% EtOAc/Hex) to yield 69 mg of the cross-benzoin product **2-44** as well as oxidized material which could not be removed (corrected yield 64%) as a pale yellow oil. R_f = 0.3 (15% EtOAc/Hex); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.09-7.12 (m, 9H), 5.38 (s, 1H), 4.31 (br s, 1H), 3.47-2.66 (m, 4H). All spectra for this substance are consistent with what is reported in the literature.[216]

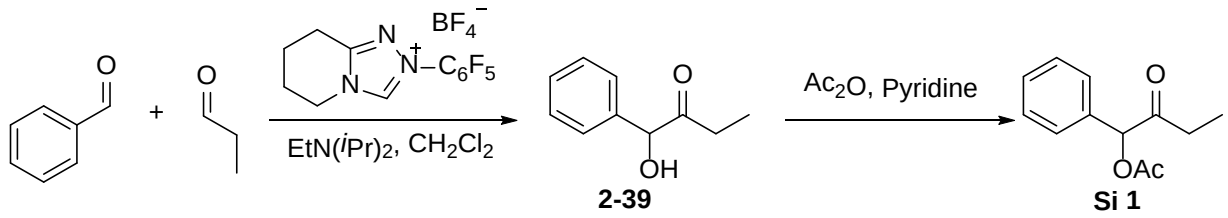
(E)-1-hydroxy-1-phenylpent-3-en-2-one (2-45)



The triazolium salt **2-14** (6.7 mg, 0.018 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Crotonaldehyde

(44 μL, 0.53 mmol), benzaldehyde (36 μL, 0.36 mmol) and CH_2Cl_2 (0.35 mL) were added. Bibenzyl (33 mg, 0.18 mmol) was added as internal standard. Lastly $(i\text{-Pr})_2$NEt was added (61 μL, 0.36 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 60 minutes then quenched with acetic acid and passed through silica. The solvent was removed *in vacuo* and the crude reaction mixture was purified via column chromatography (10% EtOAc:Hex) to give 6.6 mg (11%) of cross-benzoin product as a while solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.39-7.30 (m, 5H), 7.04 (ddt, *J*=15.5, 6.9, 6.9 Hz, 1H), 6.14 (ddd, *J*=15.5, 3.1, 1.5 Hz, 1H), 5.19 (d, *J*=4.3 Hz, 1H), 4.47 (d, *J*=4.5 Hz, 1H), 1.82 (t, *J*=5.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 197.3, 146.3, 138.4, 129.2, 128.8, 128.0, 126.3, 78.8, 18.7; **FTIR** (KBr thin film) ν_{max} (cm^{-1}):3449, 3032, 2916, 1690, 1630, 1494, 1441, 1379, 1293, 1193, 1052; **HRMS** (ESI^+) m/z calculated for $C_{11}H_{11}O_2$ $[M]^+$: 176.0837; found: 176.0837.

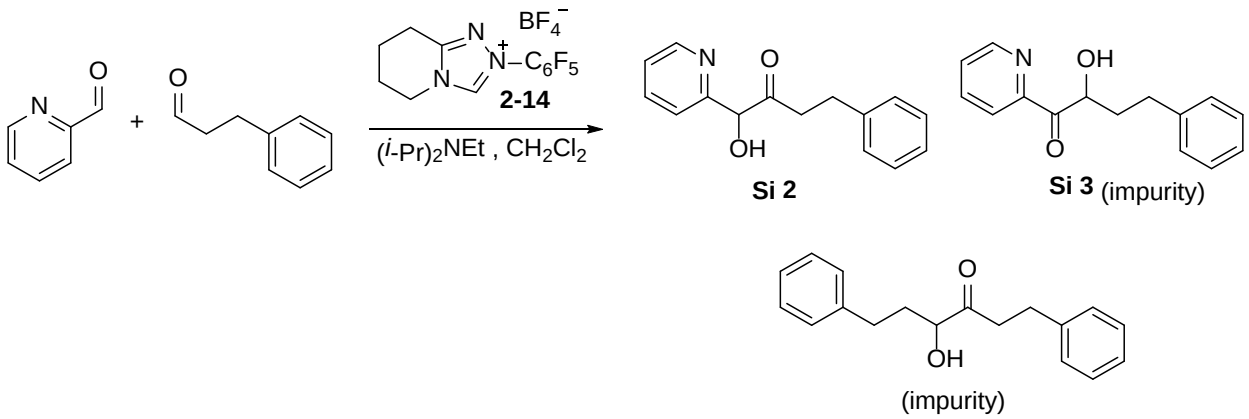
2-Oxo-1-phenylbutyl acetate (Si 1)



The triazolium salt (9 mg, 0.02 mmol) was added to a test tube with a Schlenk takeoff which was then fitted with a septum and placed under inert atmosphere. Benzaldehyde (50 μL, 0.49 mmol), propanal (54 μL, 0.74 mmol) and CH_2Cl_2 (0.50 mL) were added. Lastly Hunig's base was added (87 μL, 0.50 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 2 hours then cooled to room temperature and CH_2Cl_2 was evaporated with rotary evaporator.

Acetic anhydride (2.0 mL, 18 mmol), and pyridine (5 mL) were added and the mixture was stirred under argon at room temperature for 18 hrs. The crude mixture was then passed through silica (10% EtOAc, Hex) and purified via column chromatography, (5% EtOAc, Hex, 15% EtOAc, Hex), to give 64.1 mg of the acylated product contaminated with 5% of the opposite cross product as a yellow oil. This amounted to 62% yield of the desired cross product. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.47 (s, 5H), 5.98 (s, 1H), 2.50 (dq, *J* = 18.0, 7.3 Hz, 1H), 2.36 (dq, *J* = 18.0, 7.3 Hz, 1H), 2.19 (s, 3H), 1.00 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 204.7, 170.4, 133.6, 129.4, 129.2, 128.2, 80.6, 32.0, 20.8, 7.4; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2980, 1742, 1496, 1373, 1239; **HRMS** (EI^+) m/z calculated for $C_{12}H_{14}O_3$ $[M]^+$: 206.0943; found: 206.0936.

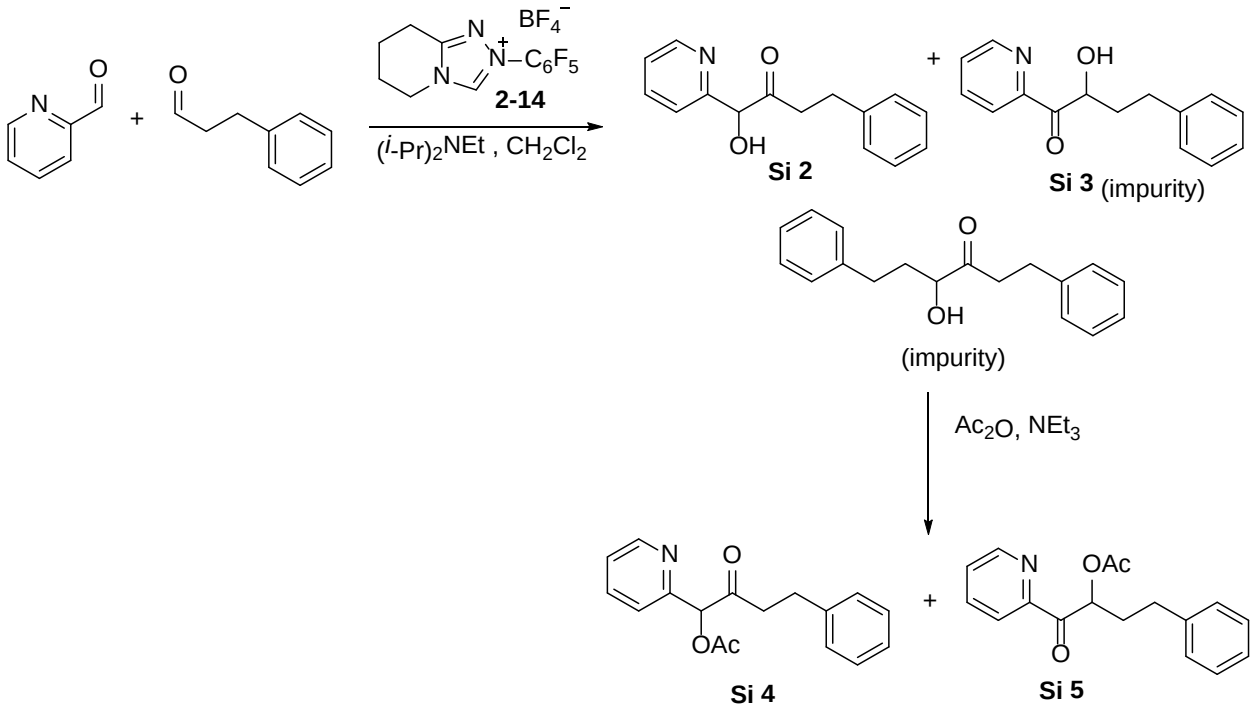
1-(2-Pyridyl)-1-hydroxy-4-phenylbutan-2-one (Si 2)



The triazolium salt **2-14** (6.7 mg, 0.018 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (69 μL, 0.52 mmol), pyridine-2-carboxaldehyde (34 μL, 0.36 mmol) and CH_2Cl_2 (0.35 mL) were added. Bibenzyl (33 mg, 0.18 mmol) was added as internal standard. Lastly (*i*-Pr)$_2$NEt was added (61 μL, 0.36 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 120 minutes, then quenched with acetic acid. Overall ratio of 0 : 3.2 : 2.6 : 1 of homo-aryl :

aryl-alcohol : aryl-ketone : homo-alkyl products. Products were unstable to column chromatography.

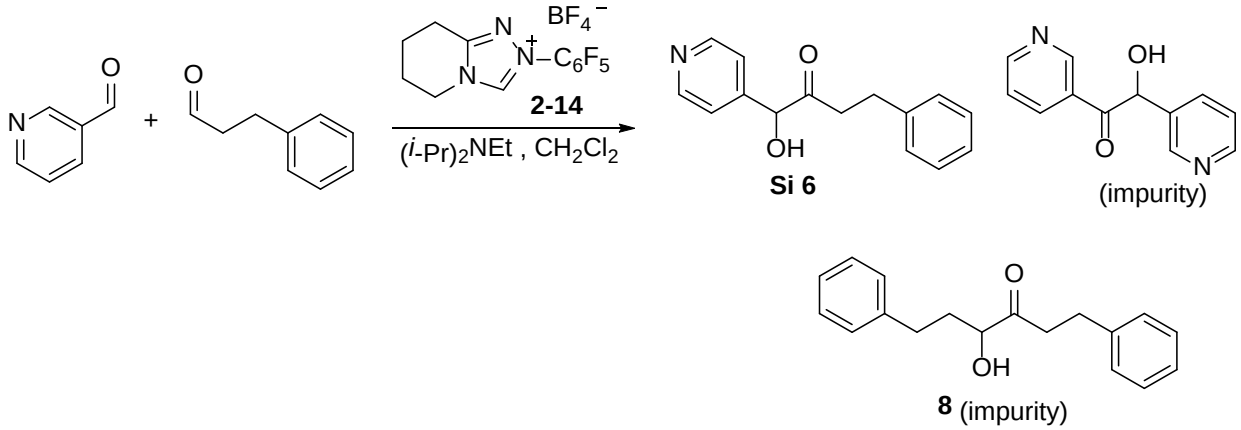
2-Oxo-4-phenyl-1-(pyridin-2-yl)butyl acetate (Si 4) and 1-oxo-4-phenyl-1-(pyridin-2-yl)butan-2-yl acetate (Si 5)



The triazolium salt **4** (6.7 mg, 0.018 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (69 μL, 0.52 mmol), pyridine-2-carboxaldehyde (34 μL, 0.36 mmol) and CH_2Cl_2 (0.35 mL) were added. Bibenzyl (33 mg, 0.18 mmol) was added as internal standard. Lastly $(i\text{-Pr})_2NEt$ was added (61 μL, 0.36 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 60 minutes. The solvent was evaporated in vacuo and acetic anhydride (1.0 mL, 110 mmol) and 100 μL triethyl amine were added. After 1 hour, the reaction was quenched with water and extracted in a sep. funnel with CH_2Cl_2. The crude product was purified via gradient column chromatography (20% EtOAc : hexanes to 1:1 EtOAc : hexanes) to give 12.9 mg (13%) of the

acylated desired product **Si 4** and 8.0 mg (8%) of the opposite cross-benzoin product **Si 5**, both as yellow oils. **Si 4** (minor) **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.85 (s, 1H), 8.03 (d, *J*=7.8 Hz, 1H), 7.84 (dd, *J*=7.6, 1.3 Hz, 1H), 7.48 (dd, *J*=7.1, 5.1 Hz, 1H), 7.30-7.16 (m, 5H), 6.39 (dd, *J*=8.9, 3.3 Hz, 1H), 2.84 (t, *J*=8.2 Hz, 2H), 2.41-2.36 (m, 1H), 2.19 (m, 4H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 196.9, 170.8, 151.7, 149.2, 141.2, 137.2, 128.8, 128.6, 128.5, 127.8, 126.3, 122.8, 75.4, 32.7, 32.1, 20.9; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3061, 3027, 2928, 1740, 1712, 1583, 1497, 1455, 1438, 1373, 1230, 1080; **HRMS** (EI^+) m/z calculated for $C_{17}H_{18}O_3N$ $[M+1]^+$: 284.1273; found: 284.1280. **Si 5** (major) **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.58 (d, *J*=4.8 Hz, 1H), 7.69 (td, *J*=7.8, 1.6 Hz, 1H), 7.39 (d, *J*=7.8 Hz, 1H), 7.29 (dd, *J*=10.2, 5.3, Hz, 1H), 7.21 (t, *J*=7.3 Hz, 2H), 7.16 (dd, *J*=14.5, 7.2 Hz, 1H), 7.09 (d, *J*=7.2 Hz, 2H), 6.14 (s, 1H), 3.01-2.91 (m, 2H), 2.90-2.2.81 (m, 2H), 2.22 (m, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 203.0, 170.2, 153.6, 149.8, 140.8, 137.4, 128.5, 126.2, 124.0, 122.8, 81.6, 41.2, 29.3, 21.4, 20.9; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3028, 2931, 1733, 1589, 1573, 1497, 1472, 1454, 1435, 1372, 1229, 1051; **HRMS** (EI^+) m/z calculated for $C_{17}H_{17}O_3N$ $[M]^+$: 283.1208; found: 283.1211.

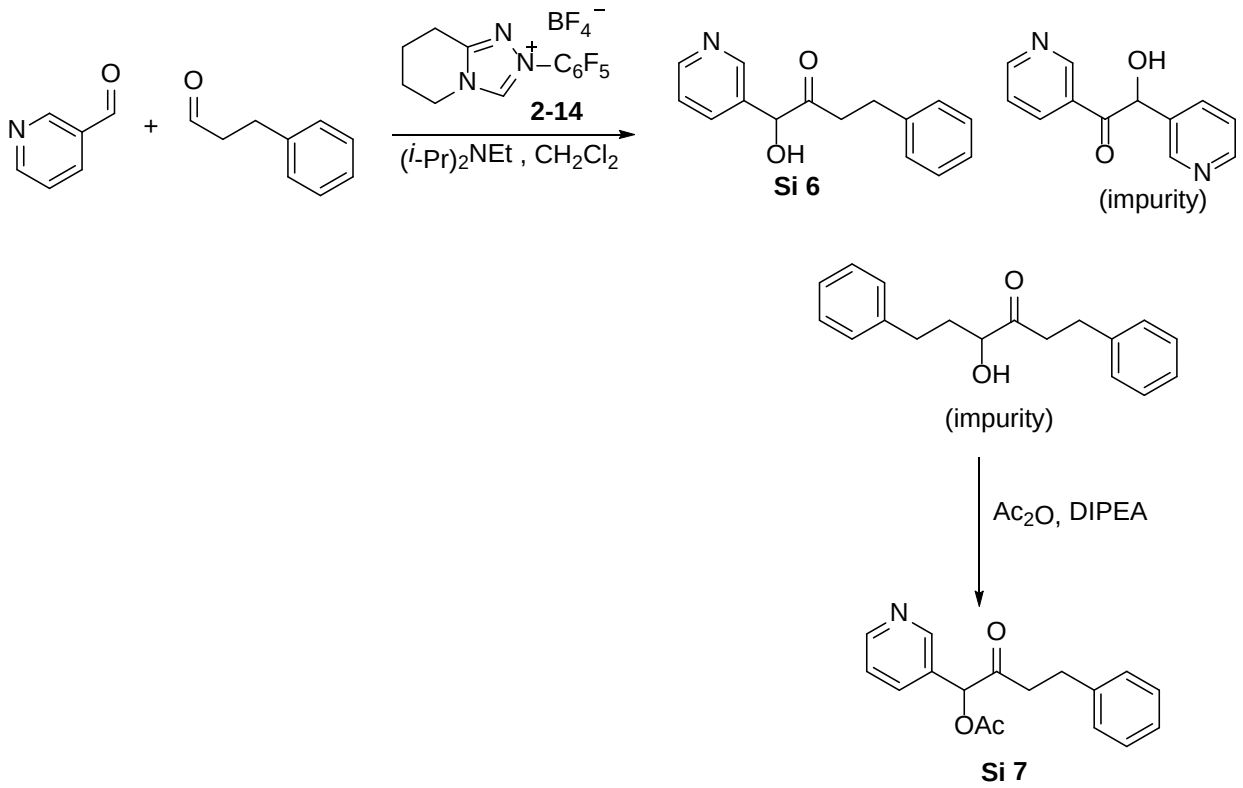
1-(3-Pyridyl)-1-hydroxy-4-phenylbutan-2-one (Si 6)



The triazolium salt **2-14** (6.7 mg, 0.018 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere.

Hydrocinnamaldehyde (69 μL, 0.52 mmol), pyridine-2-carboxaldehyde (34 μL, 0.36 mmol) and CH_2Cl_2 (0.35 mL) were added. Bibenzyl (33 mg, 0.18 mmol) was added as internal standard. Lastly $(i\text{-Pr})_2NEt$ was added (61 μL, 0.36 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 120 minutes, then quenched with acetic acid. Overall ratio of 1 : 6.4 : 0 : 1.8 of homo-aryl : aryl-alcohol : aryl-ketone : homo-alkyl products. Products were unstable to column chromatography.

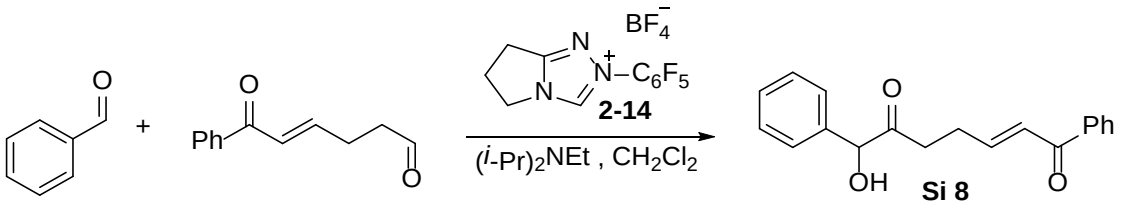
2-Oxo-4-phenyl-1-(pyridin-4-yl)butyl acetate (Si 7)



The triazolium salt **2-14** (6.7 mg, 0.018 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. Hydrocinnamaldehyde (69 μL, 0.52 mmol), pyridine-2-carboxaldehyde (34 μL, 0.36 mmol) and CH_2Cl_2 (0.35 mL) were added. Bibenzyl (33 mg, 0.18 mmol) was added as internal standard.

Lastly (i-Pr)$_2$NEt was added (61 μL, 0.36 mmol) and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 60 minutes then the solvent was removed *in vacuo* and replaced with acetic anhydride (1.0 mL, 110 mmol), and 100 μL triethyl amine. After one hour the reaction mixture was worked up via quenching with water and extraction in a sep. funnel with CH_2Cl_2. The crude product was subsequently purified via column chromatography (45% EtOAc:Hex), and pTLC (45% EtOAc:Hex) to give 44.9 mg (45%) of acylated cross-benzoin product as a yellow oil. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.64-8.60 (m, 2H), 7.59 (d, *J*=7.8, 1H), 7.30-7.23 (m, 1 H), 7.20 (t, *J*=7.1 Hz, 2H), 7.15 (t, *J*=7.2 Hz, 1H), 7.05 (d, *J*=7.3 Hz, 2H), 5.98 (s, 1H), 2.90-2.76 (m, 3H), 2.74-2.65 m, 1H), 2.18 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 202.7, 170.2, 150.7, 149.4, 140.3, 135.6, 129.3, 128.7, 128.4, 126.4, 124.0, 78.4, 40.7, 29.3, 20.8; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3029, 2933, 1732, 1577, 1497, 1479, 1454, 1427, 1373, 1231, 1050; **HRMS** (EI^+) m/z calculated for $C_{17}H_{17}O_3N[M]^+$: 283.1208; found: 283.1207.

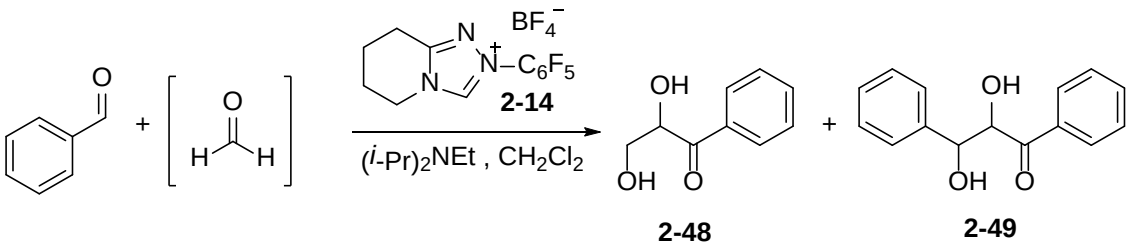
(E)-7-Hydroxy-1,7-diphenylhept-2-ene-1,6-dione (Si 8)



The ketone was produces via witting reaction from the corresponding aldehyde according to known methods.[220] The triazolium salt (5 mg, 0.014 mmol) was added to a test tube with a Schlenk take-off which was then fitted with a septum and placed under inert atmosphere. The aliphatic aldehyde (44 μL, 0.27 mmol), benzaldehyde (27 μL, 0.27 mmol) and CH_2Cl_2 (0.26 mL) were added. Lastly (i-Pr)$_2$NEt was added (46 μL, 0.27 mmol) and the septum was then quickly

exchanged for a cold finger. Once inert atmosphere was re-established the flask was sealed and heated to 70 °C for 120 minutes then quenched with acetic acid and passed through silica. The solvent was removed *in vacuo* and the crude reaction mixture was purified via column chromatography (25% EtOAc:Hex) to give 7.7 mg (16%) of cross-benzoin product as well as the cyclized material as a yellow solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.85 (d, *J*=7.1 Hz, 2H), 7.55 (t, *J*=8.5 Hz, 1H), 7.45 (t, *J*=7.8, 2H), 7.39-7.31 (m, 5H), 6.86-6.80 (m, 1H), 6.78 (t, *J*=15.4 Hz, 1H), 5.12 (s, 1H), 4.30-4.20 (br. s, 1H), 2.68-2.45 (m, 4H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 208.1, 190.6, 146.6, 138.0, 137.8, 133.0, 129.4, 129.1, 128.8, 128.7, 127.5, 127.0, 80.1, 36.3, 26.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}):3457, 2928, 1717, 1670, 1620, 1579, 1493, 1448, 1286, 1059, 669; **HRMS** (ESI^+) m/z calculated for $C_{19}H_{18}O_3$ $[M]^+$: 294.1256; found: 294.1256.

2,3-Dihydroxy-1,3-diphenylpropan-1-one and 2,3-dihydroxy-1-phenylpropan-1-one

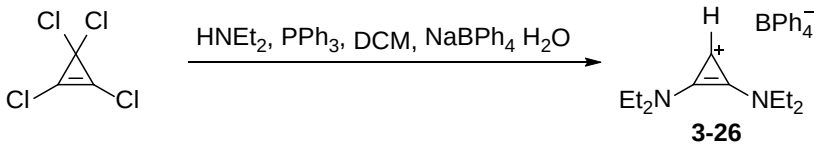


Solid paraformaldehyde polymer (64 mg, 2.6 mmol), triazolium salt (8 mg, 0.05 mmol) were charged in a microwave vial under argon. Benzaldehyde (43 μL, 0.42 mmol) was added followed by CH_2Cl_2 (420 μL) and DIPEA (45 μL, 0.26 mmol). The mixture was heated with microwave at 70 °C for 1 hour and purified via column chromatography (15% EtOAc: Hex) then pTLC (same) to give 2.3 mg (4.5%) and 3.9 mg (5.6%) of benzoin products that have been tentatively identified as **2-48** and **2-49** in nearly pure form, as white solids. Benzoin product **2-49** **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.87 (d, *J*=7.5 Hz, 2H), 7.45 (t, *J*=7.3 Hz, 3H), 7.36 (t, *J*=7.2 Hz, 2H), 7.30 (t, *J*=7.6 Hz, 3H), 4.50 (d, *J*=11.6 Hz, 1H), 4.41 (s, 1H), 3.67 (d, *J*=11.6 Hz, 1H);

2.35 (br s, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 200.7, 138.9, 133.3, 130.8, 130.1, 129.2, 128.6, 128.4, 125.3, 83.0, 69.1; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3354, 3061, 3028, 2930, 16745, 1597 1580, 1491, 1447, 1378, 1317, 1260, 1177, 1098, 1050, 1001, 947; **HRMS** (CI+NH_3) m/z calculated for $C_{15}H_{18}O_3N$ $[M]^+$: 260.1286; found: 260.1284 Benzoin product **2-48 ^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.94 (d, *J*=7.7 Hz, 2H), 7.63 (t, *J*=7.1 Hz, 1H), 7.52 (t, *J*=7.3 Hz, 2H), 5.17 (s, 1H), 4.02 (d, *J*=11.2 Hz, 2H), 3.76 (dd, *J*=11.1, 0.2 Hz, 1H), missing OH; Insufficient material for **^{13}C NMR, FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3412, 3063, 2926, 1718, 1598, 1496, 1449, 1378, 1317, 1261, 1158, 1071, 1025; **HRMS** (CI +NH_3) m/z calculated for $C_1H_{14}O_3N$ $[M]^+$: 184.0973; found: 184.09663.

7.3 Experimental Details for Chapter 3

Bis(diethylamino)cyclopropenium tetraphenylborate (3-26)



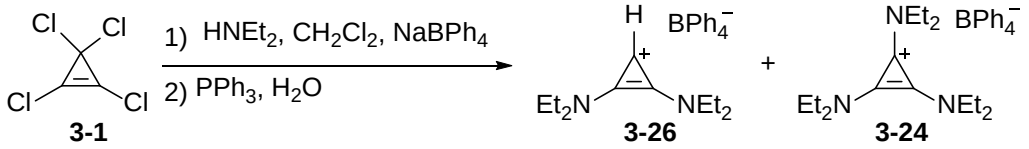
3-26

Diethylamine (2.36 mL, 22.5 mmol) was added dropwise to a solution of tetrachlorocyclopropene (0.690 mL, 5.64 mmol) in CH_2Cl_2 (100 mL) at −78 °C under nitrogen. The reaction mixture was warmed to room temperature over 3 hours, then cooled back down to −78 °C. Triphenylphosphine (1.48 g, 5.64 mmol) was then quickly added and the mixture was warmed to room temperature. Distilled water (20 mL) was added and the two-phase mixture was stirred vigorously for 16 hours. Sodium tetraphenylborate (1.93 g, 5.64 mmol) was then added and the reaction was transferred to a separatory funnel with CH_2Cl_2. The organic layer was washed with 0.5 M HCl, saturated aqueous $NaHCO_3$, and H_2O, then dried over Na_2SO_4 and concentrated *in vacuo*.

The resulting crude oil was purified by recrystallization from MeOH/water, by first dissolving it in hot MeOH. Some material failed to dissolve and instead formed a gum at the bottom of the flask. The gum was removed by hot vacuum filtration through a piece of filter paper. Then water was added to the solution until it turned cloudy. It was then left to stand at room temperature until crystallization was complete. The crude product was filtered and washed with Et_2O to give a white solid. On occasion the crystals were off white or pale yellow and a second recrystallization from MeOH was necessary to remove residual phosphine impurities.

While pre-catalyst **3-26** at this stage was often pure as judged by ^{1}H NMR analysis, a second recrystallization from CH_2Cl_2/Et_2O was occasionally required. The white solid was dissolved in a minimum of hot CH_2Cl_2 and Et_2O was added until the entire mixture turned cloudy. The mixture was then left to cool down to room temperature and crystallize. Once the material had crystallized, it was filtered, rinsed with Et_2O and dried under vacuum. More material could often be obtained from subsequent recrystallization of the mother liquors. The title compound was obtained as a white solid (920 mg, 32%). **m.p.** (°C): 132–133; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.51 (br s, 8H), 7.03 (t, *J*=7.1 Hz, 8H), 6.86 (t, *J*=7.1 Hz, 4H), 4.46 (br s, 1H), 3.20 (q, *J*=7.5 Hz, 4H), 3.10 (q, *J*=7.5, 4H), 1.21 (t, *J*=7.5, 6H), 1.11 (t, *J*=7.5, 6H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 164.4 (C-B, q, $^1J_{CB}$=49 Hz), 136.2, 135.4, 125.9 (C-B, q, $^2J_{CB}$=2.8 Hz), 122.0, 98.2, 48.1, 46.9, 14.2, 12.9; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3108, 3053, 2984, 1895, 1589; **HRMS** (ESI+) m/z calculated for $C_{11}H_{21}N_2^+$ $[M]^+$: 181.1699; found: 181.1703.

Bis(diethylamino)cyclopropenium tetraphenylborate (3-26) Reaction Optimization Table



3-1 **3-26** **3-24**

entry	# equiv. diethylamine	change from above procedure[a]	temp. (°C)[b]	ratio **3-26:3-24**[c]
1	8	no PPh_3[d]	0	0:1
2[e]	4	added PPh_3 at r.t.	−78	3.5:1
3	2	2 equiv. DIPEA	−90	1.4:1
4	4	none	−90	>6:1

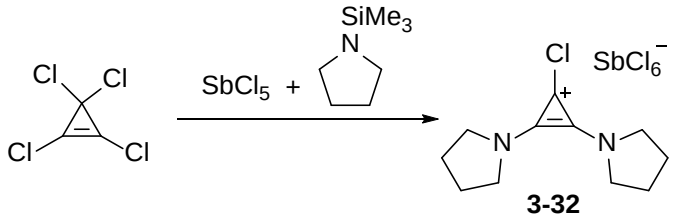
a) Reactions were performed in a manner similar to the procedure for (**3-26**) above except as stated; b) referring to the temperature the amine is first added to **3-1**; c) ratio determined by ^{1}H NMR of the crude reaction mixture; d) no phosphine reduction attempted as mixture only contained **3-24** after first step; e) reaction performed by Gravel. M.

Bis(diethylamino)cyclopropenium tetraphenylborate (3-26) Improved Synthesis

Diethylamine (0.58 mL, 5.6 mmol) was added dropwise to a solution of tetrachlorocyclopropene (0.25 mL, 1.4 mmol) and sodium tetraphenylborate (481 mg, 1.4 mmol) in dichloromethane (28 mL) at −78 °C under argon. The reaction mixture was warmed to room temperature over 3 hours. The mixture was transferred to a separatory funnel and washed with 1N HCl and H_2O. The organic layer was concentrated *in vacuo*. and the crude chloro-cyclopropenium salt was dissolved in acetone (4 mL). Granular zinc (2.21 g, 8.4 mmol) was added followed by acetic acid (7.0 mL) and the mixture was stirred at room temperature for 14 hrs. The reaction mixture was filtered through Celite, concentrated *in vacuo*. and the crude

product was crystallized from chloroform and diethyl ether. The crude product was recrystallized from methanol, to give the pure bis(diethylamino)cyclopropenium tetraphenylborate (213 mg). The liquors were found to be mainly bis(diethylamino)cyclopropenium acetate by NMR. The liquors were dissolved in dichloromethane and sodium tetraphenylborate was added. The mixture was washed with water, dried over sodium sulfate and concentrated *in vacuo*. to produce an additional quantity (86 mg, 51% total) of bis(diethylamino)cyclopropenium tetraphenylborate. This material was in all ways consistent with the material above.

1-Chloro-2,3-di(pyrrolidin-1-yl)cycloprop-2-en-1-ylium hexachlorostibate(V) (3-32)



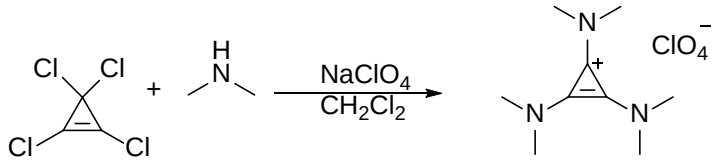
3-32

Trimethylsilylpyrrolidine is known.[221] It was prepared by adding *n*-BuLi (5.35 mL, 2.5 M in hexanes) to a solution of distilled pyrrolidine (1.0 mL, 12.2 mmol), in THF (12 mL) at 0 °C. Trimethylsilyl chloride (1.54 mL, 12.2 mmol) was added, the mixture was stirred for 3 hrs at room temp and solvent was evaporated. The crude product was purified by distillation. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 3.95-3.851(m, 4H), 2.75-2.65 (m, 4H), 0.10 (s, 9H).

Antimony pentachloride (34 μL, 0.27 mmol) was added to tetrachlorocyclopropene (34 μL, 0.28 mmol) at room temperature. After one hour the reaction was placed under high vac for 20 minutes, inert atmosphere was re-established and CH_2Cl_2 (5.0 mL) was added to the flask. The flask was cooled to -90 °C and trimethylsilylpyrrolidine (77 mg, 0.43 mmol) was added. The reaction was warmed to room temperature and solvent removed *in vacuo* to give the crude product as an orange solid. The crude product was recrystallized from acetonitrile and washed

with ether to give yellow needle-like crystals. **m.p.** (^{o}C):187-190 decomp.; **^{1}H NMR** (500 MHz, DMSO) δ 3.68 (dd, *J*=10.3, 3.9 Hz, 8H), 2.23 (d, *J*=3.9 Hz, 8H); **^{13}C NMR** (125 MHz, DMSO) δ 130.9, 89.4, 51.6, 50.8, 26.0, 25.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3200, 2968, 2886, 1946, 1608, 1454, 1386, 1345; **HRMS** (ESI^{+}) m/z calculated for $C_{11}H_{16}N_2Cl$ $[M]^{+}$: 211.0996; found: 211.0999.

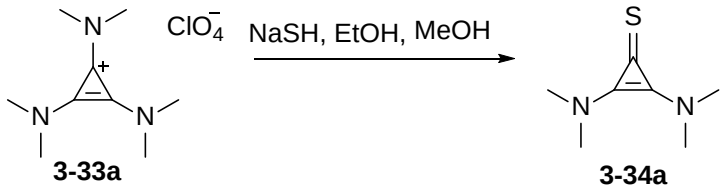
Tris(dimethylamino)cyclopropenium perchlorate (3-33a)



3-33a

Dimethyl amine (3.8 mL, 56.2 mmol) was quickly added via a pre-chilled pipette to a solution of tetrachlorocyclopropene (690 μL, 5.62 mmol) in CH_2Cl_2 (100 mL) at 0 °C (ice bath). The solution was stirred for 2 hour at 0 °C and then warmed to room temperature. The reaction was quenched with perchloric acid and water, and then transferred to a separatory funnel. It was washed with 1N HCl, $NaHCO_3$, and water. The organic layer was dried over sodium sulfate and solvent removed *in vacuo* to give 0.966 g (64%) of the amine salt as an off white solid. An estimated 36% of the material was lost to the aqueous wash (based on crude product weight and spectra). This solid was in all ways consistent with what has been reported in the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.01 (s, 12H).

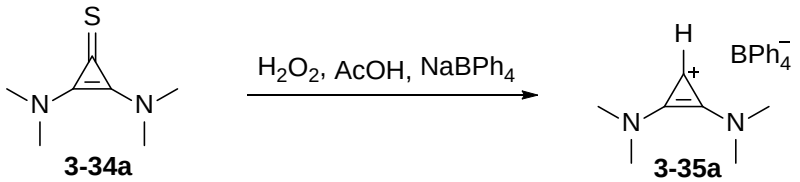
2,3-Bis(dimethylamino)cycloprop-2-enethione (3-34a)



3-33a **3-34a**

The tris(amino)cyclopropenium salt (100 mg, 0.37 mmol) was put in a round bottom flask along with sodium hydrogen sulfide (502 mg, 2.09 mmol), methanol (3.7 mL) and ethanol (3.7 mL). It was refluxed (66 °C) for 8 hours then quenched with water. The organic layer was extracted into CH_2Cl_2, it was dried by passing over sodium sulfate and the solvent was removed *in vacuo*. Partial purification was achieved with crystallization from CH_2Cl_2 and diethyl ether. The material was further purified via column chromatography (10% MeOH in CH_2Cl_2) to give 28 mg (48%) of the pure thione which was spectroscopically consistent with the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.12 (s, 12H).

2,3-Bis(dimethylamino)cycloprop-2-en-1-ylium tetraphenylborate (3-35a)

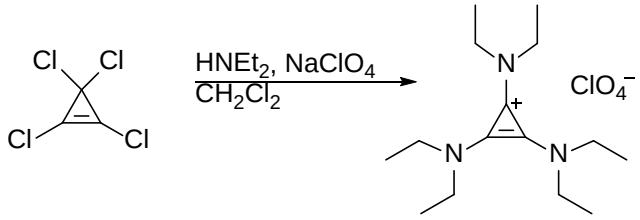


3-34a **3-35a**

Thione (124 mg, 0.793 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (3.3 mL) was added and the mixture cooled to approximately the freezing point of acetic acid. Peroxide (35%, 229 μL, 2.61 mmol) was added slowly dropwise and the reaction was warmed to room temperature over 90 minutes. The acetic acid was evaporated with high vacuum and a 2:1 mixture of methanol: H_2O was added to the flask followed by sodium tetraphenylborate (271 mg, 0.793 mmol). The crude product could then be

recrystallized/triturated from methanol to afford 145.3 mg (41%) of the bis(dimethylamino)cyclopropenium perchlorate salt as an off white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (s, 8H), 7.07 (dd, *J*=7.4, 7.4 Hz, 8H), 6.92 (t, *J*=7.1 Hz, 4H), 5.61 (s, 1H), 3.47 (s, 6H), 3.41 (s, 6H); **^{13}C NMR** (125 MHz, acetone D6) δ 165.7, 165.3, 164.9, 164.5, 139.3, 137.1, 126.1, 122.4, 96.9, 42.8, 41.7; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3450, 3112, 3052, 1916, 1615, 1408, 1265; **HRMS** (ESI^+) m/z calculated for $C_7H_{13}N_2$ $[M]^+$: 125.1073; found: 125.1087.

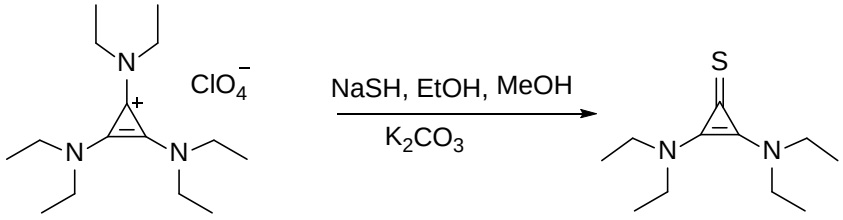
Tris(diethylamino)cyclopropenium perchlorate (3-33b)



3-33b

Diethylamine (3.7 mL, 35 mmol) was added dropwise to a solution of tetrachlorocyclopropene (550 μL, 4.49 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The solution was stirred for 15 minutes and sodium perchlorate (660 mg, 5.39 mmol) was added. The solution was transferred to a separatory funnel. It was washed with 1N HCl, $NaHCO_3$, and water. The organic layer was dried over sodium sulfate and most of the solvent was removed *in vacuo*. The crude product was recrystallized from CH_2Cl_2 and diethyl ether to give 1.74 g (quant. + some water) of the product as a white solid. This substance was in all ways consistent with what had been reported in the literature.[222] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.40 (q, *J*=7.3 Hz, 12H), 1.28 (t, *J*=7.2 Hz, 18H).

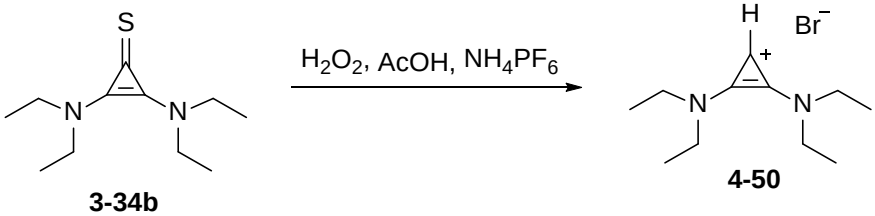
2,3-Bis(diethylamino)cycloprop-2-enethione (3-34b)



3-33b **3-34b**

The tris(amino)cyclopropenium salt (1.582 g, 4.50 mmol) was put in a round bottomed flask along with sodium hydrogen sulfide (7.0 g, 29 mmol), methanol (45 mL) and ethanol (45 mL). It was stirred at reflux for 36 hours then quenched with water. The organic layer was extracted into CH_2Cl_2, it was dried by passing over sodium sulfate and the solvent was removed *in vacuo*. The reaction was incomplete so the crude product was transferred to a pressure vessel with fresh NaSH (6.5 g, 27 mmol), methanol (20 mL), ethanol (33 mL), and CH_2Cl_2 (5 mL) and heated to 100 °C for 18 hours and again worked up as above. The material was purified via column chromatography (1.5% MeOH : CH_2Cl_2) to give 822 mg (86%) of the pure thione as a brown solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.40-3.20 (br. s, 12H), 1.21 (t, *J*=6.9 Hz, 18H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 132.8, 131.7, 46.1, 14.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2971, 2932, 2872, 1889, 1514, 1461, 1379, 1353, 1293, 1218, 1190, 1087, 1042, 962; **HRMS** (ESI^+) m/z calculated for $C_{11}H_{20}N_2S$ $[M]^+$: 212.1347; found: 212.1349

2,3-Bis(diethylamino)cycloprop-2-en-1-ylium bromide (4-50)

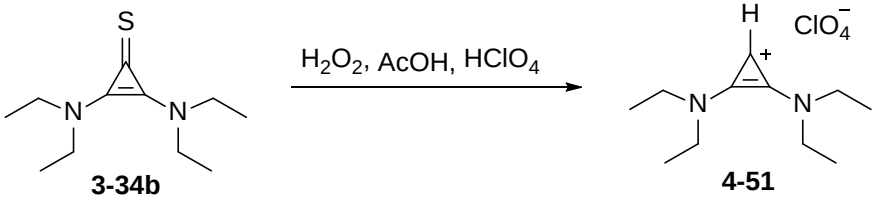


3-34b **4-50**

Thione (50 mg, 0.24 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (1.00 mL) was added and the mixture cooled to approximately the freezing

point of acetic acid. Peroxide (35%, 68 μL, 0.68 mmol) was added slowly dropwise and the reaction was kept at 0 °C for 30 minutes and warmed to room temperature over 1 hours. HBr (27 μL, 0.57 mmol) was added to the flask and the solvent was evaporated with high vacuum. This crude product was lost to an aqueous wash however drying the aqueous layer with co-evaporation followed by dissolution in CH_2Cl_2 and drying the residual moisture with magnesium sulfate. This afforded 55.7 mg (91%) of the bis(amino)cyclopropenium chloride/bromide salt as colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.91 (s, 1H), 3.51 (q, *J*=7.3 Hz, 4H), 3.45 (q, *J*=7.3, 4H), 1.23 (t, *J*=7.3 Hz, 6H), 1.20 (t, *J*=7.3 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.2, 99.3, 48.4, 47.4, 14.2, 13.0; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3450, 2977, 1894, 1590, 1446, 1386, 1351, 1315, 1175, 1100.

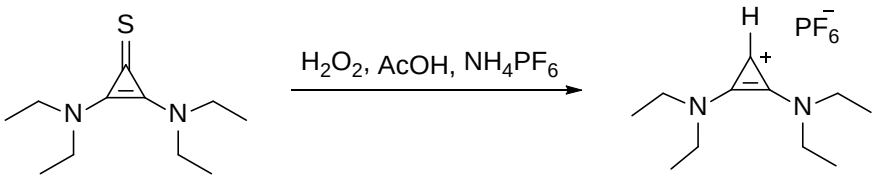
2,3-Bis(diethylamino)cycloprop-2-en-1-ylium perchlorate (4-51)



Thione (50 mg, 0.24 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (1.00 mL) was added and the mixture cooled to approximately the freezing point of acetic acid. Peroxide (35%, 68 μL, 0.68 mmol) was added slowly dropwise and the reaction was kept at 0 °C for 30 minutes and warmed to room temperature over 1 hours. Perchloric acid (20 μL, 70% aq. soln.) was added to the mixture and the solvent was evaporated with high vacuum. The crude product was dissolved in CH_2Cl_2 and washed with water to afford 42.5 mg (65%) of the pure bis(diethylamino)cyclopropenium perchlorate as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.14 (s, 1H), 3.56 (q, *J*=7.3 Hz, 4H), 3.52 (q, *J*=7.3 Hz, 4H), 1.30 (t, *J*=7.3 Hz, 6H), 1.29 (t, *J*=7.3 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.6, 97.3, 48.6, 47.3,

14.2, 12.9; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3114, 2980, 1897, 1592, 1466, 1389, 1352, 1314, 1177, 1096, 624.

2,3-Bis(diethylamino)cycloprop-2-en-1-ylium hexafluorophosphate(V) (4-52)

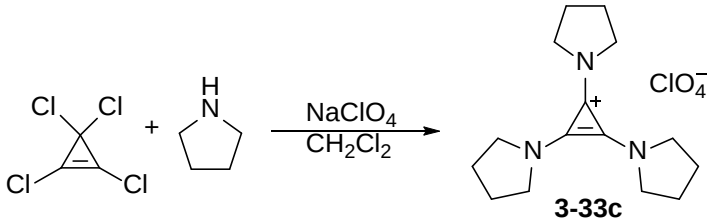


3-34b **4-52**

Thione (50 mg, 0.24 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (1.00 mL) was added and the mixture cooled to approximately the freezing point of acetic acid. Peroxide (35%, 68 μL, 0.68 mmol) was added slowly dropwise and the reaction was kept at 0 °C for 30 minutes and warmed to room temperature over 1 hours. The solvents were evaporated with high vacuum and a 2:1 mixture of CH_2Cl_2 : H_2O was added to the flask followed by ammonium hexafluorophosphate (38 mg, 0.23 mmol). The mixture was washed with water, dried over sodium sulfate and the solvent removed *in vacuo*. A recrystallization was attempted with methanol and ether giving an oily liquor and a solution. The liquor was found to be pure bis(diethylamino)cyclopropenium hexafluorophosphate (55.2 mg, 72%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 3.51 (q, *J*=7.3 Hz, 4H), 3.49 (q, *J*=7.3, 4H), 1.29 (t, *J*=7.3 Hz, 6H), 1.28 (t, *J*=7.3 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.5, 96.8, 48.5, 47.2, 14.0, 12.8; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3151, 2983, 1899, 1594, 1466, 1390, 1361, 1316, 1177, 1084, 839, 558.

The BF_4 salt **4-53** was also prepared in an identical manner however the product (also an oil) was not sufficiently pure to merit characterization, and could not be purified further.

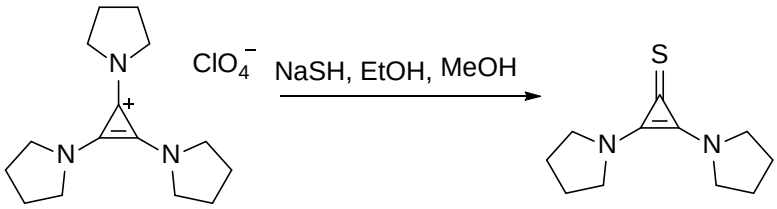
1-(2,3-Di(pyrrolidin-1-yl)cycloprop-2-en-1-ylidene)pyrrolidin-1-ium perchlorate (3-33c)



3-33c

Freshly distilled pyrrolidine (2.4 mL, 29.2 mmol) was added dropwise to a solution of tetrachlorocyclopropene (446 μL, 3.65 mmol) in CH_2Cl_2 (32 mL) at 0 °C (ice bath). The solution was stirred for 30 min as it warmed to room temperature. Sodium perchlorate (446 mg, 3.65 mmol) was added and the mixture was transferred to a separatory funnel. It was washed with 1N HCl, $NaHCO_3$, and water. The organic layer was dried over sodium sulfate and most of the solvent was removed *in vacuo*. When ~8 mL CH_2Cl_2 remained, diethyl ether was added and the fluffy white precipitate was filtered to give 1.1149 g (88%) of the salt as an off white solid which was used directly in the next step. This solid was in all ways consistent with what has been reported in the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.50 (t, *J*=6.7 Hz, 12H), 2.04 (t, *J*=6.7 Hz, 12H).

2,3-Di(pyrrolidin-1-yl)cycloprop-2-enethione (3-34c)

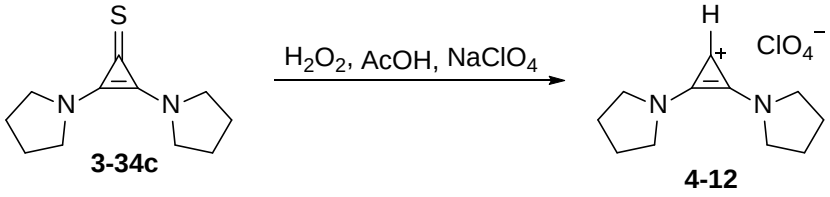


3-33c **3-34c**

The tris(amino)cyclopropenium salt (100 mg, 0.29 mmol) was put in a microwave vial along with sodium hydrogen sulfide (400 mg, 1.62 mmol), methanol (2.9 mL) and ethanol (2.9 mL). It was heated to 120 °C for 13 hours in the microwave (pressure 5 bar) then quenched with

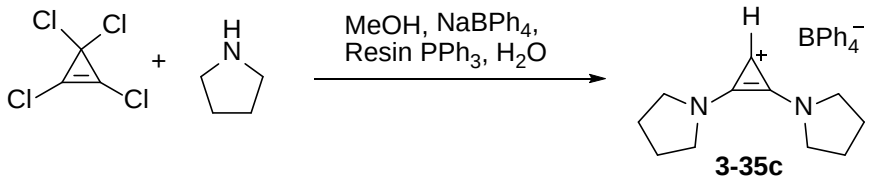
water. The organic layer was extracted into CH_2Cl_2, it was dried by passing over sodium sulfate and the solvent was removed *in vacuo*. The material was purified via column chromatography (1% MeOH in CH_2Cl_2) to give 37.7 mg (62%) of the pure thione as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.60-3.30 (br s., 8H), 1.87 (s, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 131.0, 130.3, 49.8, 25.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2977, 2870, 1889, 1500, 1447, 1378, 1323, 1248, 1158; **HRMS** (ESI^+) m/z calculated for $C_{11}H_{17}N_2S$ $[M]^+$: 209.1112; found: 209.1060.

2,3-Di(pyrrolidin-1-yl)cycloprop-2-en-1-ylium Perchlorate (4-12)



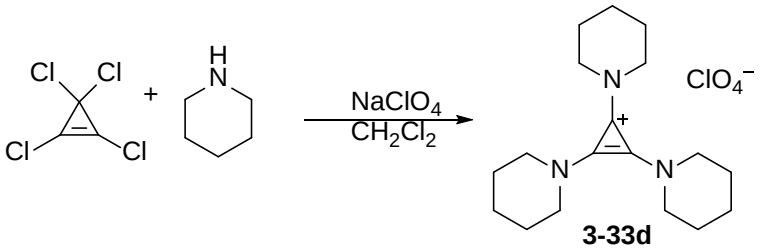
Thione (15 mg, 0.072 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (0.30 mL) was added and the mixture cooled to approximately the freezing point of acetic acid. Peroxide (35%, 21 μL, 0.23 mmol) was added slowly dropwise and the reaction was warmed to room temperature over 30 minutes. The acetic acid was evaporated with high vacuum and a 2:1 mixture of methanol: H_2O was added to the flask followed by sodium perchlorate (35 mg, 0.28 mmol). The crude product could then be recrystallized from CH_2Cl_2 and ether to afford 10.7 mg (54%) of the bis(amino)cyclopropenium perchlorate salt as a white solid. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 6.85 (s, 1H), 3.71 (t, *J*=6.7 Hz, 4H), 3.69 (t, *J*=6.6 Hz, 4H), 2.08 (t, *J*=3.5, 8H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 134.7, 95.4, 51.8, 51.0, 25.8, 25.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3114, 2972, 2882, 1909, 1597, 1456, 1350, 1255, 1092; **HRMS** (ESI^+) m/z calculated for $C_{11}H_{17}N_2$ $[M]^+$: 177.1386; found: 177.1393.

2,3-Di(pyrrolidin-1-yl)cycloprop-2-en-1-ylium tetraphenylborate (3-35c)



To a solution of tetrachlorocyclopropene (34 μL, 0.28 mmol), sodium tetraphenylborate (96 mg, 0.28 mmol) in methanol (5 mL) was chilled to -79 °C and pyrrolidine (92 μL, 1.12 mmol) was added dropwise. The mixture was warmed to room temperature and cooled back down to -79 °C, resin bound triphenylphosphine (100 mg, 3.0 mmol/g) along with CH_2Cl_2 and water (140 mg) was added and the mixture stirred for 4 hours. The mixture was transferred to a separatory funnel with CH_2Cl_2 and the organic layer was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* and the precatalyst was purified via recrystallization from methanol followed by recrystallization from CH_2Cl_2, dethyl ether to give 22.9 mg (16%) of the pre-catalyst as a white crystalline solid. Subsequent attempts to repeat this reaction produced insufficient amounts of product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (s, 8H), 6.99 (dd, *J*=7.4, 7.4 Hz, 8H), 6.86 (t, *J*=7.2 Hz, 4H), 4.76 (s, 1H), 3.19 (t, *J*=6.6 Hz, 4H), 3.06 (t, *J*=6.4 Hz, 4H), 1.87 (t, *J*=7.2, 8H); **^{13}C NMR** (125 MHz, acetone D6) δ 166.1, 165.7, 165.3, 164.9, 137.6, 136.0, 126.6, 122.8, 96.5, 52.8, 51.8, 26.8, 26.7; **HRMS** (ESI^+) m/z calculated for $C_{11}H_{17}N_2$ $[M]^+$: 177.1386; found: 177.1393.

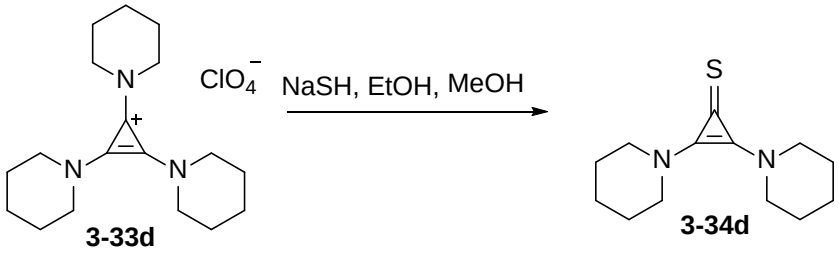
Tris(piperidino)cyclopropenium perchlorate (3-33d)



3-33d

Piperidine (4.45 ml) was added to a solution of tetrachlorocyclopropene (690 μL, 5.62 mmol) in CH_2Cl_2 (100 mL) at 0 °C and allowed to warm to 30 °C for 30 minutes. Sodium perchlorate (825 mg, 6.74 mmol) was added and the mixture was transferred to a separatory funnel. The organic layer was washed with 1 N HCl, $NaHCO_3$, and water before being dried over sodium sulfate. The majority of the solvent was removed *in vacuo* and the product was precipitated via the gradual addition of diethyl ether. Filtration gave 2.27 g (104%) of the product which was completely pure aside for some water as an off white solid. All characterization was consistent with what has been reported in the literature.[223] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.48 (t, *J*=5.8 Hz, 8H), 1.71 (t, *J*=3.7 Hz, 8H), 1.56 (t, *J*=4.3 Hz, 4H).

2,3-Di(piperidin-1-yl)cycloprop-2-enethione (3-34d)

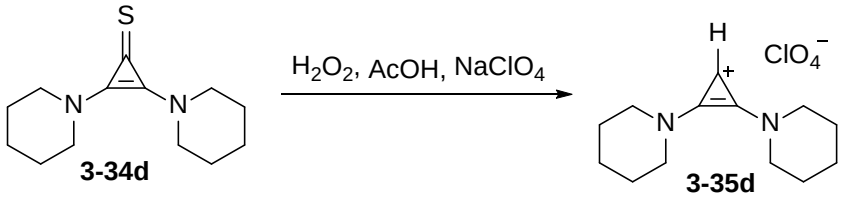


3-33d **3-34d**

To the tris(amino)cyclopropenium salt (1.00 g, 2.57 mmol), sodium hydrogen sulfide flakes (3.47 g, 14.43 mmol) were added followed by ethanol (25 mL) and methanol (25 mL). The mixture was refluxed for 3 hours under inert atmosphere followed by a quench with water

and extraction into CH_2Cl_2. The crude product was dried over sodium sulfate and solvent removed *in vacuo*. This substance was purified via recrystallization from hot benzene and hexanes to give 408 mg (76%) of a pale yellow crystalline solid. All characterization of this compound was consistent with what has been reported in the literature.[176] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.60-3.40 (br s, 8H), 1.62 (s, 12H). The yield of this reaction varies greatly (10-76%) depending in part on the quality of NaSH used. DANGER: Care must be taken disposing the aqueous waste from this reaction as it has the potential to liberate H_2S. Best protocol involves mixing it with commercial bleach and storing it separate from other aqueous waste to avoid accidental contact with acid.

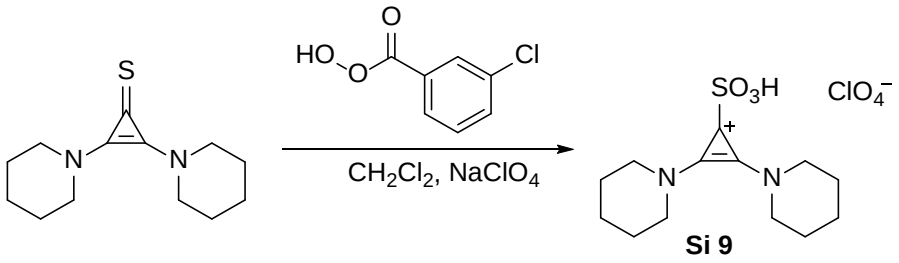
Bis(1,2-piperidino)cyclopropenium perchlorate (3-35d)



Thione (400 mg, 1.92 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (8.0 mL) was added and the mixture cooled to approximately the freezing point of acetic acid. Peroxide (35%, 555 μL, 6.34 mmol) was added slowly dropwise and the reaction was warmed to room temperature over one hour. The acetic acid was evaporated with high vacuum and a 2:1 mixture of methanol: H_2O was added to the flask followed by sodium perchlorate (968 mg, 7.91 mmol). The crude product could then be recrystallized from a mixture of ethanol and diethyl ether to afford 221.3 mg (38%) of the bis(piperidino)cyclopropenium perchlorate salt as a tan solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 3.55-3.45 (m, 8H), 1.85-1.83 (m, 8H), 1.83-1.70 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.0, 95.4, 53.0, 51.5,

25.4, 25.2, 23.0; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3100, 2939, 2860, 1899, 1597, 1447, 1288, 1258, 1092; **HRMS** (ESI^+) m/z calculated for $C_{13}H_{21}N_2$ $[M]^+$: 205.1699; found: 205.1707.

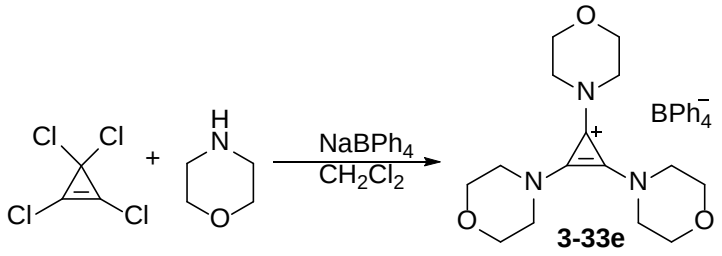
Bis(piperidino)sulfonyl-cyclopropenium perchlorate (Si 9)



Si 9

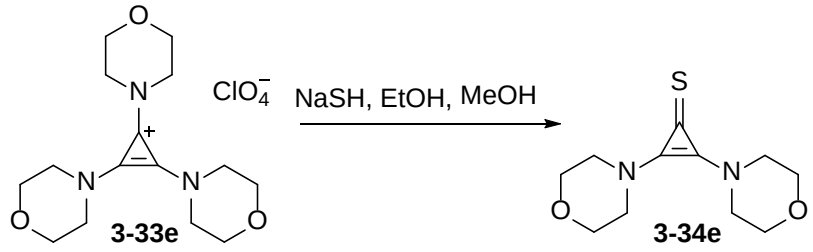
The thione (9.2 mg, 0.038 mmol) was added to a pear shaped flask with stirbar and placed under nitrogen along with CH_2Cl_2 (0.38 ml). The vessel was cooled to -50 °C using a frozen chloroform bath and a solution of *m*-CPBA (14.1 mg, 0.081 mmol) in CH_2Cl_2 (0.23 ml). The solution was allowed to warm to room temperature. A saturated solution of sodium perchlorate (a large excess) was added and the reaction was transferred to a separatory funnel. The crude reaction mixture was washed with water and extracted into CH_2Cl_2 as well as diethyl ether. The crude reaction mixture was also washed with a small amount of sodium tetraphenylborate but yielded no further material. The crude product was dissolved in CH_2Cl_2 and precipitated with ether to give 3.6 mg (24%) of what has been tentatively identified as the sulfonic acid above. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.33 (s, 1H), 3.86-3.80 (m, 4H), 3.50-3.48 (m, 4H), 1.76-1.66 (m, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 131.0, 52.6, 52.4, 25.7, 25.3, 22.9 (low signal to noise, some signals not detected); **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2946, 2861, 1925, 1605, 1449, 1379, 1289, 1242, 1117, 1044; **HRMS** (EI^+) m/z calculated for $C_{13}H_{21}N_2O_3S$ $[M]^+$: 285.1267; found: 285.2240, piperidine and SO_2 were also detected.

4-(2,3-Dimorpholinocycloprop-2-en-1-ylidene)morpholin-4-ium tetraphenylborate (3-33e)



Freshly distilled morpholine (1.33 mL, 21.2 mmol) was added dropwise to a solution of tetrachlorocyclopropene (325 μL, 2.65 mmol) in CH_2Cl_2 (100 mL) at 0 °C (ice bath). The solution was stirred for 2 hour as it warmed to room temperature. Sodium tetraphenylborate (952 mg, 2.78 mmol) was added and the mixture was transferred to a separatory funnel. It was washed with 1N HCl, $NaHCO_3$, and water. The organic layer was dried over sodium sulfate and most of the solvent was removed *in vacuo*. When ~20 mL CH_2Cl_2 remained, diethyl ether was added and the fluffy white precipitate was filtered to give ~1.6 g (quantitative yield) of the amine salt which was used directly in the next step. This solid was in all ways consistent with what has been reported in the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (s, 8H), 7.02 (t, *J*=7.4 Hz, 8H), 6.88 (t, *J*=7.2 Hz, 4H), 3.58 (d, *J*=3.6 Hz, 12H), 3.04 (d, *J*=3.1 Hz, 12H).

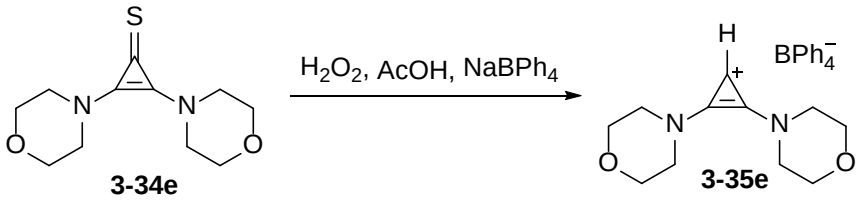
2,3-Dimorpholinocycloprop-2-enethione (3-34e)



The tris(amino)cyclopropenium salt (1.585 g, 2.58 mmol) was put in a round bottom flask along with sodium hydrogen sulfide (3.475 g, 14.5 mmol), methanol (26 mL), ethanol (26 mL) and CH_2Cl_2 (15 mL). It was refluxed (66 °C) for 18 hours then quenched with water. The

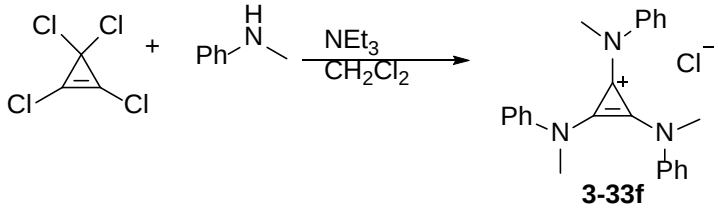
organic layer was extracted into CH_2Cl_2, it was dried by passing over sodium sulfate and the solvent was removed *in vacuo*. The material was purified via column chromatography (2% MeOH in CH_2Cl_2) to remove the majority of impurities followed by (5% MeOH in EtOAc) to give 491 mg (79% over 2 steps) of the pure thione which was spectroscopically consistent with the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.77 (t, *J*=4.7 Hz, 8H), 3.54 (s, 8H).

2,3-Dimorpholinocycloprop-2-en-1-ylium tetraphenylborate (3-35e)



Thione (420 mg, 1.74 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (7.25 mL) was added and the mixture cooled to approximately the freezing point of acetic acid. Peroxide (35%, 502 μL, 5.72 mmol) was added slowly dropwise and the reaction was warmed to room temperature over 90 minutes. The acetic acid was evaporated with high vacuum and a 2:1 mixture of methanol: H_2O was added to the flask followed by sodium tetraphenylborate (598 mg, 1.74 mmol). The crude product could then be recrystallized/triturated from chloroform to afford 667 mg (72%) of the bis(morpholino)cyclopropenium perchlorate salt as a white solid. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.35 (s, 8H), 6.98 (dd, *J*=7.4, 7.4 Hz, 8H), 6.85 (t, *J*=7.2 Hz, 4H), 5.01 (s, 1H), 3.65 (t, *J*=4.9 Hz, 8H), 3.25 (t, *J*=5.0 Hz, 4H), 3.17 (t, *J*=5.0 Hz, 4H); **^{13}C NMR** (125 MHz, CD_2Cl_2) δ 165.3, 164.9, 164.5, 164.2, 136.5, 135.1, 126.4, 122.5, 97.9, 66.2, 51.5, 49.9; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3124, 3053, 2982, 2861, 1906, 1591, 1477, 1442, 1429, 1379, 1282, 1256, 1181, 1117; **HRMS** (ESI^+) m/z calculated for $C_{11}H_{17}N_2O_2$ $[M]^+$: 209.1284; found: 209.1277.

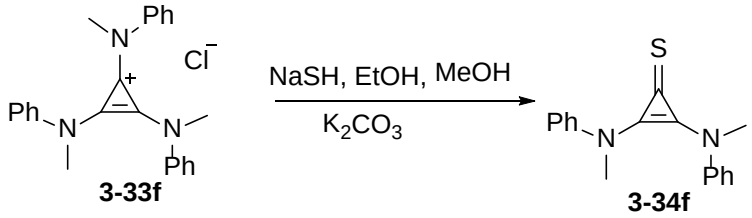
N-(2,3-Bis(methyl(phenyl)amino)cycloprop-2-en-1-ylidene)-N-methylbenzen-aminium chloride (3-33f)



3-33f

N-Methylaniline (0.36 mL, 3.28 mmol) was added dropwise to a solution of tetrachlorocyclopropene (100 μL, 0.82 mmol) in CH_2Cl_2 (8.1 mL) followed by triethylamine (0.46 mL, 3.28 mmol) at room temperature. The solution boiled briefly and was refluxed for 2 hour. Ether was added to the mixture and a yellow precipitate formed. The filtrate was re-dissolved in CH_2Cl_2 and transferred to a separatory funnel. It was washed with 1N HCl, $NaHCO_3$, and water. The organic layer was dried over sodium sulfate and most of the solvent was removed *in vacuo*. The crude product was recrystallized from CH_2Cl_2 and diethyl ether to give 225.9 mg (71%) of the product as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (d, *J*=8.9 Hz, 6H), 7.16 (dd, *J*=7.5, 7.4 Hz, 6H), 7.05 (t, *J*=7.3 Hz, 3H), 3.38 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.9, 129.7, 127.2, 123.1, 118.3, 42.8; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3036, 2899, 2457, 1589, 1527, 1494, 1454, 1412, 1287, 1248, 1182, 1108, 1078, 1027; **HRMS** (ESI^+) m/z calculated for $C_{24}H_{24}N_3$ $[M]^+$: 354.1964; found: 354.1957.

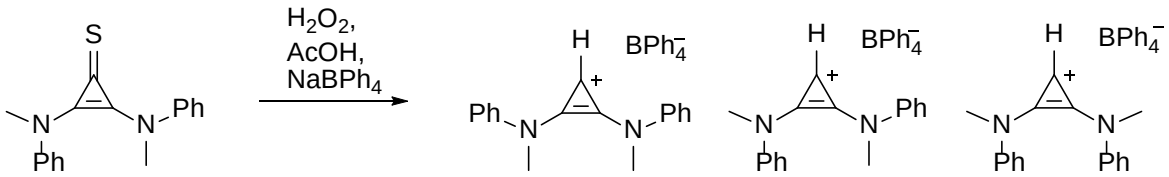
2,3-Bis(methyl(phenyl)amino)cycloprop-2-enethione (3-34f)



3-33f **3-34f**

The tris(amino)cyclopropenium salt (284 mg, 0.73 mmol) was put in a round bottomed flask along with sodium hydrogen sulfide (211 mg, 0.88 mmol), methanol (7.3 mL), ethanol (7.3 mL), CH_2Cl_2 (7.3 mL) and potassium carbonate (100 mg, 0.73 mmol). It was stirred at room temperature for 24 hours then quenched with water. The organic layer was extracted into CH_2Cl_2, it was dried by passing over sodium sulfate and the solvent was removed *in vacuo*. The material was purified via gradient column chromatography (7:3 hexanes : EtOAc to 6:4 hexanes : EtOAc) to give 140.5 mg (69%) of the pure thione as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.33 (m, 8H), 7.21-7.12 (s, 2H), 3.60-3.40 (br s., 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.2, 139.1, 132.0, 129.6, 125.1, 119.8, 40.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2925, 2359, 1599, 1494, 1431, 1385, 1351, 1277, 1197, 1117; **HRMS** (ESI^+) m/z calculated for $C_{17}H_{16}N_2S$ $[M]^+$: 280.1034; found: 280.1032.

2,3-Bis(methyl(phenyl)amino)cycloprop-2-en-1-ylium tetraphenylborate (3-35f)

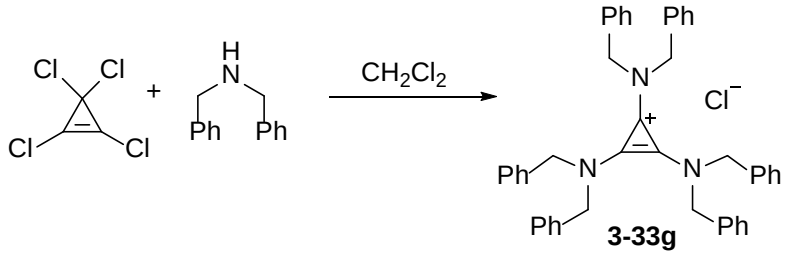


3-34f **3-35f** (as a mixture of rotomers)

Thione (160.2 mg, 0.57 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (2.40 mL) and chloroform (2 mL) were added and the mixture cooled

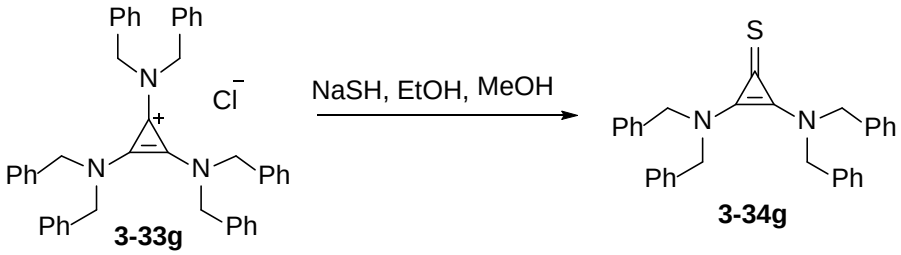
to approximately the freezing point of acetic acid. Peroxide (35%, 165 μL, 1.88 mmol) was added slowly dropwise and the reaction was kept at 0 °C for 30 minutes and warmed to room temperature over 2 hours. The solvents were evaporated with high vacuum and a 2:1 mixture of CH_2Cl_2 : H_2O was added to the flask followed by sodium tetraphenylborate (195 mg, 0.57 mmol). The crude product could then be recrystallized from methanol: water to afford 127.8 mg (39%) of the bis(amino)cyclopropenium perchlorate salt as a brown foam. Salt exists as an roughly 1:2:1 inseparable mixture of three distinct rotamers, as a colorless oil. (major rotamer integrated to one. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (s, 16H), 7.48-7.40 (m, 7H), 7.34 (dd, *J*=15.6, 7.8 Hz, 2H), 7.05 (dd, *J*=7.3, 7.2 Hz, 19H), 6.99-6.80 (m, 6H), 6.90 (t, *J*=7.1, 8H), 6.64 (d, 7.6 Hz, 2H), 4.40 (s, 0.5H), 4.35 (s, 0.5H), 4.24 (s, 1H), 3.17 (s, 3H), 3.06 (s, 3H), 2.75 (s, 3H), 2.57 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.3, 164.9, 164.5, 164.1, 141.8, 141.2, 141.0, 140.4, 136.1, 135.8, 135.5, 134.7, 134.2, 130.6, 130.2, 130.0, 129.9, 129.8, 129.6, 129.5, 128.4, 128.1, 128.0, 127.0, 126.9, 126.0, 126.0, 125.8, 123.7, 122.2, 121.9, 121.5, 119.6, 118.6, 103.0, 102.7, 101.9, 42.6, 41.7, 41.1, 40.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3070, 3054, 1892, 1596, 1550, 1493, 1455, 1413, 1177, 1110, 1031, 910; **HRMS** (ESI^+) m/z calculated for $C_{17}H_{17}N_2$ $[M]^+$: 249.1386; found: 249.1384.

N-Benzyl-N-(2,3-bis(dibenzylamino)cycloprop-2-en-1-ylidene)-1-phenylmethanaminium chloride (3-33g)



Freshly distilled dibenzyl amine (1.5 mL, 12.0 mmol) was added dropwise to a solution of tetrachlorocyclopropene (150 μL, 0.012 mmol) in CH_2Cl_2 (24 mL) at room temperature. The solution boiled briefly and was stirred for 1 hour. The precipitate (dibenzyl amine hydrochloride) was filtered and the organic layer was transferred to a separatory funnel. It was washed with 1N HCl, $NaHCO_3$, and water. The organic layer was dried over sodium sulfate and most of the solvent was removed *in vacuo*. When ~15 mL CH_2Cl_2 remained, diethyl ether was added and the fluffy white precipitate was filtered to give 905 mg (quant.) of the salt which was used directly in the next step. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.19 (m, 18H), 7.12 (d, *J*=7.2 Hz, 12H), 4.50 (s, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.7, 129.2, 128.3, 127.5, 119.4, 56.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3059, 3026, 2993, 2916, 2860, 1586, 1550, 1495, 1400, 1363, 1355, 1322, 1260, 1202, 1166 **HRMS** (ESI^+) m/z calculated for $C_{45}H_{42}N_3$ $[M]^+$: 624.3373; found: 624.3367.

2,3-Bis(dibenzylamino)cycloprop-2-enethione (3-34g)

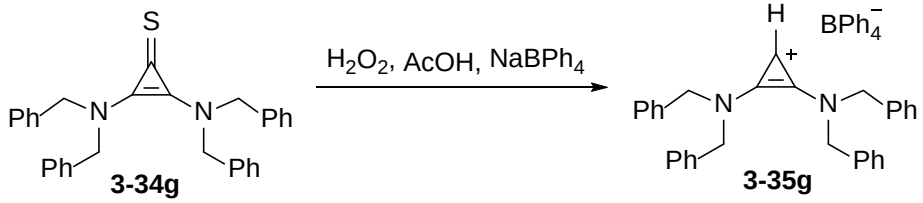


3-33g **3-34g**

The tris(amino)cyclopropenium salt (805 mg, 1.21 mmol) was put in a round bottomed flask along with sodium hydrogen sulfide (1.62 g, 6.7 mmol), methanol (12 mL) and ethanol (12 mL). It was heated to 120 °C for 48 hours then quenched with water. The organic layer was extracted into CH_2Cl_2, it was dried by passing over sodium sulfate and the solvent was removed *in vacuo*. The material was purified via column chromatography (8:2 hexanes : EtOAc) to give 296 mg (53%) of the pure thione as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48-7.02 (m, 20H), 4.80-4.30 (br s., 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.4, 133.3, 130.3, 129.2, 129.1,

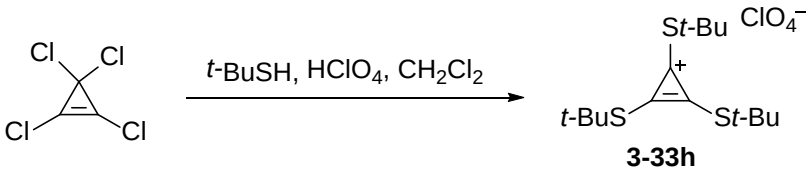
128.4, 54.4; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3084, 3060, 3027, 3001, 2922, 2860, 2795, 1955, 1880, 1811, 1734, 1673, 1602, 1585, 1496, 1452, 1430, 1382, 1346, 1300, 1244, 1205, 1179, 1145, 1089, 1076, 1028, 1001, 955; **HRMS** (ESI^+) m/z calculated for $C_{31}H_{28}N_2S$ $[M]^+$: 460.1973; found: 460.1965.

2,3-Bis(dibenzylamino)cycloprop-2-en-1-ylium tetraphenylborate (3-35g)



Thione (255 mg, 0.55 mmol) was loaded in a small round bottom flask with stirbar under nitrogen. Acetic acid (2.30 mL) was added and the mixture cooled to approximately the freezing point of acetic acid. Peroxide (35%, 160 μL, 1.82 mmol) was added slowly dropwise and the reaction was warmed to room temperature over 90 minutes. The acetic acid was evaporated with high vacuum and a 2:1 mixture of CH_2Cl_2 : H_2O was added to the flask followed by sodium tetraphenylborate (188 mg, 0.55 mmol). The crude product could then be recrystallized from CH_2Cl_2 and ether to afford 245 mg (59%) of the bis(dibenzylamino)cyclopropenium perchlorate salt as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (s, 8H), 7.46 (s, 6H), 7.38 (s, 6H), 6.99 (dd, *J*=6.9, 6.0 Hz, 12H), 6.85 (t, *J*=7.0 Hz, 4H), 6.80 (d, *J*=5.8 Hz, 4H), 4.62 (s, 1H), 4.08 (s, 4H), 4.01 (s, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.2, 164.8, 164.4, 164.0, 136.8, 136.3, 132.9, 132.8, 129.4, 129.1, 127.1, 126.1, 126.1, 122.1, 100.5, 56.3, 55.7; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3088, 3054, 3030, 2998, 2983, 2933, 1889, 1814, 1732, 1590, 1570, 1495, 1478, 1453, 1439, 1354, 1263 1208, 1182, 1133, 1077, 1029, 1001, 951; **HRMS** (ESI^+) m/z calculated for $C_{31}H_{29}N_2$ $[M]^+$: 429.2325; found: 429.2372.

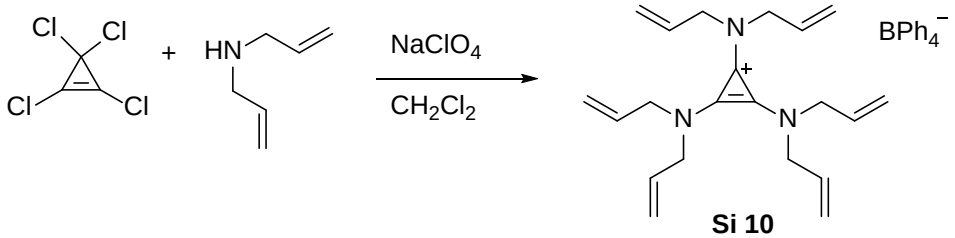
Tris(*tert*-butylsulfido)cyclopropenium perchlorate (3-33h)



3-33h

The *tert*-butyl thiol (285 μL, 2.81 mmol) was added dropwise to tetrachlorocyclopropene (69 μL, 0.56 mmol) in CH_2Cl_2 (224 mL) under nitrogen and stirred 14 hours at room temperature. The reaction was cooled with an ice bath and perchloric acid (28 mL, excess) was added and the mixture stirred a further 3 hours. The mixture was washed with water, dried over sodium sulfate and solvent removed *in vacuo*. The crude product was purified dissolution in methanol precipitation with hexanes and trituration in the resulting mixture to give 102.8 mg (45%) of the product as a beige crystalline solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 1.67 (s, 27H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 155.1, 55.0, 32.4, 32.2, 31.9, 31.7, 31.5; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2869, 2928, 1457, 1374, 1306, 1243, 1217, 1152, 1091; **HRMS** (ESI^+) m/z calculated for $C_{15}H_{27}S_3$ $[M]^+$: 303.1269; found: 303.1273.

N-Allyl-N-(2,3-bis(diallylamino)cycloprop-2-en-1-ylidene)prop-2-en-1-aminium tetraphenylborate (Si 10)

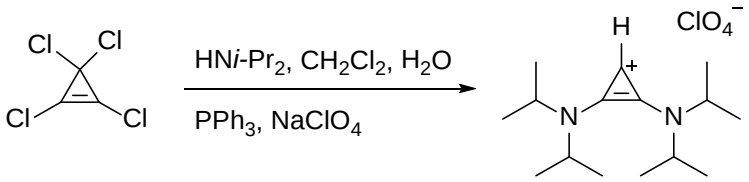


Si 10

Diallylamine (0.48 mL, 3.93 mmol) was added dropwise to tetrachlorocyclopropene (69 μL, 0.56 mmol) in CH_2Cl_2 (11.0 mL) at 0 °C. The reaction was stirred for 48 hours and sodium

perchlorate was added. The reaction was transferred to a separatory funnel and washed with 2N HCl, brine and water. The organic layer was dried over sodium sulfate and the solvent removed *in vacuo* to give the crude product as a viscous oil. When the crude product failed to crystallize an anion exchange was performed with sodium tetraphenylborate. The crude product was dissolved in CH_2Cl_2 and transferred to a separatory funnel. Sodium tetraphenylborate (192 mg, 0.56 mmol) was added and the mixture was washed 3 times with water, before the organic layer was dried over sodium sulfate and the solvent removed *in vacuo*. This material also failed to crystallize but the dry oil was sufficiently pure to carry forward 337 mg (97%) of a colorless oil. For the perchlorate **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.84 (dt, *J*=10.3, 5.4 Hz, 6H), 5.29 (d, *J*=1.1 Hz, 6H), 5.28 (d, *J*=8.1 Hz, 6H), 3.95 (d, *J*=1.0 Hz, 12H); For the BPh_4 salt **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (br. s, 8H), 7.05 (dd, *J*=7.3, 7.3 Hz, 8H), 6.90 (t, *J*=7.1 Hz, 4H), 5.61 (dt, *J*=10.3, 5.1 Hz, 6H), 5.22 (d, *J*=5.4 Hz, 6H), 5.11 (d, *J*=17.2 Hz, 6H), 3.61 (d, *J*=5.0 Hz, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.9, 164.5, 164.1, 163.7, 136.4, 131.2, 131.2, 125.6, 121.8, 119.2, 116.6, 54.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3057, 3002, 2985, 1643, 1543, 1479, 1424, 1364, 1273, 1257, 1179, 1151, 1032, 996, 938; **HRMS** (ESI^+) m/z calculated for $C_{21}H_{30}N_3$ $[M]^+$: 324.2434; found: 324.2440.

Bis(di-isopropylamino)cyclopropenium perchlorate (3-8)

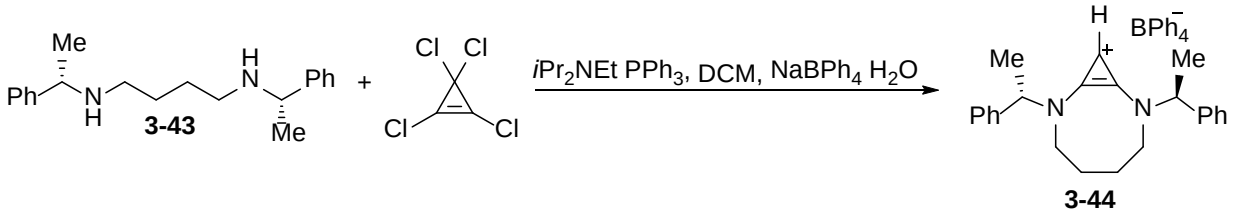


3-8

Diisopropylamine (1.13 mL, 8.01 mmol) was added dropwise to a solution of tetrachlorocyclopropene (245 μL, 2.00 mmol) in CH_2Cl_2 at 0 °C under nitrogen and stirred for 30

minutes. An aliquot was taken for NMR which showed disubstitution to be complete. Sodium perchlorate (245 mg, 2.00 mmol), water (10 mL) and triphenylphosphine (524 mg, 2.00 mmol) were added. The mixture was stirred for 18 hours. The aqueous portion of the biphasic mixture was removed with a separatory funnel. The organic layer was washed with water and dried over sodium sulfate. Solvent was removed *in vacuo* and the crude product was purified via recrystallization from CH_2Cl_2 and ether to give 436 mg (94%) of the product salt as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 4.03 (septet, *J*=7.2 Hz, 2H), 3.86 (septet, *J*=6.8 Hz, 2H), 1.40 (d, *J*=6.8 Hz, 12H), 1.39 (d, *J*=6.8 Hz, 12H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.0, 99.2, 57.2, 49.3, 21.0, 21.0; This compound is consistent with what has been reported in the literature.[224]

2-((S)-1-Phenylethyl)-7-((S)-1-phenylethyl)-2,7-diazabicyclo[6.1.0]non-1(8)-en-9-ylium tetraphenylborate (3-44)



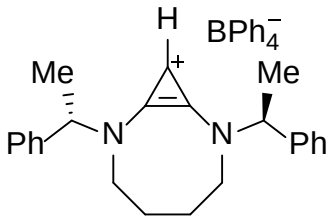
A solution of N,N'-bis[(S)-phenylethyl]butane-1,4-diamine[225] (83 mg, 28 mmol) in CH_2Cl_2 (0.6 mL, pre-cooled to −78 °C) was slowly added to a solution of tetrachlorocyclopropene (34 μL, 0.28 mmol) in CH_2Cl_2 (5.0 mL) under nitrogen at −78 °C, followed by diisopropylethylamine (98 μL, 0.56 mmol). The reaction mixture was then warmed up to room temperature over 3 hours. It was then cooled back down to -40 °C, and polystyrene-bound triphenylphosphine (3.0 mmol/g, 100 mg) was added in one portion. The nitrogen

atmosphere was restored and the mixture was warmed to room temperature over 2 hours. Distilled water (5 mL) and sodium tetraphenylborate (96 mg, 0.26 mmol) were then added and the mixture was stirred vigorously for two days. The resulting mixture was filtered through sintered glass and transferred to a separatory funnel with CH_2Cl_2. The aqueous layer was decanted and the organic layer was washed with 0.5 M HCl, saturated aqueous $NaHCO_3$, and H_2O, then dried over Na_2SO_4 and concentrated *in vacuo.*

The crude product was first recrystallized from MeOH/water in the same manner as was performed for **3-26** above to give a yellow solid. This yellow solid was then dissolved in hot EtOAc and allowed to cool and stand over several days. The liquid was decanted and crystals which adhered to the glass were washed with hexanes and collected to give 102 mg of **3-44** (56%) as a beige powder. **m.p.** (°C): 135–137; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.50 (br s, 8H), 7.40-7.36 (m, 6H), 7.09-7.05 (m, 4H), 7.00 (t, *J*=7.1 Hz, 8H), 6.86 (t, *J*=7.0 Hz, 4H), 4.83 (s, 1H), 4.34 (q, 6.8 Hz, 2H), 2.73 (dd, J=12.0, 7.5 Hz, 2H), 2.61 (dd, J=12.0, 7.6 Hz, 2H), 1.46 (d, J=7.0 Hz, 6H), 1.36-1.28 (m, 2H), 1.36-1.28 (m, 2H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 164.4 (C-B, q, $^1J_{CB}$=49 Hz), 138.2, 136.3, 132.2, 129.4, 129.0, 126.9, 125.8, 121.9, 95.5, 63.1, 48.3, 23.5, 18.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3098, 3054, 2983, 1890, 1603; **HRMS** (ESI+) m/z calculated for $C_{23}H_{27}N_2^+$ $[M]^+$: 331.2168; found: 331.2154. $[\alpha]_D^{21}$ = -4.6 (*c* = 1.3, $CHCl_3$).

X-ray crystallographic analysis of chiral pre-catalyst 3-44

Data collected and analysis performed by Gabriele Schatte

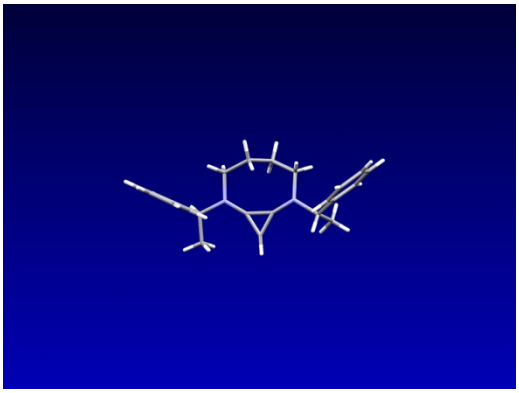


Empirical formula: $C_{47}H_{47}N_2B$

Formula weight: 650.68

Crystal Color, Habit: colorless, rectangular

Crystal dimensions (mm): 0.18 × 0.13 × 0.08

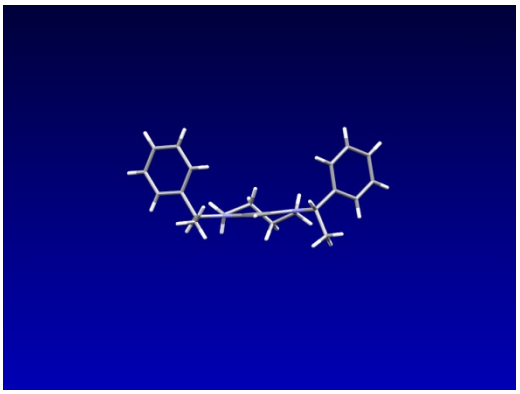


Crystal system: monoclinic

Space group: *P 21*

Unit cell parameters:

a (Å)	9.0660(4)
b (Å)	20.9710(13)
c (Å)	9.8060(6)
α (°)	90
β (°)	90.204(4)
γ (°)	90
V (Å^3)	1864.34(18)
Z^b	2



F(000) 696

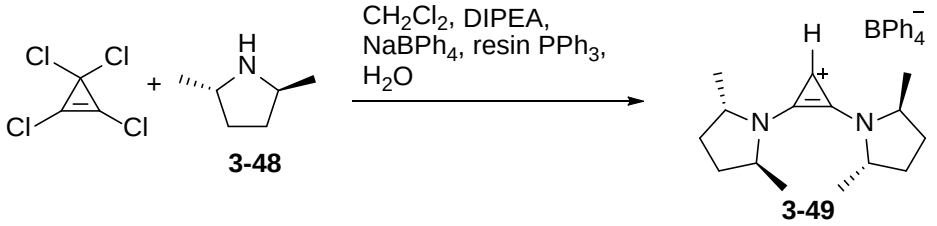
Density (ρ_{calcd}): 1.159 Mg/m^3

Absorption coefficient (μ): 0.066 mm^{-1}

Images rendered using Mercury version 3.6

Crystallographic data for compound **3-24** have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 960736). Copies of the data can be obtained free of charge at http://www.ccdc.cam.ac.uk/data_request/cif.

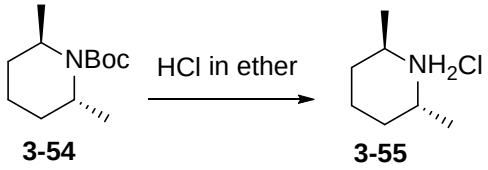
2,3-Bis((2S,5S)-2,5-dimethylpyrrolidin-1-yl)cycloprop-2-en-1-ylium tetraphenylborate (3-49)



To tetrachlorocyclopropene (25 μL, 0.21 mmol) in CH_2Cl_2 (5.0 mL) under nitrogen at -80 °C an ethereal solution (0.61%) of the amine (40.8 mg, 0.41 mmol) was added in along with DIPEA (70 μL, 0.40 mmol). The reaction was warmed to room temperature over 2 hours. The solution was cooled to -80 °C and resin bound triphenylphosphine (102 mg, 3.0 mmol/g) was added. The reaction was allowed to warm up to room temperature over 3 hours and water (10 mL) was added. The solution was stirred for 16 hours before being worked up via filtration. The crude product was transferred to a separatory funnel and the organic layer was washed with water and dried over sodium sulfate. When the reaction was found to be incomplete the crude product was dissolved in CH_2Cl_2 (5.0 mL), water (5.0 mL), and methanol (2.0 mL) along with resin bound phosphine (100 mg, 3.0 mmol/g) and stirred for a further 18 hours. The workup was repeated as above. The solvent was removed *in vacuo*, and the product was purified via recrystallization from CH_2Cl_2 and ether to give 18.8 mg (24%) of the product as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (s, 8H), 7.03 (dd, *J*=7.4, 7.4 Hz, 8H), 6.87 (t, *J*=7.2 Hz, 4H), 4.53 (s, 1H) 3.96-3.85 (m, 2H), 3.73-3.60 (m, 2H), 2.25-2.04 (m, 4H), 1.69-1.55 (m, 4H), 1.20 (d, *J*=6.5 Hz, 6H), 1.06 (d, *J*=6.5 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.2, 164.8, 164.4, 164.0, 136.3, 132.1, 125.9, 121.9, 100.0, 58.9, 57.9, 31.3, 31.0, 21.2, 19.1; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3101, 3055, 2981, 1885, 1565, 1480, 1457, 1426, 1382, 1312, 1109, 1033, 911, 845,

732, 705, 626, 615; **HRMS** (ESI^+) m/z calculated for $C_{15}H_{25}N_2$ $[M]^+$: 233.2012; found: 233.2009.

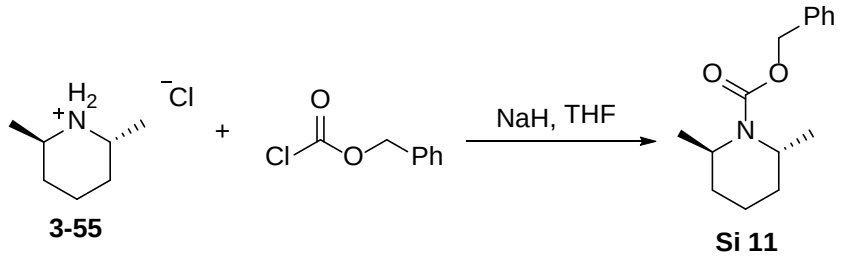
1-Chloro-2,3-bis((2R,6R)-2,6-dimethylpiperidin-1-yl)cycloprop-2-en-1-ylium tetraphenylborate (3-55)



3-54 **3-55**

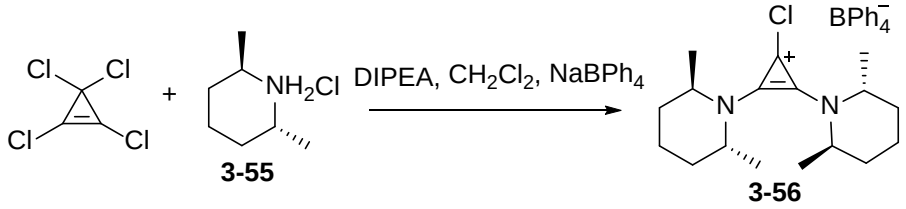
The Boc amine was prepared in highly enantioenriched form according to the procedure of Aggarwal.[226] The Boc amine (4.46 g, 20.9 mmol) was dissolved in diethyl ether (60 mL) and HCl (22 mL, 2.0 M in diethyl ether) was added at room temperature. After 24 hrs the solution was filtered to isolate some of the desired amine salt. Dichloromethane (10 mL) was added to the solution along with HCl (15 mL, 2.0 M in diethyl ether), and the mixture was stirred a further 24 hrs and filtered to give the desired amine salt (81%, 2.53 g) as a white solid. This compound is known and all spectra are consistent with what is reported in the literature. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.60-9.40, (br s, 2H), 3.60-3.50 (br. s, 2H), 2.00-1.90 (m, 2H), 1.80-1.60 (m, 4H), 1.47 (d, *J*=6.8 Hz, 6H).

(2R,6R)-Benzyl 2,6-dimethylpiperidine-1-carboxylate (Si 11)



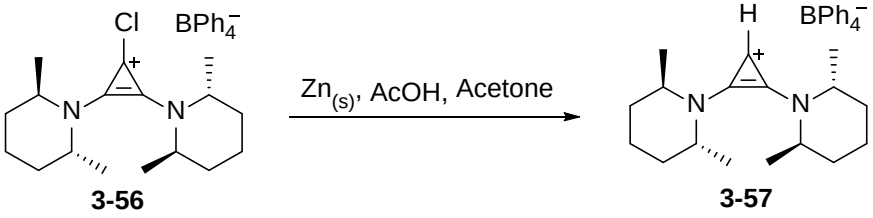
The amine salt (40 mg, 0.27 mmol) was loaded into a round bottomed flask with stirbar and placed under argon atmosphere. THF (1.3 mL) was added followed by sodium hydride (64 mg, 1.33 mmol). Carboxybenzoyl chloride (60 μL, 0.40 mmol) was added dropwise. After 1 hour more sodium hydride was added. Full conversion was obtained after 3 hours. The reaction was quenched with water and the product extracted into ether. The product phase was dried over sodium sulfate and evaporated *in vacuo*. The crude reaction mixture was purified by column chromatography (9:1 hexanes : EtOAc) to give 64.2 mg (97%) of the carbamate product as a colorless oil. R_f = 0.25 (10% EtOAc : hexanes); **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.40-7.20 (m, 5H), 5.19 (d, *J*=12.5 Hz, 1H), 5.13 (d, *J*=12.5 Hz, 1H), 4.11-4.02 (m, 2H), 1.93 (dddd, *J*=14.2, 9.3, 9.3, 4.9 Hz, 2H), 1.73 (dd, *J*=9.1, 4.5 Hz, 2H), 1.59 (ddd, *J*=13.9, 8.4, 4.9 Hz, 2H), 1.25 (d, *J*=6.8 Hz, 6H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 155.8, 137.4, 128.5, 127.9, 66.6, 47.3, 26.4, 20.9, 13.3 (missing quaternary carbon); **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2947, 2871, 1694, 1455 1404, 1376, 1350, 1311, 1284, 1217, 1162, 1130, 1117, 1091; **HRMS** (ESI^+) m/z calculated for $C_{15}H_{21}O_2N$ $[M]^+$: 247.1572; found: 247.1579. A single stereoisomer was detected by chiral HPLC (compared to a racemic sample). HPLC: Chiralpak AS-H 2.1×150mm column, 3% *i*PrOH/ 3% EtOAc/Hex, 25 deg, 0.1mL/min. Major 28.4 min.

2,3-Bis((2R,6R)-2,6-dimethylpiperidin-1-yl)chloro-cycloprop-2-en-1-ylium tetraphenylborate (3-56)



The amine salt (100 mg, 0.668 mmol) was placed in a round bottomed flask under argon atmosphere with CH_2Cl_2 (6.4 mL), sodium tetraphenylborate (109 mg, 0.318 mmol) and tetrachlorocyclopropene (39 μL, 0.32 mmol). At room temperature DIPEA (277 μL, 1.59 mmol) was added dropwise and the reaction was stirred for 2 hours. The mixture was transferred to a separatory funnel where the organic layer was washed with 1 N HCl, water and dried over sodium sulfate. This material was purified via recrystallization from chloroform : ether to give 158 mg (79%) of the chloro-bis(amino)cyclopropenium tetraphenylborate as a tan solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 (s, 8H), 7.01 (dd, *J*=7.3, 7.3 Hz , 8H), 6.87 (t, *J*=7.2 Hz, 4H), 3.95-3.85 (br. s, 2H), 3.50-3.40 (m, 2H), 1.78 (d, *J*=13.7 Hz, 2H), 1.75-1.40 (m, 8H), 1.34 (d, *J*=6.3 Hz, 6H), 1.33-1.25 (m, 2H), 1.24 (d, *J*=6.9 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.0, 164.6, 164.2, 163.9, 136.4, 134.2, 125.6, 121.8, 92.3, 58.4, 52.6, 34.1, 30.3, 20.6, 18.2, 17.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3249, 3055, 3035, 2982, 2942, 1907, 1587, 1480, 1456, 1440, 1429, 1410, 1387, 1363, 1332, 1316, 1139, 1084, 732, 704, 612; **HRMS** (ESI^+) m/z calculated for $C_{17}H_{28}N_2{}^{35}Cl$ $[M]^+$: 295.1936; found: 295.1967; m/z calculated for $C_{17}H_{28}N_2{}^{37}Cl$ $[M]^+$: 297.1907; found: 297.1940.

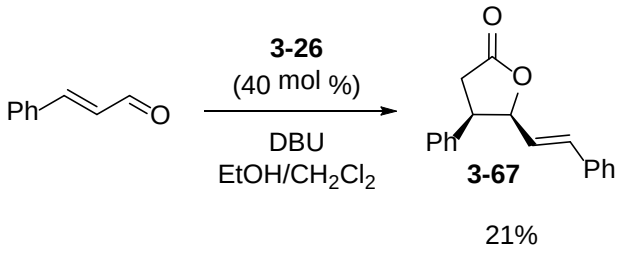
2,3-Bis((2R,6R)-2,6-dimethylpiperidin-1-yl)cycloprop-2-en-1-ylium tetraphenylborate (3-57)



3-56 **3-57**

The starting chloro-bis(amino)cyclopropenium salt (2.035 g, 3.30 mmol) was dissolved in acetone (3.3 mL) and acetic acid (16.5 mL). Granular elemental zinc (1.211 g, 18.5 mmol) was added to the mixture and it was stirred under argon for 18 hours. The mixture was filtered through Celite and washed with CH_2Cl_2 before the solvent was removed *in vacuo*. Addition of ethyl acetate triggered precipitation of most of the desired target compound in a pure state. The liquors were found to contain the desired cation as an acetate salt and so were washed in a separatory funnel with sodium tetraphenylborate (283 mg, 0.82 mmol) and water. The organic layer was washed with water, dried over sodium sulfate and the solvent was evaporated in vacuo. Trituration of this material with ethyl acetate and some diethyl ether gave rise to more of the desired product as a white solid. (1.400 g total, 73%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (s, 8H), 7.01 (dd, *J*=7.3, 7.3 Hz, 8H), 6.84 (t, *J*=7.2 Hz, 4H), 4.25 (s, 1H) 3.80-3.70 (br. s, 2H), 3.50-3.40 (m, 2H), 1.75-1.40 (m, 10H), 1.31 (d, *J*=6.5 Hz, 8H), 1.05 (d, *J*=5.6 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.7, 165.3, 164.9, 164.5, 136.5, 133.6, 126.1, 122.0, 98.9, 58.1, 53.0, 34.3, 30.6, 20.4, 18.5, 17.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3102, 3053, 2982, 2945, 1869, 1653, 1576, 1479, 1457, 1437, 1329, 1141, 1085, 909, 732, 704; **HRMS** (ESI^+) m/z calculated for $C_{17}H_{29}N_2$ $[M]^+$: 261.2325; found: 261.2329.

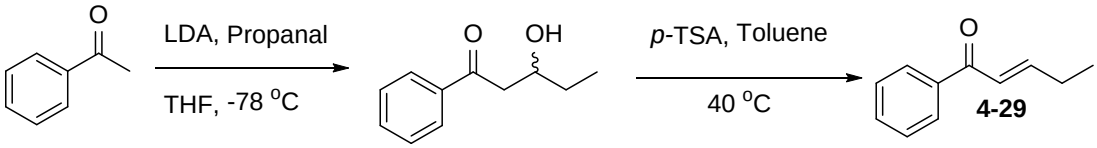
Lactone Dimer (3-67)



To catalyst **3-26** (22 mg, 0.04 mmol) in a test tube with Schlenk takeoff under nitrogen, cinnamaldehyde (30 μL, 0.22 mmol), CH_2Cl_2 (0.20 mL), and ethanol (30 μL, 0.66 mmol) were added followed by DBU (5 μL, 0.03 mmol). The mixture was stirred at room temperature overnight, and then worked up by being passed through a plug of silica using EtOAc as the eluent. The product was purified by column chromatography (15% EtOAc: hexanes) to give 6.4 mg of **3-67** (21% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.22 (m, 5H), 5.95 (s, 1H), 5.07 (s, 1H), 3.21 (dd, *J*=14.5, 4.0 Hz, 1H), 2.89 (dd, *J*=14.6, 6.8 Hz, 1H), 2.17 (s, 3H). Lactone **3-67** was identical to what was reported previously and its relative configuration was assigned by comparison of the ^{1}H NMR spectrum to the reported *cis* and *trans* lactones.[227]

7.4 Experimental Details for Chapter 4

***trans*-1-Phenyl-2-penten-1-one 4-29**

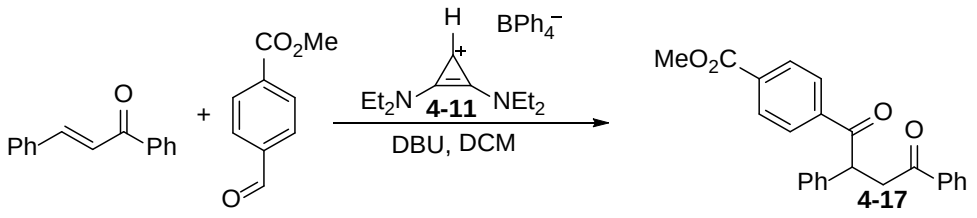


This acceptor was made in two steps from acetophenone. A solution of n-butyl lithium (17.9 mL, 41.5 mmol, 2.32 M in THF) was added to a solution of diisopropylamine (5.85 mL, 41.7 mmol) in 140 mL of THF at −78 °C under inert atmosphere. The mixture was allowed to warm to -30 °C over 30 minutes and then cooled down to −78 °C. Acetophenone (5.00 g, 41.7

mmol) was added and the mixture stirred for an additional 30 minutes. Freshly distilled propanal (6.0 mL (84 mmol) was then added. After 80 minutes at −78 °C, the reaction was quenched with 10 mL water mixed with 10 mL acetic acid. The solvent was then removed *in vacuo* and the crude product was transferred to a separatory funnel with Et_2O and washed with saturated aqueous $NaHCO_3$, brine, and water. It was then dried over sodium sulfate and purified by column chromatography (7:1 petroleum ether: EtOAc) to yield 6.63 g of the hydroxy ketone as a colorless oil. This product was used directly in the next step.

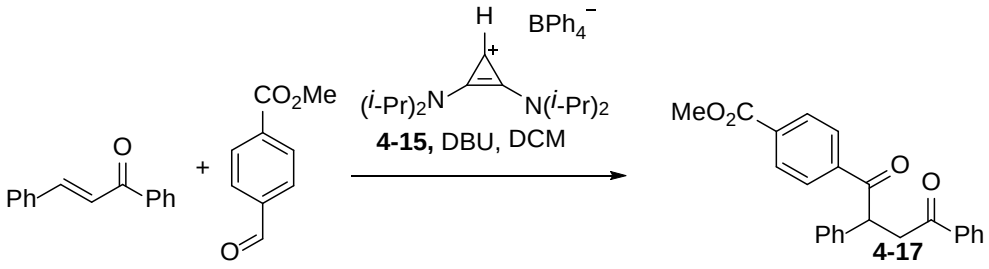
The aldol product (2.37 g, 13 mmol) was then dissolved in toluene (130 mL) and *p*-toluenesulfonic acid (2.4 g, 13 mmol) was added in one portion. This mixture was then heated to 40 °C for 3 hours until the starting material was no longer detected by TLC. The mixture was dried over sodium sulfate and purified by column chromatography (5% EtOAc: hexanes) to afford 1.64 g (77% yield) of pure *trans*-1-phenyl-2-penten-1-one. A small amount of the cis isomer was also isolated. Both the intermediate and product are known and all spectra matched the literature reported.[228]

1-(4-Methylbenzoate)-2-4-diphenylbutane-1,4-dione (4-17)

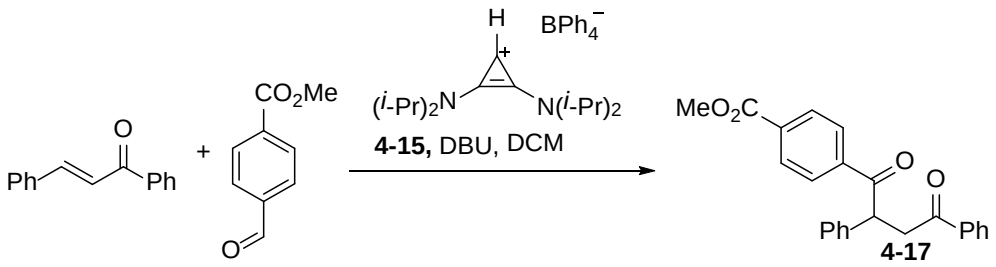


In a test tube fitted with a septum and Schlenk takeoff, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (4 μL, 0.03 mmol) was added to a solution of *trans*-chalcone (50 mg, 0.24 mmol), methyl-4-formyl-benzoate (43 mg, 0.26 mmol), and bis(diethylamino)cyclopropenium tetraphenylborate (12 mg, 0.024 mmol) in CH_2Cl_2 (0.24 mL) under nitrogen at room temperature.

After the reaction was determined to be completed by TLC (3 hours), it was quenched by being passed through a plug of neutral silica using EtOAc as the eluent. The product was purified by column chromatography (15% EtOAc: hexanes), which afforded 87 mg (98%) of **4-17** as a white solid. R_f = 0.3 (15% EtOAc, Hex); **m.p.** (°C): 109–112; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.06 (s, 4H), 7.98 (d, *J*=7.5 Hz , 2H), 7.56 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 7.35-7.30 (m, 4H), 7.24 (t, *J*=6.9 Hz, 1H), 5.31 (dd, *J*=10.3, 3.4 Hz, 1H), 4.23 (dd, *J*=18.1, 10.2 Hz, 1H), 3.91 (s, 3H), 3.34 (dd, *J*=18.1, 3.5 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 198.8, 198.1, 166.4, 140.1, 138.2, 136.5, 133.8, 133.5, 129.9, 129.5, 129.0, 128.8, 128.4, 128.3, 127.8, 52.6, 49.3, 44.1; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2951, 1725, 1681, 1281; **HRMS** (EI^+) m/z calculated for $C_{24}H_{21}O_4$ $[M]^+$: 373.1439; found: 373.1434.

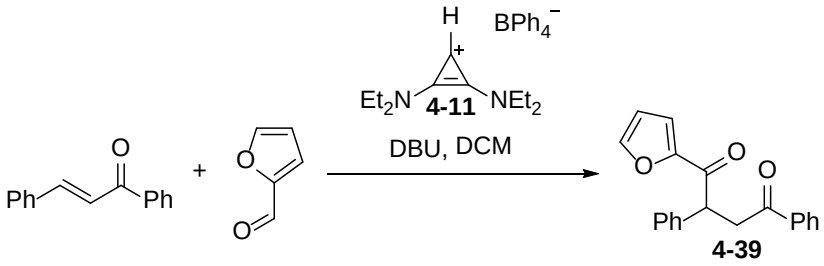


To *trans*-chalcone (30 mg, 0.14 mmol), methyl-4-formyl-benzoate (24 mg, 0.14 mmol), and bis(diisopropylamino)cyclopropenium tetraphenylborate (8.0 mg, 0.014 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added CH_2Cl_2 (1.0 mL) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2 μL, 0.01 mmol). After 3 hours, the reaction was quenched by being passed through a plug of neutral silica using EtOAc as the eluent. This afforded yield of <10% as judged by ^{1}H NMR spectroscopy, the bulk of the crude reaction mixture consisting of recovered starting materials.



To *trans*-chalcone (40 mg, 0.19 mmol), methyl-4-formyl-benzoate (35 mg, 0.21 mmol), and bis(diisopropylamino)cyclopropenium tetraphenylborate (32 mg, 0.057 mmol), in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added CH_2Cl_2 (0.20 mL) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (8 μL, 0.05 mmol). After 16 hours the reaction was quenched by being passed through a plug of neutral silica using EtOAc as the eluent. The product was purified by column chromatography (15% EtOAc: hexanes), which afforded 17 mg (24%) of **4-17** as a white solid.

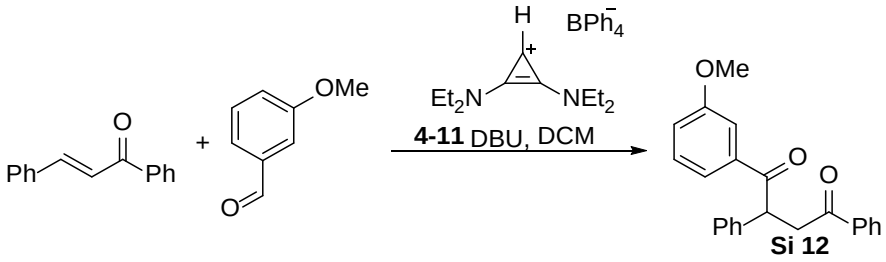
1-(2-Furyl)-2-4-diphenylbutane-1,4-dione (4-39)



To *trans*-chalcone (50 mg, 0.24 mmol), furfural (33 μL, 0.41 mmol), and bis(diethylamino)cyclopropenium tetraphenylborate (12 mg, 0.024 mmol), in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added CH_2Cl_2 (0.24 mL) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) 3.2μL, 0.02 mmol). After the reaction was determined to be completed by TLC (1.5 hours), it was quenched by being passed through a plug of neutral silica using EtOAc as the eluent. The product was purified by column chromatography (15% EtOAc: hexanes), which afforded 72 mg (99%) of **4-39** as a white solid. R_f = 0.3 (15% EtOAc:

hexanes); **m.p.** (°C): 109–111; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.97 (d, *J*=7.7 Hz, 2H), 7.57-7.54 (m, 2H), 7.46-7.39 (m, 4H), 7.32 (t, *J*=8.6 Hz, 2H), 7.26-7.23 (m, 2H), 6.48 (s, 1H), 5.12 (dd, *J*=10.2, 3.7 Hz, 1H), 4.18 (dd, *J*=18.0, 10.2 Hz, 1H), 3.33 (dd, *J*=18.1, 3.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 198.1, 187.9, 152.4 146.7, 138.5, 136.6, 133.5, 129.2, 128.8, 128.6, 128.4, 127.7, 118.4, 112.5, 48.9, 43.0; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 1672, 1466; **HRMS** (EI^+) m/z calculated for $C_{20}H_{16}O_3$ $[M]^+$: 304.1099; found: 304.1102.

1-(3-Methoxybenzyl)-2-4-diphenylbutane-1,4-dione (Si 12, Table 4.2, entry 1**)**

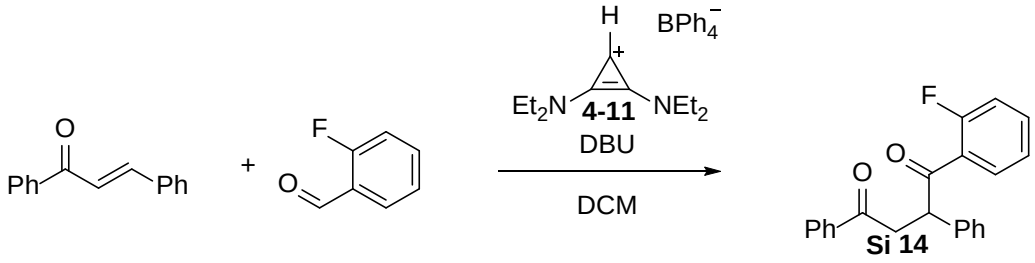


Si 12

To *trans*-chalcone (50 mg, 0.24 mmol), 3-methoxy-benzaldehyde (30 μL, 0.25 mmol), and bis(diethylamino)cyclopropenium tetraphenylborate (12 mg, 0.024 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added CH_2Cl_2 (0.30 mL), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (3.6 μL, 0.024 mmol). After the reaction was determined to be completed by TLC (1.5 hour), it was quenched by being passed through a plug of neutral silica using EtOAc as the eluent. The product was purified by column chromatography (10% EtOAc: hexanes), which afforded 60 mg (72%) of **Si 12**, as a white solid. R_f = 0.3 (10% EtOAc: hexanes); **m.p.** (°C): 139–141; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.99 (d, *J*=7.5 Hz, 2H), 7.68 (d, *J*=7.7 Hz, 1H), 7.60-7.50 (m, 2H), 7.44 (t, *J*=7.7 Hz, 2H), 7.39 (d, *J*=7.2 Hz, 2H), 7.31 (q, *J*=7.3 Hz, 3H), 7.23 (t, *J*=7.2 Hz, 1H), 7.03 (dd, *J*=8.2, 1.7 Hz, 1H), 5.33 (dd, *J*=13.5, 3.5 Hz, 1H), 4.20 (dd, *J*=18.0, 10.1 Hz, 1H), 3.80 (s, 3H), 3.31 (dd, *J*=18.0, 3.6 Hz, 1H); **^{13}C NMR** (125

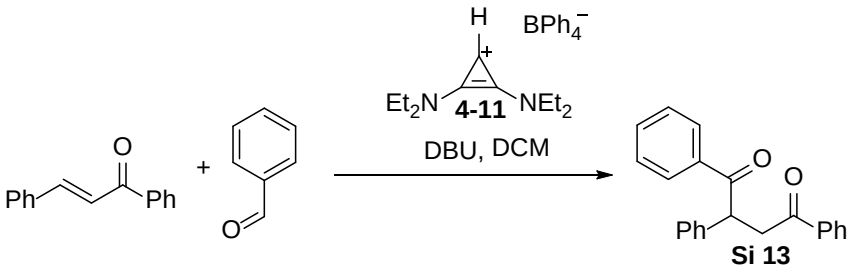
MHz, $CHCl_3$) δ 198.9, 198.2, 159.9, 138.9, 138.0, 136.7, 133.4, 129.7, 129.4, 128.8, 128.4, 128.3, 127.6, 121.8, 119.8, 113.3, 55.5, 49.1, 44.1; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 1679, 1597, 1581, 1288; **HRMS** (EI^+) m/z calculated for $C_{23}H_{20}O_3$ $[M]^+$: 344.1412; found: 344.1411.

1-(2-Fluorophenyl)-2,4-diphenylbutane-1,4-dione (Si 14, Table 4.2, entry 3**)**



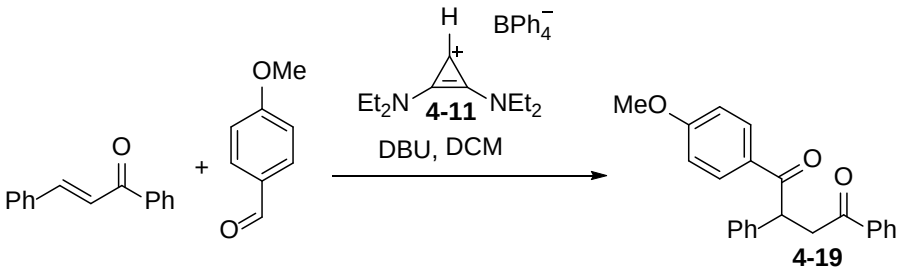
To the freshly distilled starting aldehyde (61 mg, 0.58 mmol), chalcone (40 mg, 0.19 mmol), bis(diethylamino)cyclopropenylidene tetraphenylborate precatalyst (19 mg, 0.037 mmol) and CH_2Cl_2 (48 μL) were placed in a sealed Schlenk test tube under argon and DBU (7 μL, 0.05 mmol) was added. After 16 hours the reaction was quenched with acetic acid and worked up by passing through a short pad of silica. The crude product was purified by column chromatography (10% EtOAc: hexanes) to give 13.4 mg (21%) of the Stetter product as a brown solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.97 (d, *J*=7.4 Hz, 2H), 7.90 (td, *J*=7.7, 1.7 Hz, 1H), 7.55 (t, *J*=7.3 Hz, 1H), 7.44 (t, *J*=7.8 Hz, 3H), 7.33 (t, *J*=7.5 Hz, 2H), 7.30 (t, *J*=7.3 Hz, 2H), 7.22 (t, *J*=7.2 Hz, 1H), 7.16 (t, *J*=7.4 Hz, 1H), 7.05 (dd, *J*=11.2, 8.4 Hz, 1H), 5.25 (dd, *J*=10.2, 3.7 Hz, 1H), 4.21 (ddd, *J*=18.0, 10.2, 1.7 Hz, 1H), 3.21 (dd, *J*=18.1, 3.8 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 198.2, 160.6, 137.9, 136.7, 134.6, 134.5, 133.4, 131.5, 131.5, 129.1, 128.8, 128.8, 128.4, 127.6, 125.6, 124.5, 124.5, 117.0, 116.9, 52.5, 52.5, 44.1; **FTIR** (KBr thin film) νmax (cm^{-1}): 3344, 3061, 3029, 2958, 2927, 2858, 1722, 1681, 1608, 1580, 1525, 1492, 1481, 1449, 1397, 1346, 1333, 1274, 1221; **HRMS** (ESI+) m/z calculated for $C_{22}H_{17}O_2F$ [M]+:332.1213; found: 332.1208.

1, 2, 4-Triphenylbutane-1,4-dione (Si 13, Table 4.2, entry 6**)**

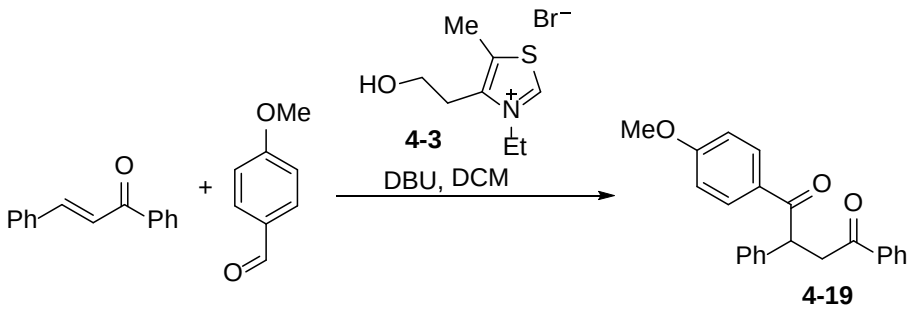


To *trans*-chalcone (40 mg, 0.19 mmol), benzaldehyde (20 μL, 0.19 mmol), and bis(diethylamino)cyclopropenium tetraphenylborate (19 mg, 0.04 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added CH_2Cl_2 (0.20 mL), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (6 μL, 0.04 mmol). After the reaction was determined to be completed by TLC (overnight), it was quenched by being passed through a plug of neutral silica using EtOAc as the eluent. The product was purified by column chromatography (10% EtOAc: hexanes), which afforded 39 mg (65%) of **Si 13**, as a white solid. R_f = 0.3 (10% EtOAc,: hexanes); All spectra are identical to those that have been described previously.[229] **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.02 (d, *J*=7.3 Hz, 2H), 7.99 (d, *J*=7.4 Hz, 2H), 7.55 (t, *J*=7.4 Hz, 1H), 7.49 (t, *J*=7.4 Hz, 1H), 7.44 (t, *J*=7.8 Hz, 2H), 7.44-7.35 (m, 4H), 7.33 (t, *J*=7.4 Hz, 2H), 7.23 (t, *J*=7.3 Hz, 1H), 5.34 (dd, *J*=10.1, 3.5 Hz, 1H), 4.17 (dd, *J*=18.0, 10.1 Hz, 1H), 3.30 (dd, *J*=18.0, 3.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 199.1, 198.2, 138.8, 136.6, 133.4, 133.1, 129.4, 129.1, 128.8, 128.7, 128.7, 128.4, 128.3, 127.5, 48.9, 44.0.

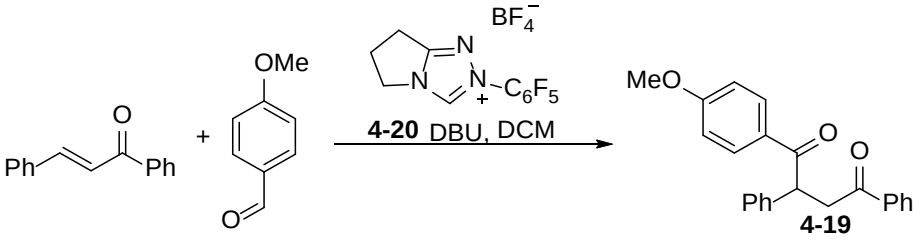
1-(4-Methoxybenzyl)-2-4-diphenylbutane-1,4-dione (4-19)



To *trans*-chalcone (50 mg, 0.24 mmol), 4-methoxybenzaldehyde (88 μL, 0.72 mmol), and bis(diethylamino)cyclopropenium tetraphenylborate (18 mg, 0.036 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added CH_2Cl_2 (0.12 mL), followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.4 μL, 0.036 mmol). After the reaction was determined to be completed by TLC (15 hours), it was quenched by being passed through a plug of neutral silica using EtOAc the eluent. The product was purified by column chromatography (10% EtOAc: hexanes), which afforded 63 mg (76%) of **4-19**, as white solid. An analytically pure sample was obtained by removing the last traces of 4-methoxybenzaldehyde in a Kulgelröhr (150 °C, 45 mm Hg). R_f = 0.20 (10% EtOAc: hexanes); **m.p.** (°C): 79–81; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.02 (d, *J*=8.8 Hz, 2H), 7.98 (d, *J*=7.8 Hz, 2H), 7.55 (t, *J*=7.3 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 2H), 7.36 (d, *J*=7.4 Hz, 2H), 7.30 (t, *J*=7.5 Hz, 2H), 7.22 (t, *J*=7.2 Hz, 1H), 6.87 (d, *J*=8.8 Hz, 2H), 5.30 (dd, *J*=9.9, 3.7 Hz, 1H), 4.20 (dd, *J*=18.0, 9.9 Hz, 1H), 3.82 (s, 3H), 3.27 (dd, *J*=18.0, 3.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 198.4, 197.5, 163.6, 139.4, 136.8, 133.4, 131.5, 129.6, 129.4, 128.8, 128.8, 128.4, 127.5, 113.9, 55.6, 48.6, 44.0; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 1672, 1599, 1251, 1201; **HRMS** (EI^+) m/z calculated for $C_{23}H_{20}O_3$ $[M]^+$: 344.1412; found: 344.1410.

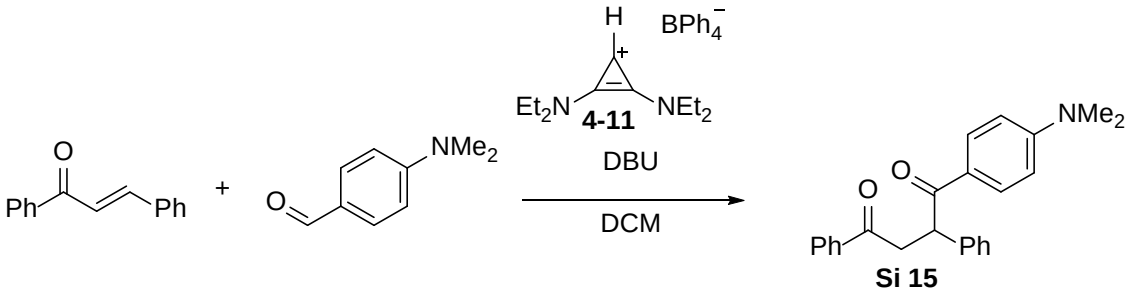


To *trans*-chalcone (50 mg, 0.24 mmol), 4-methoxybenzaldehyde (88 μL, 0.72 mmol), and thiazolium salt **4-3** (9.1 mg, 0.036 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added CH_2Cl_2 (0.12 mL) followed by 1, 8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.4 μL, 0.036 mmol). After 15 hours, the reaction was quenched by being passed through a plug of neutral silica using EtOAc as the eluent. The yield was determined by ^{1}H NMR using bibenzyl as an internal standard: 14% of the desired Stetter product and 10% of the homobenzoin product.



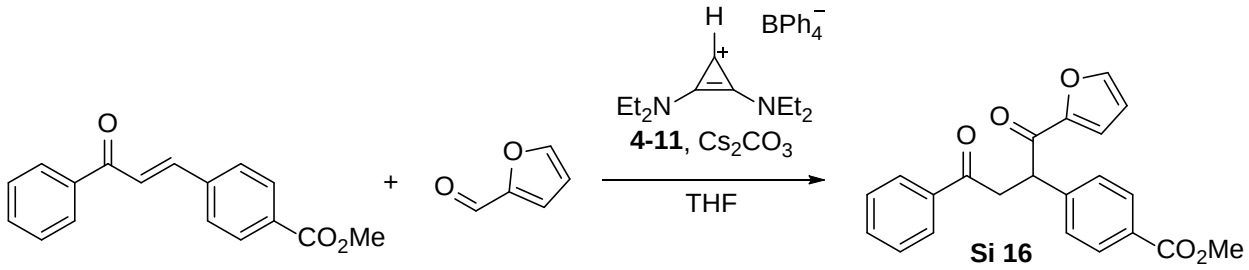
To *trans*-chalcone (50 mg, 0.24 mmol), 4-methoxybenzaldehyde (88 μL, 0.72 mmol), and triazolium salt **4-20** (13 mg, 0.036 mmol), in a test tube fitted with a septum and Schlenk takeoff under nitrogen I added CH_2Cl_2 (0.12 mL) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5.4 μL, 0.036 mmol). After 15 hours the reaction was quenched by being passed through a plug of neutral silica using EtOAc as the eluent. The yield was determined by ^{1}H NMR using bibenzyl as an internal standard: 9% of the desired Stetter product and 73% of the homobenzoin product.

1-(4-(Dimethylamino)phenyl)-2,4-diphenylbutane-1,4-dione (Si 15, Table 4.2, entry 8**)**



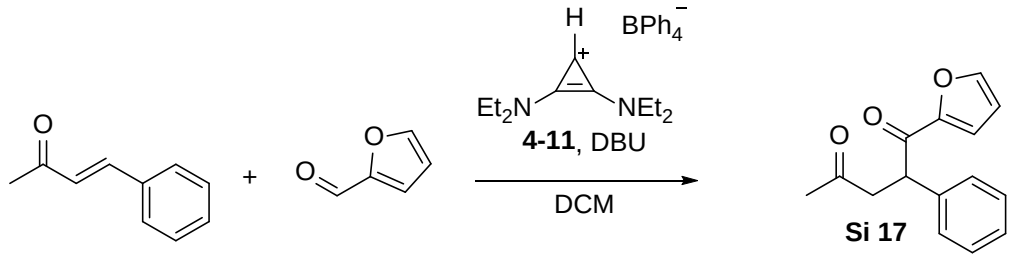
To the starting aldehyde (43 mg, 0.29 mmol), chalcone (40 mg, 0.19 mmol), bis(diethylamino)cyclopropenylidene tetraphenylborate precatalyst (19 mg, 0.037 mmol) and CH_2Cl_2 (48 μL), in sealed Schlenk test tube under argon, DBU (6 μL, 0.04 mmol) was added. After 16 hours the reaction was quenched with acetic acid and worked up by passing through a short pad of silica. The crude product was purified by column chromatography (2% EtOAc: toluene) to give 10.1 mg (15%) of the Stetter product as a tan solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.97 (t, *J*=7.4 Hz, 4H), 7.53 (t, *J*=7.4 Hz, 1H), 7.41 (t, *J*=7.5 Hz, 2H), 7.37 (d, *J*=7.2 Hz, 2H), 7.28 (t, *J*=7.4 Hz, 2H), 7.19 (t, *J*=7.4 Hz, 1H), 6.65 (d, *J*=8.9 Hz, 2H), 5.29 (dd, *J*=9.6, 4.1 Hz, 1H), 4.21 (dd, *J*=17.5, 7.9 Hz, 1H), 3.21 (dd, *J*=17.9, 4.1 Hz, 1H), 3.01 (s, 6H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 198.6, 196.9, 146.2, 140.2, 137.0, 133.3, 131.4, 129.2, 128.7, 128.4, 128.4, 128.1, 127.2, 111.3, 48.2, 43.8, 40.4; **FTIR** (KBr thin film) νmax (cm^{-1}): 3058, 3026, 2906, 2818, 1739, 1683, 1657, 1595, 1550, 1529, 1492, 1448, 1371, ; **HRMS** (ESI+) m/z calculated for $C_{24}H_{24}O_2N$ [M]+:358.1807; found: 358.1758.

Methyl 4-(1-(furan-2-yl)-1,4-dioxo-4-phenylbutan-2-yl)benzoate Si 16, Table 4.3, entry 1**)**



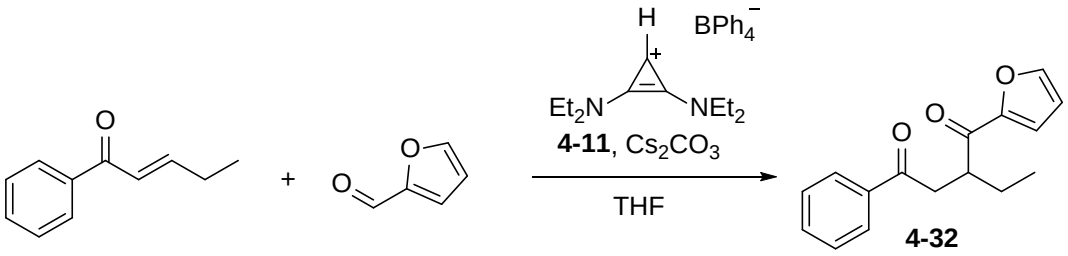
The enone was prepared by E. Sanchez Larios according to literature procedures.[230] To the freshly distilled starting aldehyde (34 μL, 0.41 mmol), the enone (105 mg, 0.396 mmol) and cesium carbonate (130 mg, 0.39 mmol) in THF (0.4 mL) bis(diethylamino)cyclopropenylidene tetraphenylborate precatalyst (20 mg, 0.040 mmol) was added. Upon completion as judged by TLC (25 minutes), the reaction was worked up. The crude product was purified by column chromatography (10% EtOAc: Hex) to give 136 mg (95%) of the pure Stetter product as an off white solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.96 (t, *J*=8.5 Hz, 4H), 7.56 (t, *J*=7.5 Hz, 2H), 7.48 (d, *J*=8.3 Hz, 2H), 7.45 (t, *J*=7.6 Hz, 2H), 7.24 (d, *J*=3.6 Hz, 1H), 6.49 (dd, *J*=3.6, 1.7 Hz, 1H), 5.20 (dd, *J*=9.9, 3.9 Hz, 1H), 4.17 (dd, *J*=18.0, 10.0 Hz, 1H), 4.14 (s, 3H), 3.35 (dd, *J*=18.0, 4.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 197.4, 187.0, 166.6, 152.0, 146.8, 143.4, 136.3, 133.4, 130.3, 129.4, 128.6, 128.4, 128.1, 118.4, 112.5, 52.1, 48.7, 42.4; **FTIR** (KBr thin film) νmax (cm^{-1}): 2952, 1721, 1374, 1609, 1568, 1448, 1435, 1282; **HRMS** (ESI+) m/z calculated for $C_{22}H_{18}O_5$ [M]+:362.1154; found: 362.1161.

1-(Furan-2-yl)-2-phenylpentane-1,4-dione (Si 17, Table 4.3, entry 8**)**



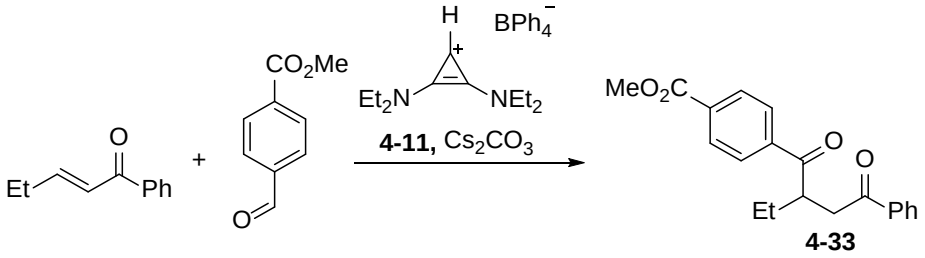
To the freshly distilled starting aldehyde (22 μL, 0.27 mmol), Michael acceptor (40 mg, 0.27 mmol), bis(diethylamino)cyclopropenylidene tetraphenylborate precatalyst (13.7 mg, 0.027 mmol) and THF (270 μL), in sealed Schlenk test tube under argon, cesium carbonate (89 mg, 0.0.274 mmol) was added. After 18 hours the reaction was quenched with acetic acid and worked up by passing through a short pad of silica. The crude product was purified by column chromatography (15% EtOAc: hexanes) to give 5.0 mg (9% isolated) of the Stetter product a yellow oil, in addition to 4.4 mg (7%) the aldol product. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.52 (s, 1H), 7.31-7.26 (m, 4H), 7.26-7.23 (m, 1H), 7.17 (d, *J*=3.6 Hz, 1H), 6.44 (dd, *J*=5.3, 1.7 Hz, 1H), 4.89 (dd, *J*=10.2, 4.1 Hz, 1H), 3.60 (dd, *J*=18.1, 10.2 Hz, 1H), 2.76 (dd, *J*=18.1, 4.1 Hz, 1H), 2.17 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 206.7, 187.8, 152.3, 146.7, 138.4, 129.2, 128.4, 127.6, 118.5, 112.5, 48.9, 47.2, 30.2; **HRMS** (ESI+) m/z calculated for $C_{15}H_{14}O_3$ [M]+: 242.0943; found: 242.0944. Aldol product **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.60 (d, *J*=16.2 Hz, 1H), 7.56 (dd, *J*=5.5, 1.8 Hz, 1H), 7.42-7.39 (m, 4H), 6.73 (d, *J*=16.2 Hz, 1H), 6.33 (dd, *J*=14.5, 1.8 Hz, 1H), 5.28 (dd, *J*=9.0, 3.2 Hz, 1H), 3.60-4.40 (br. s, 1H), 3.30 (dd, *J*=17.3, 8.8 Hz, 1H), 3.19 (dd, *J*=17.4, 3.2 Hz, 1H); Spectra for the aldol product are consistent with the literature.[231]

2-Ethyl-1-(furan-2-yl)-4-phenylbutane-1,4-dione (4-32)

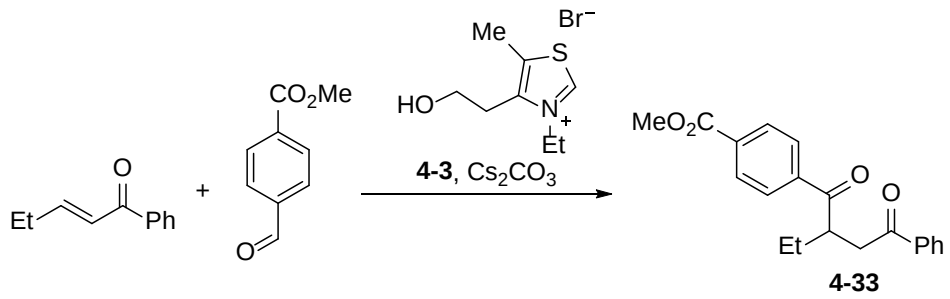


To the freshly distilled starting aldehyde (34 μL, 0.41 mmol), the enone (63 mg, 0.40 mmol) and cesium carbonate (130 mg, 0.39 mmol) in THF (0.4 mL) bis(diethylamino)cyclopropenylidene tetraphenylborate precatalyst (20 mg, 0.040 mmol) was added. After 3 hours the reaction was worked up by passing through a short pad of silica. The crude product was purified by column chromatography (10% EtOAc: Hex) to give 35 mg (34%) of the pure Stetter product as a orange oil as well as 30 mg (47%) of recovered Michael acceptor. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.96 (d, *J*=7.3 Hz, 2H), 7.60 (d, *J*=0.5 Hz, 1H), 7.53 (t, *J*=7.4 Hz, 1H), 7.44 (t, *J*=7.7 Hz, 2H), 7.28 (d, *J*=3.5 Hz, 1H), 6.54 (dd, *J*=3.5, 1.7 Hz, 1H), 3.84 (dddd, *J*=9.2, 6.6, 6.6, 4.3 Hz, 1H), 3.65 (dd, *J*=17.9, 9.3 Hz, 1H), 3.13 (dd, *J*=18.0, 4.2 Hz, 1H), 1.80 (ddq, *J*=6.9, 6.9, 13.9 Hz, 1H), 1.65 (ddq, *J*=7.4, 7.4, 14.8 Hz, 1H) 0.96 (t, *J*=7.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 198.6, 192.1, 153.0, 146.6, 136.8, 133.3, 128.7, 128.2, 117.7, 112.4, 43.6, 40.2, 25.8, 11.9; **FTIR** (KBr thin film) νmax (cm^{-1}): 2966, 1671, 1567, 1467, 1400, 1239, 1435, 1282; **HRMS** (ESI+) m/z calculated for $C_{16}H_{16}O_3$ [M]+:256.1099; found: 256.1096.

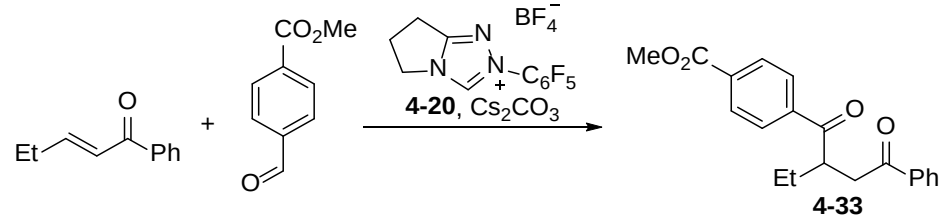
1-(Methyl-4-formyl benzyl)-2-ethyl-4-phenylbutane-1,4-dione (4-33)



To methyl-4-formyl benzoate (40 mg, 0.31 mmol), cesium carbonate (79 mg, 0.243 mmol), and catalyst **4-11** (24 mg, 0.05 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen, was added the acceptor (38 μL, 0.24 mmol) followed by CH_2Cl_2 (40 μL). After 3 hours, the reaction was quenched with acetic acid followed by being passed through a plug of neutral silica using EtOAc as the eluent. The acceptor was completely consumed as determined by ^{1}H NMR spectroscopy. The product was purified by column chromatography (12% EtOAc: hexanes), which afforded 73 mg (96%) of **4-33** as a white solid. R_f = 0.4 (20% EtOAc: hexanes); **m.p.** (°C): 88–89. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.15 (d, *J*=8.1 Hz, 2H), 8.10 (d, *J*=10.8 Hz, 2H), 7.96 (d, *J*=8.2 Hz, 2H), 7.56 (t, *J*=7.3 Hz, 1H), 7.44 (t, *J*=7.6 Hz, 2H), 4.15-4.05 (m, 1H), 3.94 (s, 3H), 3.76 (dd, *J*=18.0, 7.4 Hz, 1H), 3.18 (dd, *J*=18.0, 3.7 Hz, 1H), 1.80 (ddq, *J*=7.4, 7.3, 6.8 Hz, 1H), 1.65 (ddq, *J*=7.4, 7.1, 7.0 Hz, 1H), 0.95 (t, *J*=7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 203.2, 198.8, 166.5, 140.6, 136.7, 133.8, 130.8, 128.7, 128.5, 128.4, 128.3, 128.2, 52.6, 52.5, 43.2, 40.6, 11.9; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 2964, 1725, 1681; **HRMS** (EI^+) m/z calculated for $C_{20}H_{20}O_4$ $[M]^+$: 324.1361; found: 324.1366.

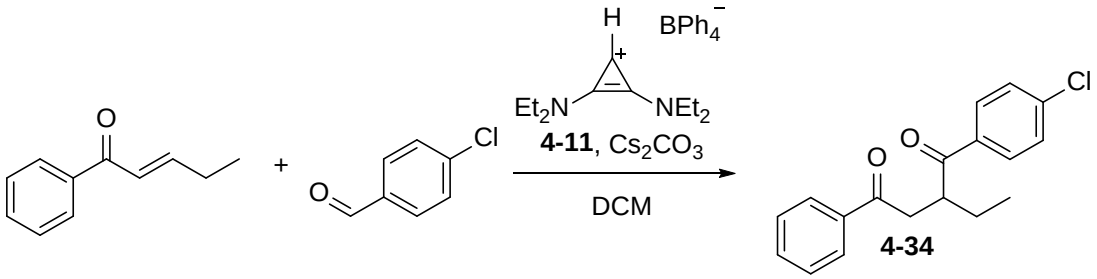


To methyl-4-formyl benzoate (40 mg, 0.31 mmol), cesium carbonate (79 mg, 0.243 mmol), and thiazolium **4-3** (12.3 mg, 0.05 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added the unsaturated acceptor (38 μL, 0.24 mmol) followed by CH_2Cl_2 (40 μL). After 3 hours, the reaction was quenched with acetic acid followed by being passed through a plug of neutral silica using EtOAc as the eluent. The acceptor was completely consumed as determined by ^1H NMR analysis. The product was purified by column chromatography (12% EtOAc: hexanes), which afforded 29 mg (38%) of **4-33** as a white solid.



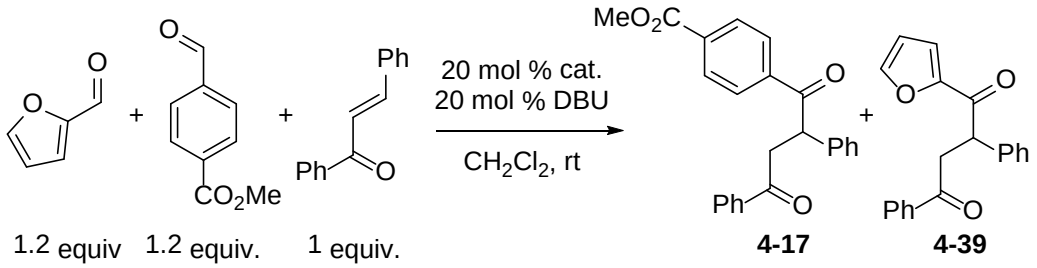
To methyl-4-formyl benzoate (40 mg, 0.31 mmol), cesium carbonate (79 mg, 0.24 mmol), and triazolium **4-22** (18 mg, 0.05 mol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added the unsaturated acceptor (38 μL, 0.24 mmol) followed by CH_2Cl_2 (40 μL). After 3 hours, the reaction was quenched with acetic acid followed by being passed through a plug of neutral silica using EtOAc as the eluent. The yield was determined by ^1H NMR using bibenzyl as an internal standard: 4 mg (5%) of **4-33**, along with 15% homo-benzoin product and a large amount of recovered starting material.

1-(4-Chlorophenyl)-2-ethyl-4-phenylbutane-1,4-dione (4-34)



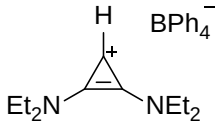
To the starting aldehyde (34 mg, 0.24 mmol), the Michael acceptor (38 μL, 0.24 mmol) and cesium carbonate (120 mg, 0.36 mmol) in CH_2Cl_2 (0.4 mL) bis(diethylamino)-cyclopropenylidene tetraphenylborate precatalyst (24 mg, 0.047 mmol) was added. After 16 hours the reaction was quenched with acetic acid and worked up by passing through a short pad of silica. The conversion was assessed to be approximately 60% by NMR of the crude reaction mixture. The crude product was purified by column chromatography (15% EtOAc: Hex) to give 8.8 mg (12%) of the pure Stetter product as a colorless oil. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.97 (d, *J*=10.5 Hz, 2H), 7.94 (d, *J*=16.7 Hz, 2H), 7.54 (t, *J*=6.4 Hz, 1H), 7.46 (d, *J*=8.7 Hz, 2H), 7.45 (t, *J*=9.7 Hz, 2H), 4.01 (dddd, *J*=9.8, 6.7, 6.7, 4.0 Hz, 1H), 3.72 (dd, *J*=18.0, 9.5 Hz, 1H), 3.17 (dd, *J*=18.0, 3.9 Hz, 1H), 1.79 (ddq, *J*=7.4, 7.4, 14.8 Hz, 1H), 1.60 (ddq, *J*=7.3, 7.3, 14.6 Hz, 1H) 0.94 (t, *J*=7.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 202.4, 198.9, 139.5, 136.7, 135.6, 133.5, 130.1, 129.2, 128.8, 128.3, 42.8, 40.7, 25.8, 11.9; **FTIR** (KBr thin film) νmax (cm^{-1}): 2965, 2932, 1679, 1590, 1590, 1488, 1448, 1258, 1091; **HRMS** (ESI+) m/z calculated for $C_{18}H_{17}O_2Cl$ [M]+:300.0917; found: 300.0914.

Aldehyde Competition Reactions

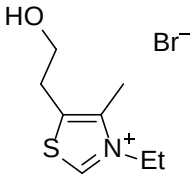


All three competition reactions were performed in parallel under otherwise identical conditions.

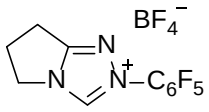
To *trans*-chalcone (50 mg, 0.24 mmol), methyl-4-formyl benzoate (48 mg, 0.29 mmol), and catalyst (0.048 mmol) in a test tube with Schlenk takeoff under nitrogen was added CH_2Cl_2 (0.50 mL) and furfural (24 μL, 0.29 mmol), followed by DBU (7.2 μL, 0.048 mmol). The reaction was stirred overnight and quenched by passing through a short plug of silica using EtOAc as the eluent. The products were purified by column chromatography (5% EtOAc: hexanes) to give **4-17** and **4-39** as an inseparable mixture.



Using **4-11** (24 mg, 0.048 mmol), 88 mg were obtained (quantitative yield with respect to *trans*-chalcone). Ratio of **4-17**:**4-39** = 85:15 as determined by ^{1}H NMR spectroscopy on the crude reaction mixture.



Using thiazolium salt **4-3** (12 mg, 0.048 mmol), 63 mg were obtained (80% yield with respect to *trans*-chalcone). Ratio of **4-17**:**4-39** = 37:63 as determined by ^{1}H NMR spectroscopy on the crude reaction mixture.



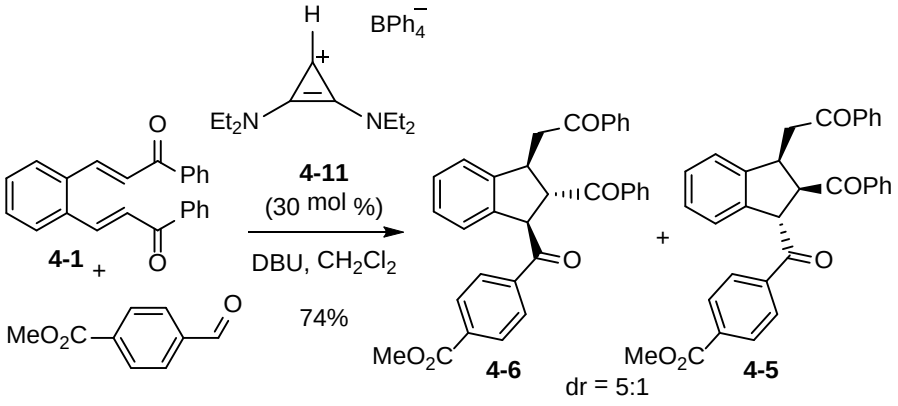
Using triazolium salt **4-20** (17 mg, 0.048 mmol), 64 mg was obtained (85% yield with respect to *trans*-chalcone). Ratio of **4-17**:**4-39** = 12:88 as determined by ^{1}H NMR spectroscopy on the crude reaction mixture.

^{1}H NMR monitoring experiments

The competition reactions were also performed in an NMR tube and the distribution of products was monitored over time.

To *trans*-chalcone (42 mg, 0.2 mmol) in an NMR tube under an active flow of argon gas was added furfural (18 μL, 0.22 mmol), methyl-4-formyl-benzoate (37 mg, 0.22 mmol), bibenzyl (20 mg, internal standard), catalyst (0.04 mmol), and $CDCl_3$ (0.40 mL). To this mixture was added DBU (6 μL, 0.04 mmol), then the NMR tube was shaken and sonicated for 1 minute. ^{1}H NMR spectra were acquired (relaxation delay = 10 seconds) at regular intervals for 260 minutes.

Stetter- Michael Reaction (4-5 and 4-6)

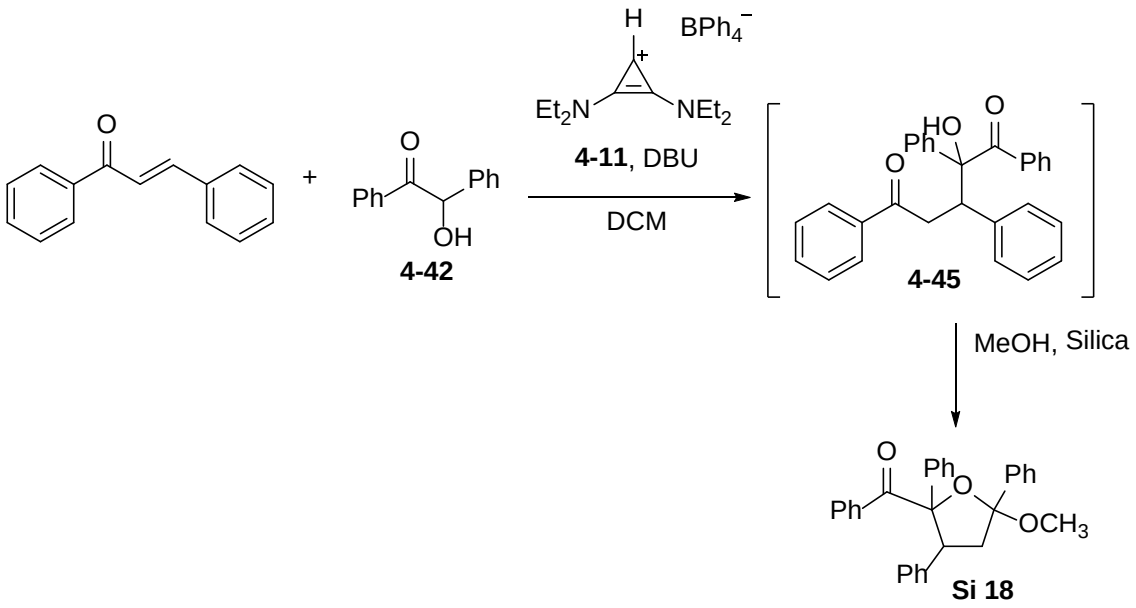


To a mixture of the ketone (50 mg, 0.147 mmol), methyl-4-formyl benzoate, (24 mg, 0.146 mmol), and precatalyst **4-11** (22 mg, 0.043 mmol) in CH_2Cl_2 (0.15 mL) in a test tube with

Schlenk takeoff under nitrogen was added DBU (6.7 μL, 0.043 mmol). The reaction was followed by TLC for one hour until starting material was consumed. The reaction was then quenched by passing through a plug of silica using EtOAc as the eluent, and purified by column chromatography (15% EtOAc: hexanes). To remove some remaining impurities, a second column chromatography was performed (100% CH_2Cl_2). This procedure yielded 53 mg (74%) of the products shown above as a mixture of diastereomers (5:1 dr). Both compounds have been reported previously.[147]

2-Hydroxy-1, 2, 3, 5-tetraphenylpentane-1, 5-dione (4-45) and

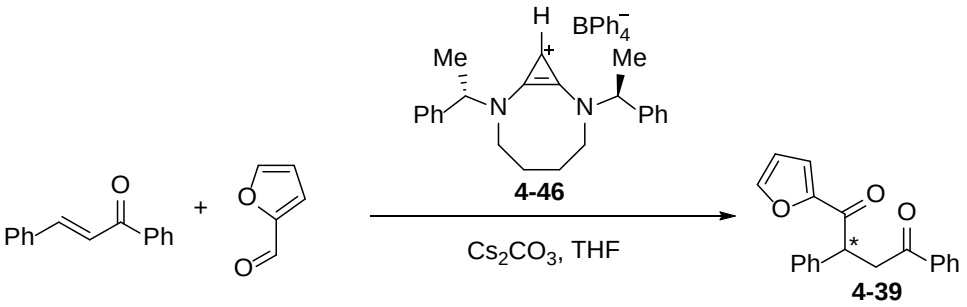
(5-methoxy-2, 3, 5-triphenyltetrahydrofuran-2-yl)(phenyl)methanone (Si 18)



To a Schlenk test tube with takeoff benzoin (41 mg, 0.19 mmol), chalcone (40 mg, 0.19 mmol), and EtBAC (9.6 mg, 0.019 mmol) in CH_2Cl_2 (200 μL) were added and placed under an argon atmosphere. DBU (3 μL, 0.02 mmol) was added and the reaction was run at room temp for 16 hours. The reaction was worked up to give a new material which was purified by column chromatography (10: 1 hexanes: EtOAC+ 2% MeOH) and pTLC (100% CH_2Cl_2), (3% EtOAC: toluene) to give small amounts of what has been identified as the open form Stetter product as

well as the cyclized acetal as a mixture of diastereomers (as a yellow oil). **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.04 (d, *J*=7.7 Hz, 2H), 7.75 (d, *J*=7.2 Hz, 2H), 7.49 (t, *J*=7.3 Hz, 2H), 7.40 (dt, *J*=10.4, 7.5 Hz, 2H), 7.30 (t, *J*=7.6 Hz, 2H), 7.18-7.00 (m, 5H), 7.00-6.90 (m, 5H), 5.13 (dd, *J*=11.5, 7.3 Hz, 1H), 2.81 (dd, *J*=12.8, 7.2 Hz, 1H), 2.53 (s, 3H), 2.52 (dd, *J*=12.5, 7.7 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 199.2, 139.9, 139.1, 139.0, 135.5, 132.5, 131.0, 129.7, 128.7, 128.5, 128.2, 128.1, 127.7, 127.4, 126.7, 126.4, 125.6, 109.3, 95.1, 50.5, 50.5, 45.9; **FTIR** (KBr thin film) νmax (cm^{-1}): 3062, 2360, 1787, 1722, 1684, 1598, 1494, 1449, 1317, 1251, 1213, 1175, 1023, 1000; **HRMS** (EI^+) m/z calculated for $C_{29}H_{23}O_2$ ($C_{30}H_{26}O_3 - CH_4O$) [M]+:402.1620; found: 402.1648.

Enantioselective Stetter Reaction (4-39)



To *trans*-chalcone (40 mg, 0.19 mmol) and cesium carbonate (62 mg, 0.19 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added THF (0.10 mL) and furfural (16.7 μL, 0.20 mmol) followed by catalyst **4-46** (19 mg, 0.029 mmol). After 2 hours, the reaction was complete as judged by TLC and was quenched with acetic acid. The mixture was then passed through a plug of neutral silica using EtOAc as the eluent. The product was purified by column chromatography (15% EtOAc: hexanes), which afforded 58 mg (99%) of **4-39** as a white solid. Analysis by ^{1}H NMR spectroscopy was consistent with **4-39** as listed above. HPLC: Chiralpak IC 2.1×150mm column, 5% *i*PrOH/Hex, 25 deg, 0.1mL/min. Major 33.1 min, minor 53.4 min, 36% ee.

HPLC Trace for Stetter Reaction using Catalyst 4-46 to form Stetter Product 4-39

```
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    ======================================================================
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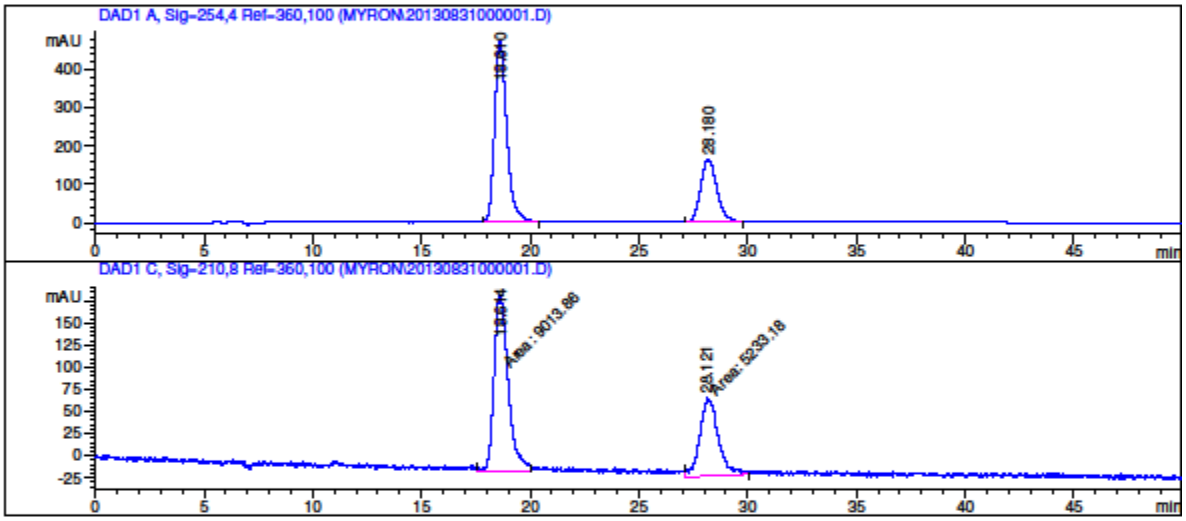
    Acq. Instrument : Instrument 1                    Location : Vial 51
    Injection Date  : 08-08-2013 3:02:07 PM
                                                    Inj Volume : 0.5 µl
    Acq. Method     : C:\CHEM32\1\METHODS\5PERCENTIPROH.M
    Last changed    : 08-08-2013 3:00:40 PM by Myron
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\MYRON\20130831000001.D\DA.M (5PERCENTIPROH.M)
    Last changed    : 12-23-2015 5:36:41 PM by mehran
    Method Info     :


    Sample Info     : IC, 5% isopropanol in hexanes, 0.1 mL/min, 0.5, injecti
                      on volume


    ======================================================================
```



Data File C:\CHEM32\1\DATA\MYRON\20130831000001.D
Sample Name: MW-5-19B-aug8

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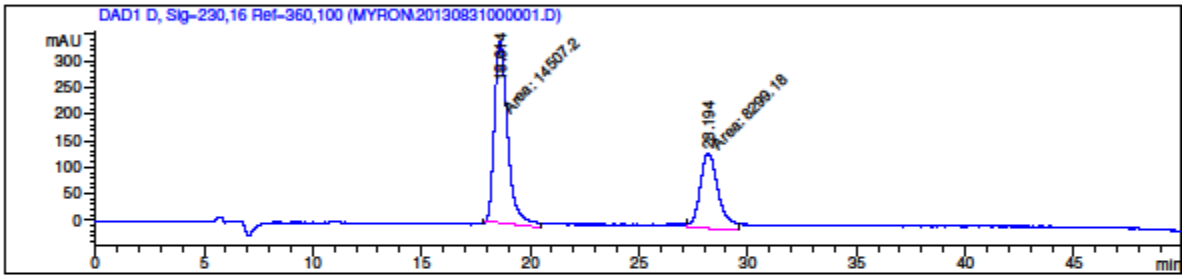
    ======================================================================
    Acq. Operator   : Myron
    Acq. Instrument : Instrument 1                    Location : Vial 51
    Injection Date  : 08-08-2013 3:02:07 PM
                                                    Inj Volume : 0.5 µl
    Acq. Method     : C:\CHEM32\1\METHODS\5PERCENTIPROH.M
    Last changed    : 08-08-2013 3:00:40 PM by Myron
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\MYRON\20130831000001.D\DA.M (5PERCENTIPROH.M)
    Last changed    : 12-23-2015 5:36:41 PM by mehran
    Method Info     :


    Sample Info     : IC, 5% isopropanol in hexanes, 0.1 mL/min, 0.5, injecti
                      on volume

    ======================================================================
```

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    ======================================================================
                              Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  18.610 BB    0.5959 1.84837e4   472.97900  68.2149
       2  28.180 BB    0.8110 8612.58105  164.99361  31.7851

    Totals :                  2.70963e4   637.97261


    Signal 2: DAD1 C, Sig=210,8 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  18.614 MM    0.7594 9013.86133  197.83961  63.2683
       2  28.121 MM    0.9880 5233.18311   88.27748  36.7317
```

Data File C:\CHEM32\1\DATA\MYRON\20130831000001.D
Sample Name: MW-5-19B-aug8

Acq. Operator : Myron
Acq. Instrument : Instrument 1 Location : Vial 51
Injection Date : 08-08-2013 3:02:07 PM
Inj Volume : 0.5 µl
Acq. Method : C:\CHEM32\1\METHODS\5PERCENTIPROH.M
Last changed : 08-08-2013 3:00:40 PM by Myron
(modified after loading)
Analysis Method : C:\CHEM32\1\DATA\MYRON\20130831000001.D\DA.M (5PERCENTIPROH.M)
Last changed : 12-23-2015 5:36:41 PM by mehran
Method Info :

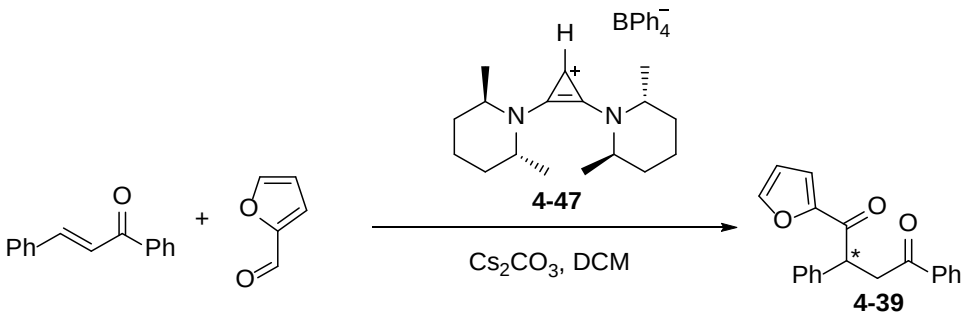
Sample Info : IC, 5% isopropanol in hexanes, 0.1 mL/min, 0.5, injecti
on volume

Totals :			1.42470e4	286.11710		

Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.614	MM	0.7103	1.45072e4	340.38028	63.6103
2	28.194	MM	0.9737	8299.17676	142.05055	36.3897
Totals :				2.28064e4	482.43083	

*** End of Report ***



To *trans*-chalcone (40 mg, 0.19 mmol) and cesium carbonate (62 mg, 0.19 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added DCM (0.20 mL) and furfural (19 μL, 0.23 mmol) followed by catalyst **4-47** (17 mg, 0.029 mmol). After 6 hours, the reaction was quenched with acetic acid. The mixture was then passed through a plug of neutral silica using EtOAc as the eluent. The product was purified by column chromatography (10% EtOAc: hexanes), which afforded 23 mg (39%) of **4-39** as a white solid. Analysis by ^{1}H NMR spectroscopy was consistent with **4-39** as listed above. HPLC: Chiralpak IC 2.1×150mm column, 5% *i*PrOH/Hex, 25 deg, 0.1mL/min. Major 37.5 min, minor 66.5 min, 48% ee.

HPLC Trace for Stetter Reaction using Catalyst 4-47 to form Stetter Product 4-39

```
Data File C:\CHEM32\1\DATA\MYRON\20140516000003.D
Sample Name: MW-6-197Cch

    ======================================================================
    Acq. Operator   : Myron
    Acq. Instrument : Instrument 1                    Location : Vial 14
    Injection Date  : 05-16-2014 6:09:40 PM
                                                    Inj Volume : 0.6 µl
    Acq. Method     : C:\CHEM32\1\METHODS\1PERCENTIPROH.M
    Last changed    : 05-16-2014 6:08:23 PM by Myron
                      (modified after loading)
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    Last changed    : 05-16-2014 7:24:35 PM by Myron
    Method Info     :


    Sample Info     : IC, 5% iPrOH hexanes, 0.1 mL/min, 0.5 uL injection volu
                      me, 25 oC
                      chiral
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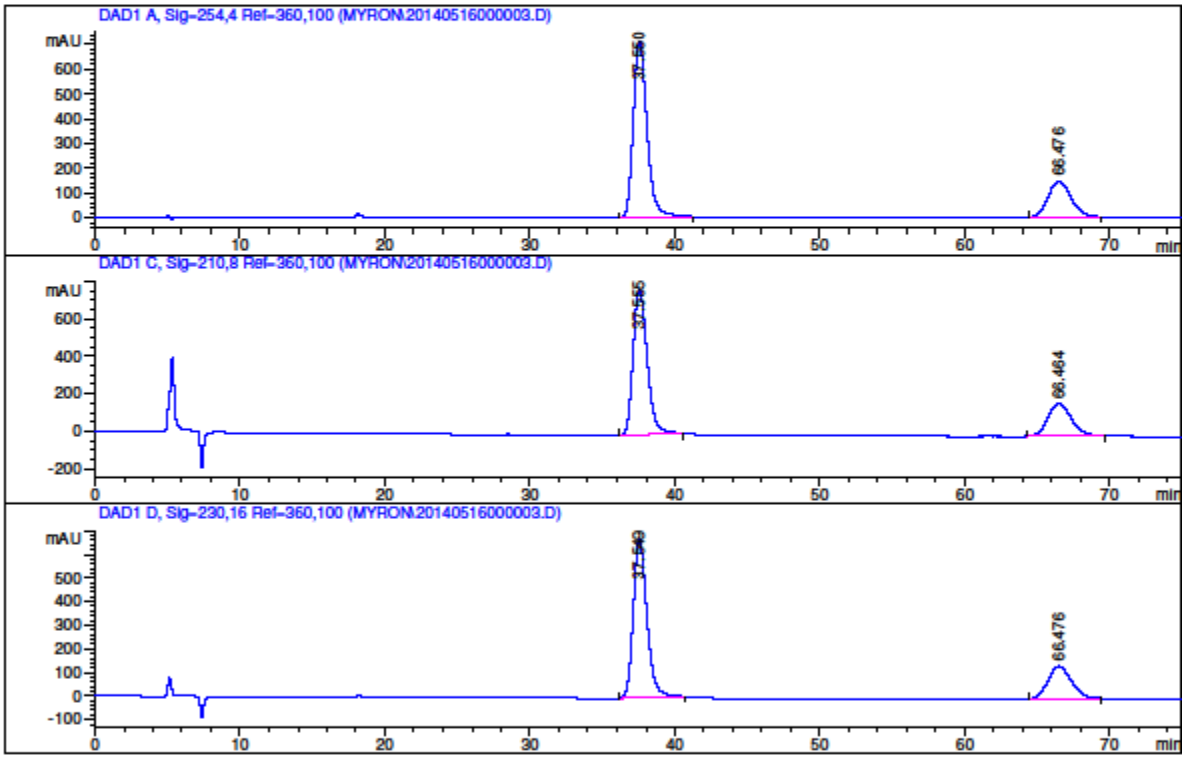


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    ======================================================================
                            Area Percent Report
    ======================================================================

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    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs
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Data File C:\CHEM32\1\DATA\MYRON\20140516000003.D
Sample Name: MW-6-197Cch

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.550	BB	1.0186	4.70997e4	713.05066	74.3189
2	66.476	BB	1.6926	1.62754e4	145.55014	25.6811
Totals :				6.33751e4	858.60080	

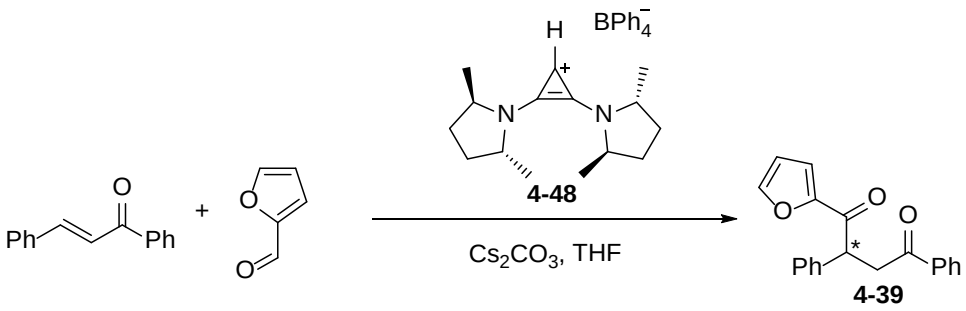
Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.555	BB	0.8709	5.25196e4	772.76276	72.8685
2	66.464	VB	1.3335	1.95549e4	173.42468	27.1315
Totals :				7.20744e4	946.18744	

Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.549	BB	1.0186	4.40282e4	671.81445	74.1411
2	66.476	BB	1.6600	1.53562e4	137.59920	25.8589
Totals :				5.93844e4	809.41365	

*** End of Report ***



To *trans*-chalcone (23 mg, 0.11 mmol) and cesium carbonate (35 mg, 0.11 mmol) in a test tube fitted with a septum and Schlenk takeoff under nitrogen was added THF (1.0 mL) and furfural (9 μL, 0.1 mmol) followed by catalyst **4-48** (6 mg, 0.01 mmol). After 3 hours, the reaction was quenched with acetic acid. The mixture was then passed through a plug of neutral silica using EtOAc as the eluent. The product was purified by column chromatography (15% EtOAc: hexanes), which afforded 15 mg (46%) of **4-39** as a white solid. Analysis by ^{1}H NMR spectroscopy was consistent with **4-39** as listed above. HPLC: Chiralpak IC 2.1×150mm column, 3% *i*PrOH/ 3% EtOAc/Hex, 25 deg, 0.1mL/min. Major 10.5 min, minor 17.9 min, 73% ee.

HPLC Trace for Stetter Reaction using Catalyst 4-48 to form Stetter Product 4-39

```
Data File C:\CHEM32\1\DATA\MYRON\20150717000007.D
Sample Name: MW-3-161CEnant

    ========================================================================
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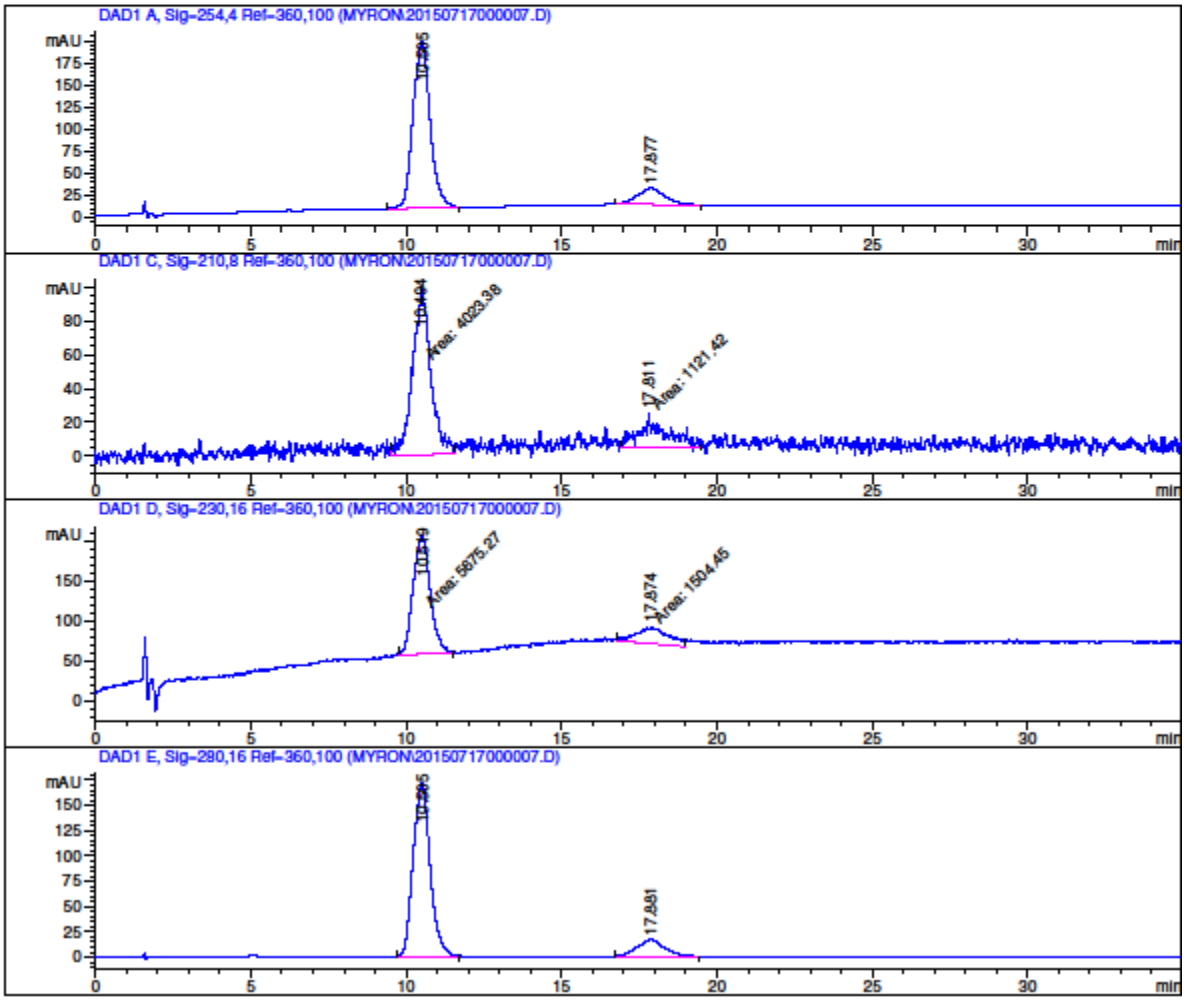
    Acq. Instrument : Instrument 1                    Location : Vial 43
    Injection Date  : 07-17-2015 10:25:23 PM
                                                    Inj Volume : 0.5 µl
    Acq. Method     : C:\CHEM32\1\METHODS\1PERCENTIPROH.M
    Last changed    : 07-17-2015 10:23:02 PM by Myron
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\MYRON\20150717000007.D\DA.M (1PERCENTIPROH.M)
    Last changed    : 12-23-2015 5:27:19 PM by mehran
                      (modified after loading)
    Method Info     :
                      IC, 1% isopropanol in hexane. 0.1 ml/min, 0.5 ul  injection, 25 oC

    Sample Info     : IA, 3% iPrOH/3%EtOAc/Hexanes 0.3mL/min, 0.5 uL injectio
                      n volume, 25 oC
```



Data File C:\CHEM32\1\DATA\MYRON\20150717000007.D
Sample Name: MW-3-161CEnant

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.505	BB	0.6097	7257.85303	189.14218	86.3630
2	17.877	BB	0.8550	1146.03650	18.34007	13.6370
Totals :				8403.88953	207.48225	

Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.494	MM	0.6806	4023.38110	98.52566	78.2029
2	17.811	MM	0.9118	1121.41956	20.49796	21.7971
Totals :				5144.80066	119.02362	

Signal 3: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.519	MM	0.6354	5675.27344	148.86844	79.0458
2	17.874	MM	1.1508	1504.45325	21.78819	20.9542
Totals :				7179.72668	170.65663	

Signal 4: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.505	BB	0.6072	6513.45166	171.46489	86.5500
2	17.881	BB	0.8497	1012.19653	16.40857	13.4500
Totals :				7525.64819	187.87346	

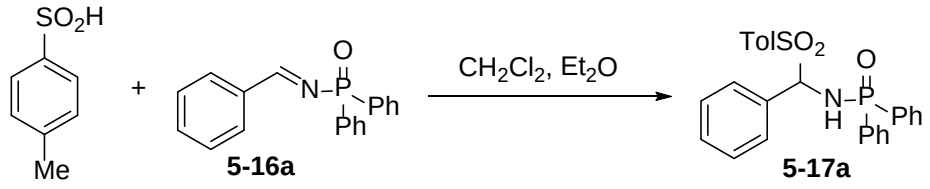
*** End of Report ***

7.5 Experimental Details for Chapter 5

Authors' Note: The presence of the phosphorous heteroatom in the phosphinic amide group gives rise to carbon phosphorous doublets along both attached phenyl rings, as well as small coupling at other more distant atoms. Further, the presence of the newly created stereocenter in the product makes the two phenyl groups on the phosphinic amide motif diastereotopic. For simplicity, all carbon resonances are reported directly and carbon phosphorous coupling are not reported.

Imine acceptors were prepared in the manner of Charette and co-workers where credited.[232] E-*N*-(4-Methylbenzylidene)-*P*, *P*-diphenylphosphinic amide was also prepared using the methodology of Ruano and Cid.[233]

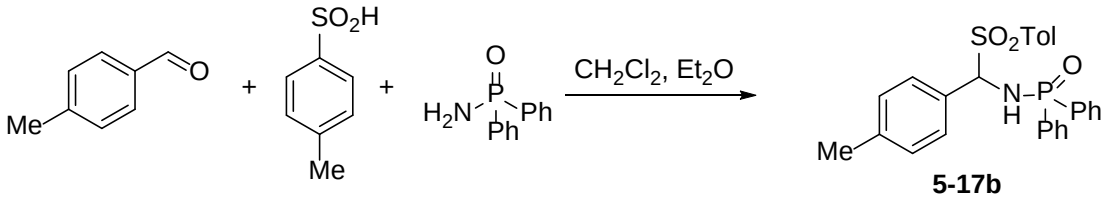
N-[(4-Methylphenyl]sulfonyl](phenyl)methyl-P,P-diphenylphosphinic amide (5-17a)



To a solution of imine **5-16a** (437 mg, 1.54 mmol) in CH_2Cl_2 (2.6 mL) and diethyl ether (13 mL), a solution of *p*-toluene sulfinic acid (242 mg, 1.54 mmol) in CH_2Cl_2 (2.6 mL) and diethyl ether (13 mL) was added dropwise at room temperature. After 1 hour the solution became clear with a fine precipitate which was filtered, washed with diethyl ether and dried under vacuum to afford pure compound **5-17a** as a fine white solid (644 mg, 90%). Both the starting material and product are consistent with what has been reported in the literature. **m.p.** (^oC): 147-149; **^{1}H NMR** (500 MHz, CD_3OD) δ 7.90 (dd, *J*=11.9, 6.7 Hz, 2H), 7.77 (dd, *J*=12.1, 7.2 Hz, 2H), 7.61-7.30 (m, 15H), 5.20 (d, *J*=8.5 Hz, 1H), 2.38 (s, 3H).

N-[(4-Methylphenyl)sulfonyl](4-methylphenyl)methyl-P,P-diphenylphosphinic amide

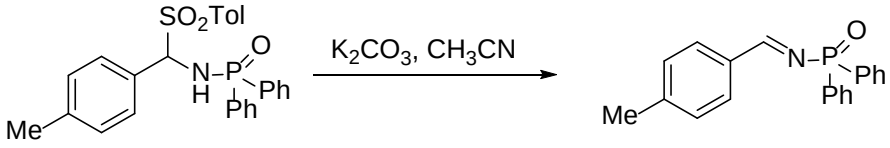
(5-17b)



5-17b

Compound **5-17b** was synthesized in the manner of Côté and Charette. CH_2Cl_2 (7.7 mL) and diethyl ether (19 mL), were added to *P,P*-diphenylphosphinic amide (500 mg, 2.30 mmol) and *p*-tolualdehyde (415 mg, 407 μL, 3.45 mmol) under inert atmosphere. To this stirred suspension, solid *p*-toluene sulfinic acid (518 mg, 3.45 mmol) was added. *p*-Toluene sulfinic acid was prepared from commercial sodium *p*-toluene sulfinate in the manner described by Baine *et al.*[234] Upon addition, the suspension became homogenous and the reaction proceeded for 12 hours at room temperature. The reaction mixture was filtered and the white precipitate was washed with diethyl ether and dried under vacuum to afford the title compound as an off white amorphous solid (949 mg, 87%). **m.p.** (^{o}C): 147-149; **^{31}P NMR** (DMSO) δ 23.62; for reasons of low solubility a sufficiently clear **^{1}H** or **^{13}C NMR** could not be obtained.

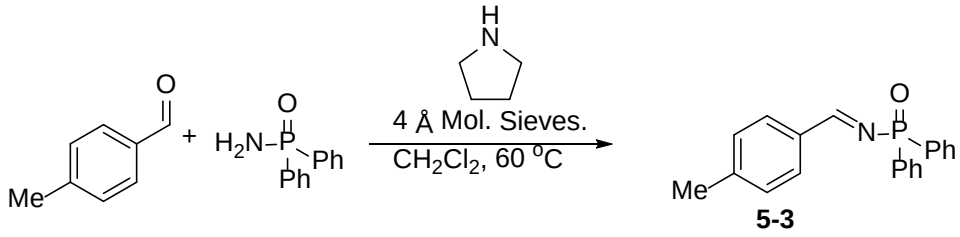
***E*-N-(4-Methylbenzylidene)-P,P-diphenylphosphinic amide 5-3**



5-17b **5-3**

Compound **5-3** was prepared according to the procedure of Côté and Charette[2] by adding potassium carbonate (2.34 g, 16.9 mmol) to sulfinic acid adduct **5-17b** (1.61 g, 3.38 mmol) in dry acetonitrile (6.4 mL) under nitrogen at room temperature and vigorously stirring the mixture

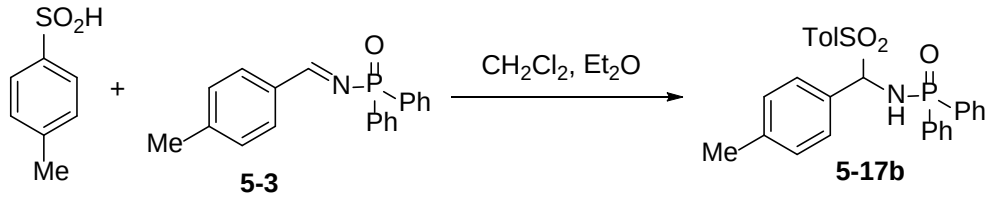
for 14 hours. The mixture is purified by passing through a plug of silica with 100% ethyl acetate and evaporating the solvent *in vacuo* to afford pure imine **5-3** as a white solid (605 mg, 86%) Material is identical in all respects to that previously reported **^{31}P NMR** (DMSO) δ 25.27, **^{1}H NMR** (500 MHz, $CHCl_3$) δ 9.28 (d, *J*=32.1 Hz, 1H), 7.90-7.88 (m, 6H), 7.50-7.42 (m, 6H), 7.29 (d, *J*=7.9 Hz, 2H), 2.39 (s, 3H).



5-3

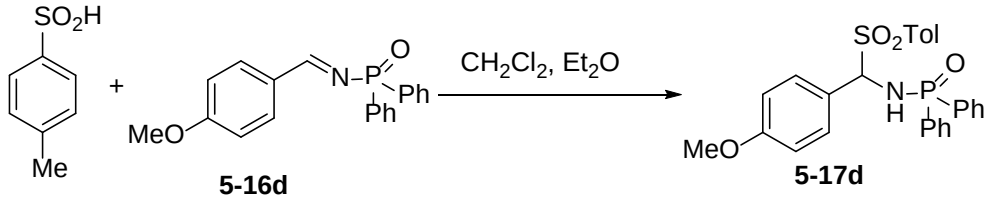
Compound **22** was also prepared in the manner of Ruano and Cid.[235] Freshly distilled *p*-tolualdehyde (133 μL, 2.76 mmol) was added to diphenylphosphinamide (500 mg, 2.30 mmol) and freshly dried molecular sieves (1.3 g) under inert atmosphere. Pyrrolidine (20 μL, 0.32 mmol) was added followed by dichloromethane (8.3 mL) the mixture was refluxed at 60 °C for 18 hours. Material was passed through a plug of silica to remove residual diphenylphosphinamide and purified via recrystallization ($CHCl_3$; hexanes) to afford the pure product **5-3** as a white fluffy powder (59% yield). The recrystallized material was found to be more resistant to hydrolysis, all other properties consistent with 5-3 above.

N-[(4-Methylphenyl]sulfonyl](4-methylphenyl)methyl-P,P-diphenylphosphinic amide (5-17b)



To a solution of **5-3** (500 mg, 1.56 mmol) in CH_2Cl_2 (5.2 mL) and diethyl ether (13 mL), a solution of *p*-toluene sulfinic acid (244 mg, 1.56 mmol) in CH_2Cl_2 (5.2 mL) and diethyl ether (13 mL) was added dropwise at room temperature to afford a milky white solution. After 2 hours the solution became clear with a fine white precipitate which was filtered, washed with diethyl ether and dried under vacuum to afford pure **5-17b** (683 mg, 92%) as a uniform fine white powder. Characterization was consistent with **5-17b** above.

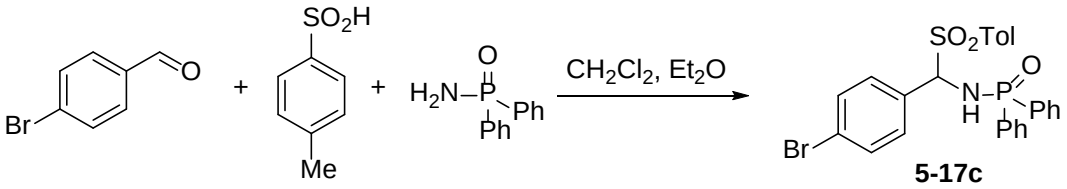
N-[(4-Methylphenyl]sulfonyl](4-methoxy-phenyl)methyl-P,P-diphenylphosphinic amide (5-17d)



To a solution of imine **5-16d** (260 mg, 0.742 mmol) in CH_2Cl_2 (2.3 mL) and diethyl ether (6.2 mL), a solution of *p*-toluene sulfinic acid (116 mg, 1.54 mmol) in CH_2Cl_2 (2.3 mL) and diethyl ether (13 mL) was added dropwise at room temperature. After 1 hour the solution became clear with a fine precipitate which was filtered, washed with diethyl ether and dried under vacuum to afford pure **5-17d** as a fine white solid (342 mg, 89%). Both the starting material and product are consistent with what has been reported in the literature.

N-[(4-Methylphenyl]sulfonyl](4-bromo-phenyl)methyl-P,P-diphenylphosphinic amide

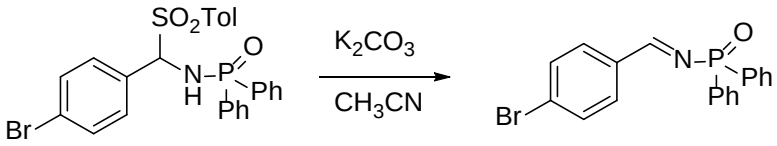
(5-17c)



5-17c

Compound **5-17c** was synthesized in the manner of Côté and Charette. CH_2Cl_2 (3.8 mL) and diethyl ether (19 mL), were added to *P,P*-diphenylphosphinic amide (500 mg, 2.30 mmol) and *p*-bromobenzaldehyde (415 mg, 407 μL, 3.45 mmol) under inert atmosphere. To this stirred suspension solid *p*-toluene sulfinic acid (538 mg, 3.45 mmol) was added. *p*-toluene sulfinic acid was prepared from commercial sodium *p*-toluene sulfinate in the manner described by Baine *et al.*[6] Upon addition, the suspension dissolved and the reaction proceed for 12 hours at room temperature. The reaction mixture was filtered and the white precipitate was washed with diethyl ether and dried under vacuum to afford the title compound (989 mg, 80%). For reasons of low solubility a sufficiently clear **^{1}H** or **^{13}C NMR** could not be obtained. The material also proved incompatible with our mass spectrometer injectors.

(*E*)-N-(4-Bromobenzylidene)-P, P-diphenylphosphinic amide (5-16c)



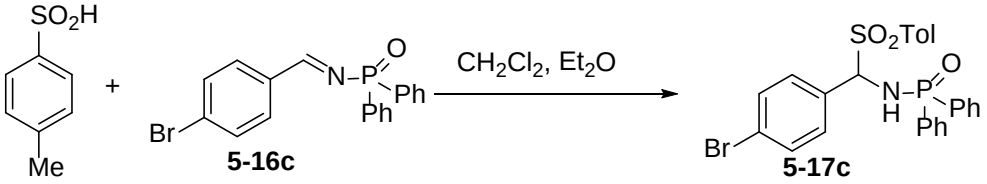
5-17c **5-16c**

Potassium carbonate (841 mg, 6.0 mmol) was added to adduct **5-17c** (658 mg, 1.22 mmol) and placed under inert atmosphere. Acetonitrile was added (2.2 mL) and the mixture stirred at room temperature for 12 hours. Acetonitrile was removed by evaporation *in vacuo* and

the product was purified by passing thorough a plug of silica (3 : 7 ethyl acetate to hexanes then 100% ethyl acetate) to afford 342 mg of the imine **5-16c** in 73% yield. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 9.23 (d, *J*=31.6 Hz, 1H), 7.91 (ddd, *J*=11.9, 7.7, 1.4 Hz, 4H), 7.78 (d, *J*=8.4 Hz, 2H), 7.54 (d, *J*=8.4 Hz, 2H), 7.44-7.35 (m, 6H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 172.4, 172.3, 134.7, 134.5, 133.2, 132.3, 132.2, 131.9, 131.9, 131.6, 131.5, 131.4, 128.6, 128.6, 128.5; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3224, 3076, 3056,1618, 1588, 1565, 1483, 1205, 1124, ; **HRMS** (EI^+) m/z calculated for $C_{19}H_{15}NO_1P^{81}Br$ $[M]^+$: 385.0054; found: 385.0049; (EI^+) m/z calculated for $C_{19}H_{15}NO_1P^{79}Br$ $[M]^+$: 383.0074; found: 383.0090.

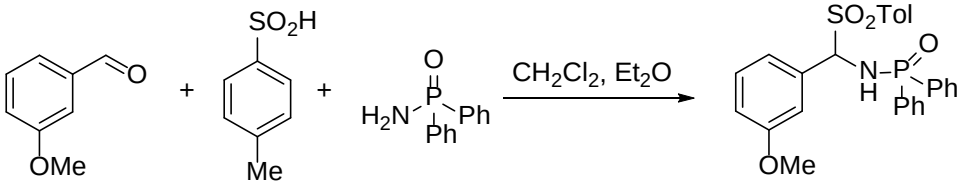
N-[(4-Methylphenyl]sulfonyl](4-bromo-phenyl)methyl-P, P-diphenylphosphinic amide

(5-17c)



To a solution of imine **5-16c** (342 mg, 0.887 mmol) in CH_2Cl_2 (1.5 mL) and diethyl ether (7.5 mL), a solution of *p*-toluene sulfinic acid (136 mg, 0.887 mmol) in CH_2Cl_2 (1.5 mL) and diethyl ether (7.5 mL) was added dropwise at room temperature. After 1 hour the solution became clear with a fine precipitate which was filtered, washed with diethyl ether and dried under vacuum to afforded pure **5-17c** as a white solid (417 mg, 87%). **m.p.** (^{o}C): 162-164. For reasons of low solubility a sufficiently clear **^{1}H** or **^{13}C NMR** could not be obtained.

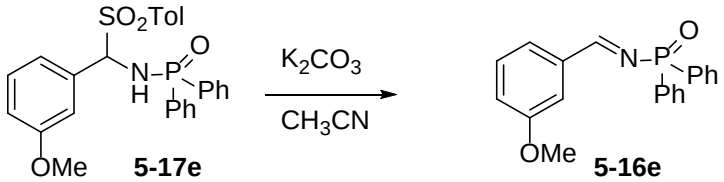
N-[(4-Methylphenyl]sulfonyl](3-methoxy-phenyl)methyl-P, P-diphenylphosphinic amide (5-17e)



5-17e

Compound **5-17e** was synthesized in the manner of Côté and Charette. CH_2Cl_2 (3.1 mL) and diethyl ether (6.1 mL), were added to *P,P*-diphenylphosphinic amide (400 mg, 2.30 mmol) and *m*-methoxybenzaldehyde (337 μL, 2.76 mmol) under inert atmosphere. To this stirred suspension solid *p*-toluene sulfinic acid (431 mg, 2.75 mmol) was added. *p*-toluene sulfinic acid was prepared from commercial sodium *p*-toluene sulfinate in the manner described by Baine *et al*. Upon addition, the suspension dissolved and the reaction proceeded for 12 hours at room temperature. The reaction mixture was filtered and the white precipitate was washed with diethyl ether and dried under vacuum to afford the title compound (808 mg, 89%). For reasons of low solubility a sufficiently clear **^{1}H** or **^{13}C NMR** could not be obtained.

(*E*)-N-(3-Methoxy-benzylidene)-P, P-diphenylphosphinic amide (5-16e)

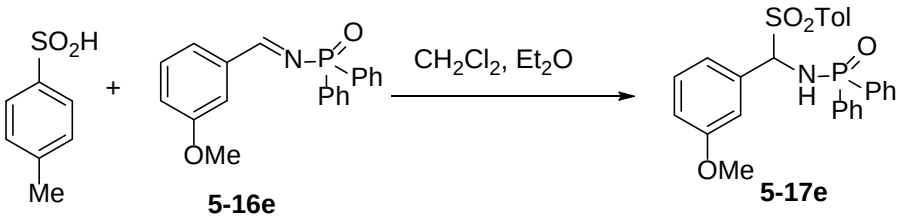


5-17e **5-16e**

Potassium carbonate (782 mg, 5.66 mmol) was added to adduct **5-17e** (604 mg, 1.22 mmol) and placed under inert atmosphere. Acetonitrile was added (2.3 mL) and the mixture stirred at room temperature for 12 hours. Acetonitrile was removed by evaporation *in vacuo* and the product was purified by passing thorough a plug of silica (3 : 7 ethyl acetate to hexanes then

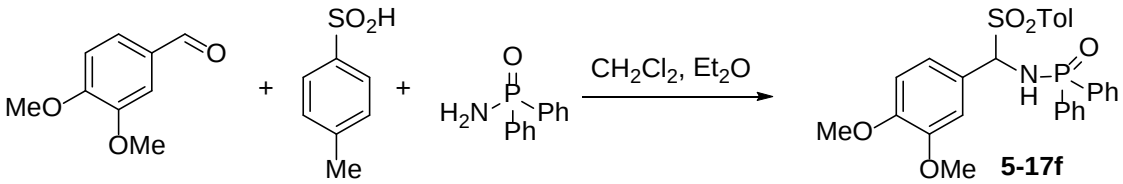
100% ethyl acetate) to afford 327 mg of the imine **5-16e** as a sticky white solid 92% yield. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 9.31 (d, *J*=32.0 Hz, 1H), 7.92 (ddd, *J*=12.0, 7.0, 1.0 Hz, 4H), 7.56 (dd, *J*= 12, 7.0 Hz, 2H), 7.51-7.46 (dt, *J*=5.0, 1.5 Hz, 2H), 7.47-7.40 (m, 5H), 7.13 (dd, *J*=8.0, 2.0 Hz, 1H); 3.88 (s, 3H). All spectra are consistent with what is reported in the literature.[236]

N-[(4-Methylphenyl]sulfonyl](3-methoxy-phenyl)methyl-P,P-diphenylphosphinic amide (5-17e)



To a solution of imine **5-16e** (402 mg, 1.13 mmol) in CH_2Cl_2 (3.8 mL) and diethyl ether (7.6 mL), a solution of *p*-toluene sulfinic acid (176 mg, 1.33 mmol) in CH_2Cl_2 (3.8 mL) and diethyl ether (7.6 mL) was added dropwise at room temperature. After 2 hour the solution became clear with a fine precipitate which was filtered, washed with diethyl ether and dried under vacuum to afforded pure **5-17e** as a white solid (442 mg, 80%).

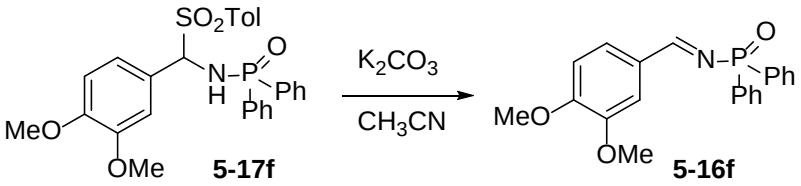
N-[(4-Methylphenyl]sulfonyl](3,4-dimethoxy-phenyl)methyl-P,P-diphenylphosphinic amide (5-17f)



Compound **5-17f** was synthesized in the manner of Côté and Charette. CH_2Cl_2 (3.0 mL) and diethyl ether (6.6 mL), were added to *P*,*P*-diphenylphosphinic amide (400 mg, 2.30 mmol)

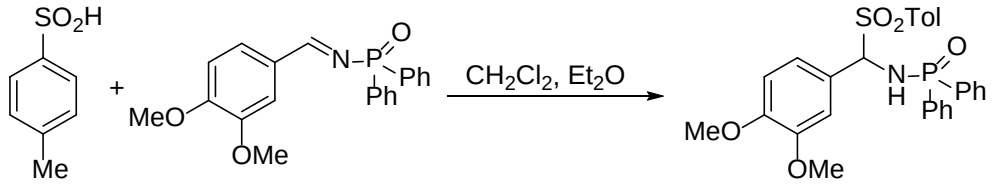
and *m*,*p*-dimethoxybenzaldehyde (459 mg, 2.76 mmol) under inert atmosphere. To this stirred suspension solid *p*-toluene sulfinic acid (431 mg, 2.75 mmol) was added. *p*-toluene sulfinic acid was prepared from commercial sodium *p*-toluene sulfinate in the manner described by Baine *et al*. Upon addition, the suspension dissolved and the reaction proceeded for 12 hours at room temperature. The reaction mixture was filtered and the white precipitate was washed with diethyl ether and dried under vacuum to afford the title compound (788 mg, 83%). For reasons of low solubility a sufficiently clear **^{1}H** or **^{13}C NMR** could not be obtained.

(*E*)-N-(3, 4-Dimethoxy-benzylidene)-P, P-diphenylphosphinic amide (5-16f)



Potassium carbonate (782 mg, 5.66 mmol) was added to adduct **5-17f** (590 mg, 1.13 mmol) and placed under inert atmosphere. Acetonitrile was added (8.0 mL) and the mixture stirred at room temperature for 12 hours. Acetonitrile was removed by evaporation *in vacuo* and the product was purified by passing thorough a plug of silica (3 : 7 ethyl acetate to hexanes then 100% ethyl acetate) to afford 327 mg of the imine **5-16f** as a sticky white solid 81% yield. This substance differed from the previously reported[237] in the proton NMR spectrum (difference in bold). The carbon NMR spectrum was consistent with the literature reported. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 9.23 (d, *J*=32.0 Hz, 1H), 7.92 (ddd, *J*=11.5, 6.5, 1.0 Hz, 4H), 7.62 (d, *J*= 2.0 Hz, 1H), 7.51-7.46 (m, 7H), 6.95 (d, *J*= 8.0 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 3H).

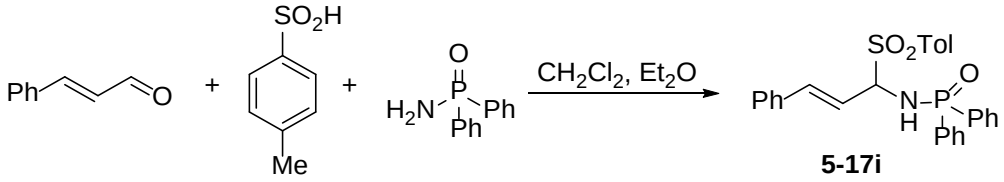
N-[(4-Methylphenyl]sulfonyl](3,4-dimethoxy-phenyl)methyl-P,P-diphenylphosphinic amide (5-17f)



5-16f **5-17f**

To a solution of imine **5-16f** (285 mg, 0.779 mmol) in CH_2Cl_2 (2.6 mL) and diethyl ether (5.3 mL), a solution of *p*-toluene sulfinic acid (122 mg, 0.779 mmol) in CH_2Cl_2 (2.6 mL) and diethyl ether (5.3 mL) was added dropwise at room temperature. After 2 hour the solution became clear with a fine precipitate which was filtered, washed with diethyl ether and dried under vacuum to afforded pure **5-17f** as a white solid (316 mg, 78%). **m.p.** (^oC): 119-121.

N-[(4-Methylphenyl]sulfonyl]((*E*)-2-phenylethene)methyl-P,P-diphenylphosphinic amide (5-17i)

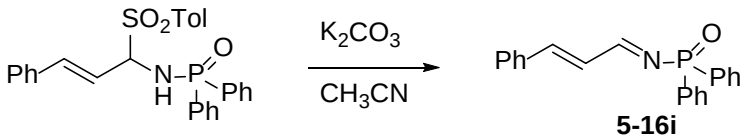


5-17i

Compound **5-17i** was synthesized in the manner of Côté and Charette. CH_2Cl_2 (3.0 mL) and diethyl ether (15 mL), were added to *P,P*-diphenylphosphinic amide (400 mg, 2.30 mmol) and cinnamaldehyde (347 μL, 2.76 mmol) under inert atmosphere. To this stirred suspension solid *p*-toluene sulfinic acid (431 mg, 2.75 mmol) was added. *p*-toluene sulfinic acid was prepared from commercial sodium *p*-toluene sulfinate in the manner described by Baine *et al*. Upon addition, the suspension dissolved and the reaction proceeded for 12 hours at room

temperature. The reaction mixture was filtered and the white precipitate was washed with diethyl ether and dried under vacuum to afford the title compound (231 mg, 26%). For reasons of low solubility a sufficiently clear **^{1}H** or **^{13}C NMR** could not be obtained.

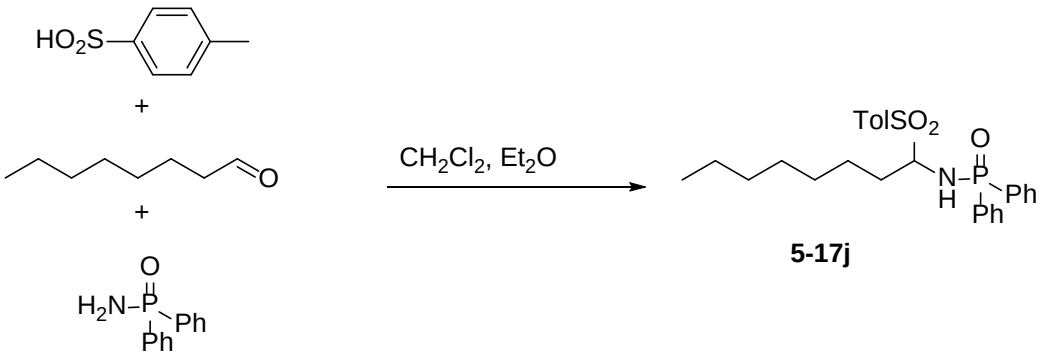
(*E*)-N-((*E*)-2-Phenylethene)-P, P-diphenylphosphinic amide (5-16i)



5-17i **5-16i**

Potassium carbonate (323 mg, 2.34 mmol) was added to adduct **5-17i** (590 mg, 1.13 mmol) and placed under inert atmosphere. Acetonitrile was added (0.9 mL) and the mixture stirred at room temperature for 12 hours. Acetonitrile was removed by evaporation *in vacuo* and the product was purified by passing thorough a plug of silica (3 : 7 ethyl acetate to hexanes then 100% ethyl acetate) to afford 76 mg of the imine **5-16i** as a sticky white solid 49% yield. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 9.05 (dd, *J*=31.8, 9.1 Hz, 1H), 7.89 (dd, *J*=10.7, 7.1 Hz, 4H), 7.55-7.36 (m, 12H) 7.12 (dd, *J*=9.0, 7.3 Hz, 1H). All spectra are consistent with what has been reported previously.[238]

N-[(4-Methylphenyl)sulfonyl](octyl)methyl-P,P-diphenylphosphinic amide (5-17j)

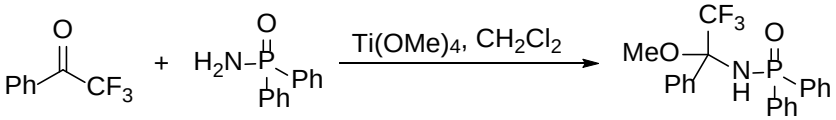


5-17j

To the starting aldehyde (539 μL, 3.45 mmol) and diphenylphosphinamide (500 mg, 2.30 mmol) in a mixture of CH_2Cl_2 (3.8 mL) and diethyl ether (19 mL) under argon, sulfinic acid (518

mg, 3.45 mmol) was added. The mixture became clear and was stirred for 2 days at room temperature. The crude product was isolated by filtration and purified by recrystallization from chloroform and diethyl ether to give 0.5055 g of sulfinic acid adduct **5-17j** (52%) as a white solid that resembled plastic granules. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.80 (dd, *J*=12.0, 7.7 Hz, 2H), 7.70 (d, *J*=5.0 Hz, 2H), 7.54-7.45 (m, 6H), 7.32-7.29 (m, 4H), 4.30 (ddt, *J*=17.5, 8.5, 4.0 Hz,1H), 3.49-3.35 (br s., 1H), 2.45 (s, 3H), 2.08 (dddd, *J*=14.1, 9.9, 9.9, 4.9 Hz, 1H), 1.77 (dddd, *J*=17.5, 9.3, 9.3, 4.5 Hz, 1H), 1.68-1.56 (br. s, 1H), 1.45-1.38 (br. s, 1H), 1.32-1.12 (m, 8H), 0.85 (t, *J*=6.9 Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 145.1, 134.1, 133.1, 133.1, 132.5, 132.5, 132.3, 132.2, 132.2, 132.2, 132.1, 132.0, 131.3, 130.3, 129.9, 129.6, 128.8, 128.7, 128.6, 128.5, 72.6, 31.9, 30.9, 29.3, 29.1, 25.3, 22.8, 21.9, 14.3 **^{31}P NMR** (202 MHz, uncalibrated) δ 23.54; **FTIR** (KBr thin film) ν_{max} (cm^{-1}):3148, 2926, 2856, 1596, 1437, 1300, 1190, 1126, 1084; **HRMS** (CI^+) m/z calculated for $C_{27}H_{34}NO_3PS$+Na $[M]^+$: 506.1889; found: 506.1881.

P,P-Diphenyl-N-(2,2,2-trifluoro-1-methoxy-1-phenylethyl)phosphinic amide (5-21)

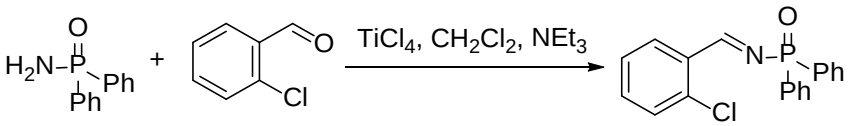


5-21

To titanium methoxide (187 mg, 1.67 mmol) and diphienylphosphinamide (200 mg, 0.92) in CH_2Cl_2, trifluoromethyl ketone (352 μL, 2.50 mmol), was added under argon. The reaction was stirred at reflux for 24 hours and then quenched with saturated sodium sulfate (created by adding water to sodium sulfate mixed with sand until the sodium sulfate began to dissolve), this mixture was filtered and dried through a plug of sodium sulfate. The crude product was purified by column chromatography (6:4 hexanes : EtOAc) to give 58.9 mg (17%) of the product as a white solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.92 (dd, *J*=12.2, 7.3 Hz, 2H), 7.78 (dd, *J*=12.2, 7.4

Hz, 2H), 7.60 (d, *J*=7.5 Hz, 2H), 7.51 (d, *J*=14.6 Hz, 1H), 7.52-7.44 (m, 3H), 7.37 (dt, *J*=7.6, 3.2 Hz, 2H), 7.31-7.24 (m, 3H), 4.11 (d, *J*=1.9 Hz, 1H), 3.57 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 134.0, 133.8, 133.7, 133.2, 133.0, 132.4, 132.4, 132.3, 132.2, 132.1, 132.1, 132.0, 131.9, 131.6, 131.5, 129.8, 129.1, 128.9, 128.8, 128.7, 128.6, 128.6, 128.5, 128.3, 128.2, 128.2, 124.6, 124.5, 122.3, 122.2, 89.9, 89.9, 89.7, 89.6, 52.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3393, 3062, 2899, 1653, 1592, 1559, 1451, 1439, 1270, 1177; **HRMS** (CI^+) m/z calculated for $C_{21}H_{19}NO_2PF_3$ +Na $[M]^+$: 428.0997; found: 428.0992.

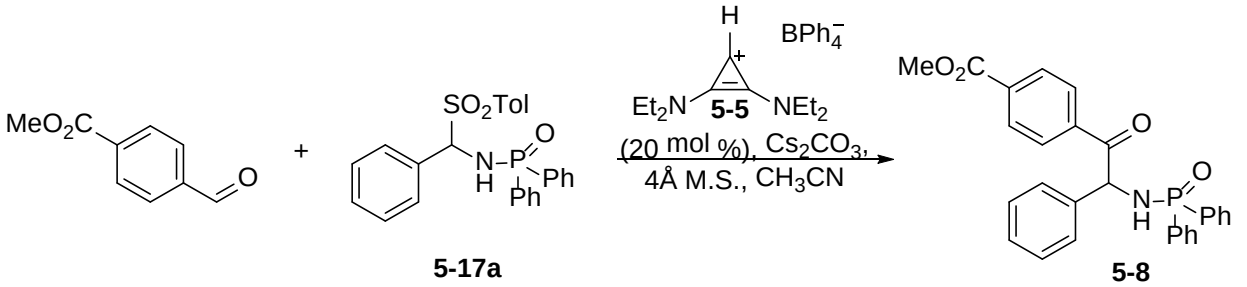
(*E*)-N-(2-Chlorobenzylidene)-P,P-diphenylphosphinic amide (5-23)



5-23

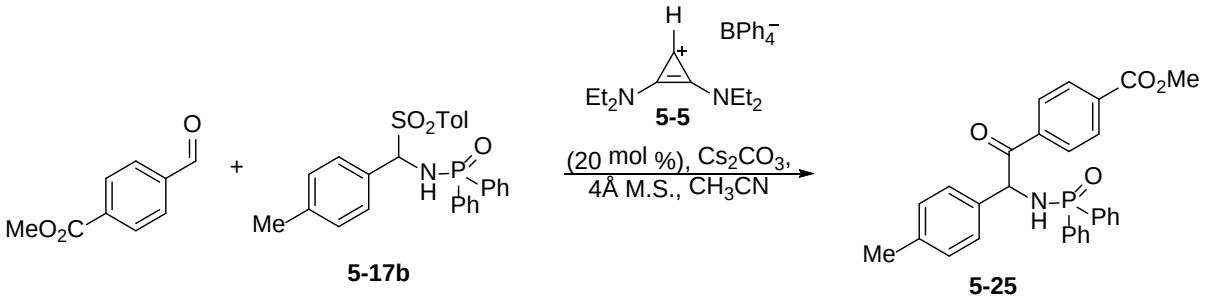
In a round bottomed flask a solution of *o*-chlorobenzaldehyde (207 μL, 1.84 mmol), diphenylphosphinamide (400 mg, 1.84 mmol), triethylamine (0.898 mL, 6.44 mmol) in CH_2Cl_2 (9.2 mL) was prepared and placed under argon. At 0 °C with vigorous stirring freshly distilled titanium tetrachloride (101 μL, 0.92 mmol) was added dropwise. The flask was kept at 0 °C for one hour followed by one hour at room temperature with stirring. The crude reaction mixture was filtered through silica and purified by column chromatography (1:1 CH_2Cl_2: EtOAc) to give 372.8 mg (60%) of the imine as a colorless oil; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 9.74 (d, *J*=31.4 Hz, 1H), 8.28 (dd, *J*=7.9 Hz, 1.1 Hz, 1H), 7.94 (dd, *J*=8.3, 7.0 Hz, 4H), 7.50-7.41 (m, 8H), 7.35 (t, *J*=7.2 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 170.6, 170.5, 138.4, 134.5, 133.3, 133.0, 132.8, 132.3, 132.1, 132.1, 131.8, 131.7, 130.6, 129.5, 128.7, 128.6, 127.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}):3058, 1612, 1590, 1566, 1438, 1368, 1273, 1207, 1124, 1053; **HRMS** (EI^+) m/z calculated for $C_{19}H_{15}NOP$ $[M]^+$: 339.0580; found: 339.0586.

Methyl 4-(2-((diphenylphosphoryl)amino)-2-phenylacetyl)benzoate (5-8)



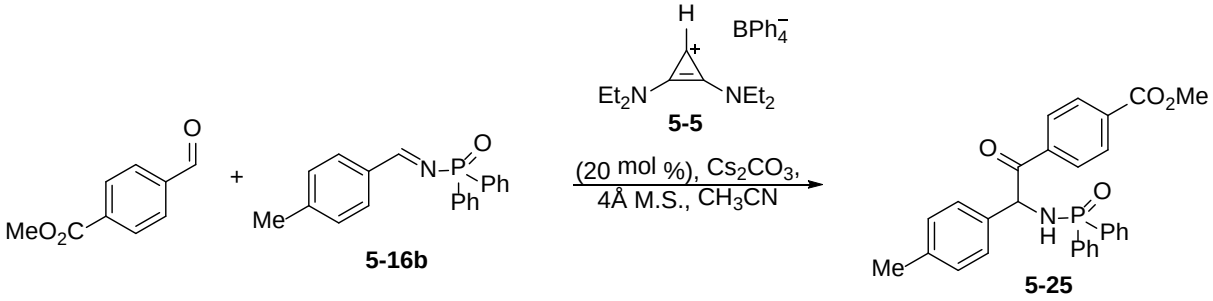
In a test tube with Schlenk takeoff acceptor **5-17a** was added (60 mg, 0.13 mmol) along with cesium carbonate, (192 mg, 0.59 mmol) and dry molecular sieve (104 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.4 mL) and methyl-4-formyl benzoate (20 mg, 0.12 mmol) were added along with pre-catalyst **5-5** (11.8 mg, 0.024 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (1:1 EtOAc to toluene) to afford 42.0 mg (76%) of **5-8** as a white solid. **m.p.** (^{o}C): 173-175; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.96 (d, *J*=8.4 Hz, 2H), 7.87 (d, *J*=8.4 Hz, 2H), 7.81 (dd, *J*=12.0, 7.4 Hz, 2H), 7.67 (dd, *J*=12.2, 8.0 Hz, 2H), 7.50-43 (m, 1H), 7.43-7.38 (m, 3H), 7.29-7.24 (m, 2H), 7.19-7.02 (m, 5H), 5.95 (dd, *J*=8.6, 8.5 Hz, 1H), 4.88 (dd, *J*=8.0, 8.0 Hz, 1H) 3.87 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 196.5, 166.1, 138.3, 138.3, 137.8, 134.4, 133.4, 132.7, 132.6, 132.4, 132.3, 132.2, 131.9, 131.9, 131.8, 131.8, 131.6, 129.9, 129.3, 129.1, 128.8, 128.7, 128.4, 128.4, 128.3, 128.3, 59.8, 52.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3335, 3059, 2951, 1726, 1692, 1438, 1279, 1109; **HRMS** (EI^+) m/z calculated for $C_{28}H_{24}NO_4P$ $[M]^+$: 469.1443; found: 469.1443.

2-(Diphenylphosphinamide)-1-(p-methylbenzoate)-2-p-tolylethanone (5-25)



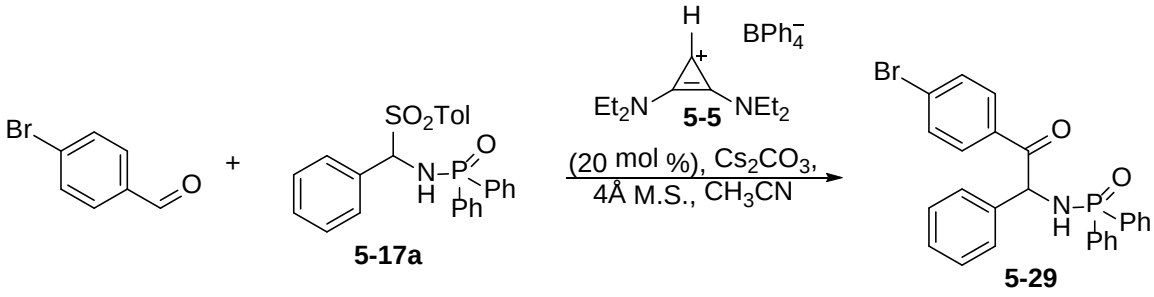
In a test tube with Schlenk takeoff imine analogue **5-25** was added (90 mg, 0.19 mmol) along with cesium carbonate, (308 mg, 0.945 mmol), dry molecular sieve (150 mg) and methyl-4-formyl-benzoate (38 mg, 0.23 mmol). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.63 mL) was added along with pre-catalyst **5-5** (19 mg, 0.038 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react for 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (4:6 EtOAc to hexanes) to afford 84.4 mg (92%) of **5-25** as a white solid. R_f = 0.3 (40%EtOAc, hexanes); **m.p.** (^oC): 144-147; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.96 (d, *J*=7.0 Hz, 2H), 7.87 (d, *J*=7.2 Hz, 2H), 7.81 (dd, *J*=12.0, 7.8 Hz, 2H), 7.68 (dd, *J*=12.2, 7.8Hz, 2H), 7.50-7.38 (m, 4H), 7.32-7.24 (m, 2H), 6.99 (d, *J*=7.9 Hz, 2H), 6.95 (d, *J*=7.4 Hz, 2H), 5.91 (dd, *J*=9.7, 9.5 Hz, 1H), 4.84 (dd, *J*=8.1, 8.1 Hz, 1H), 3.87 (s, 3H), 2.21 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 196.6, 196.5, 166.1, 138.3, 137.9, 135.3, 135.3, 134.3, 133.4, 132.7, 132.7, 132.4, 132.3, 132.3, 131.9, 131.9, 131.9, 131.8, 130.0, 129.9, 129.2, 128.9, 128.8, 128.4, 128.3, 128.1, 59.5, 52.6, 21.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3331, 3148, 3057, 2952, 1726, 1691, 1437, 1279, 1197, 1109; **HRMS** (EI^+) m/z calculated for $C_{29}H_{26}NO_4P$ $[M]^+$: 483.1599; found: 483.1599.

2-(Diphenylphosphinamide)-1-(p-methylbenzoate)-2-p-tolylethanone (5-25) from imine 5-16b



In a test tube with Schlenk takeoff imine **5-16b** was added (51 mg, 0.16 mmol) along with cesium carbonate, (260 mg, 0.80 mmol), dry molecular sieve (125 mg) and methyl-4-formyl-benzoate (40 mg, 0.24 mmol). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.53 mL) was added along with pre-catalyst **5-5** (16 mg, 0.032 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react for 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (1:1 EtOAc to hexanes+2% MeOH) to afford 57.5 mg (75%) of **5-25** as a white solid. Material was completely identical with the above reported.

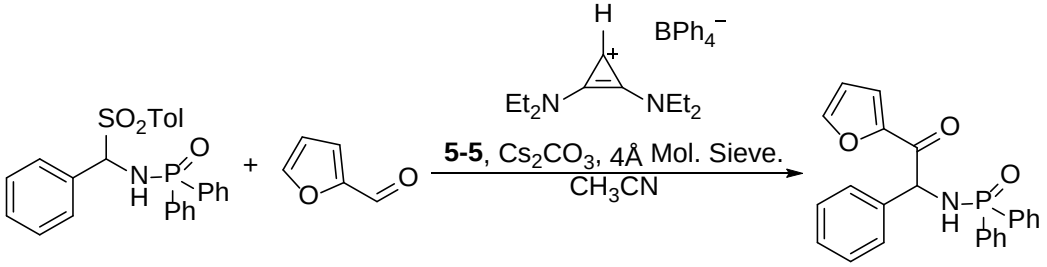
N-(2-(4-Bromophenyl)-2-oxo-1-phenylethyl)-P, P-diphenylphosphinic amide (5-29)



In a test tube with Schlenk takeoff acceptor **5-17a** was added (90 mg, 0.19 mmol) along with cesium carbonate, (289 mg, 0.89 mmol) and dry molecular sieve (150 mg). The test tube

was put under inert atmosphere and a septum was added. Acetonitrile (0.6 mL) and *p*-bromobenzaldehyde (33 mg, 0.18 mmol) were added along with pre-catalyst **5-5** (17.8 mg, 0.024 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (3:7 EtOAc to toluene) to afford 70.9 mg (82%) of **5-29** as a white solid. **m.p.** (^{o}C): 153-155; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.81 (dd, *J*=11.9 7.4 Hz, 2H), 7.69 (d, *J*=8.1 Hz, 2H), 7.67 (dd, *J*=12.2, 7.6 Hz, 2H), 7.50-7.36 (m, 6H), 7.24 (dt, *J*=7.5, 3.0 Hz, 2H), 7.18-7.08 (m, 5H), 5.89 (dd, *J*=9.9, 8.3 Hz, 1H), 4.91 (dd, *J*=8.1, 8.1 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 195.8, 195.7, 138.5, 138.5, 133.4, 133.0, 132.6, 132.6, 132.6, 132.4, 132.2, 132.2, 132.1, 131.8, 131.8, 131.8, 131.7, 131.6, 130.7, 130.2, 129.0, 128.8, 128.7, 128.3, 128.3, 128.2, 128.0, 59.3; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3330, 3167, 3059, 2926, 2248, 1686, 1586, 1455, 1396, 1200, 1125, 1110, 990; **HRMS** (EI^+) m/z calculated for $C_{26}H_{21}NO_2P^{81}Br$ $[M]^+$: 491.0473; found: 491.0461, (EI^+) m/z calculated for $C_{26}H_{21}NO_2P^{79}Br$ $[M]^+$: 489.0493; found: 489.0490.

N-(2-(Furan-2-yl)-2-oxo-1-phenylethyl)-P, P-diphenylphosphinic amide (5-30)

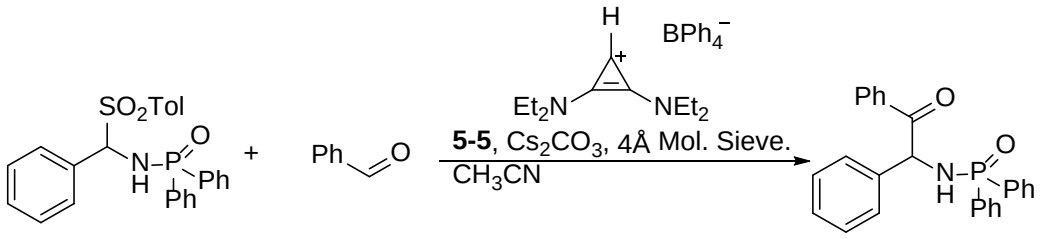


5-17a **5-30**

In a test tube with Schlenk takeoff acceptor **5-17a** was added (75 mg, 0.16 mmol) along with cesium carbonate, (264 mg, 0.812 mmol) and dry molecular sieve (128 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.54 mL) and furfural (20

μL, 0.24 mmol) were added along with bis(diethylamino)cyclopropenylidene tetraphenylborate (15.7mg, 0.031 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated and product was purified via column chromatography (1:1 EtOAc to hexanes with 1% MeOH) to give 41.2 mg (63%) of **5-30** as an off white solid. **m.p.** (^{o}C):169-172; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.82 (dd, *J*=12.0, 7.4 Hz, 2H), 7.66 (dd, *J*=12.2, 7.6 Hz, 2H), 7.50-7.44 (m, 2H), 7.44-7.36 (m, 3H), 7.27 (dt, *J*=7.6, 3.2 Hz, 2H), 7.23-7.14 (m, 5H), 7.13 (d, *J*=3.6 Hz, 1H), 6.40 (dd, *J*=3.6, 1.6, Hz, 1H), 5.72 (dd, *J*=8.8, 8.7 Hz, 1H), 4.83 (dd, *J*=8.6, 8.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 185.3, 150.5, 147.3, 138.7, 138.7, 133.3, 132.7, 132.6, 132.3, 132.2, 132.2, 131.9, 131.9, 131.5, 128.9, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 119.7, 112.7, 59.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3327, 3147, 3059, 2956, 1675, 1567, 1464, 1438, 1287, 1199,1110; **HRMS** (EI^{+}) m/z calculated for $C_{24}H_{20}NO_3P$ $[M]^{+}$: 401.1180; found: 401.1175.

N-(2-(Phenyl)-2-oxo-1-phenylethyl)-P,P-diphenylphosphinic amide (5-31)

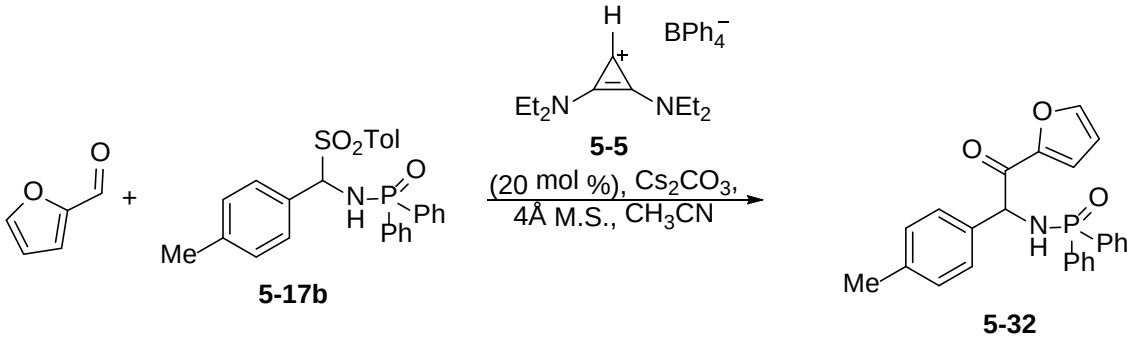


5-17a **5-31**

In a test tube with Schlenk takeoff acceptor **5-17a** was added (90 mg, 0.19 mmol) along with cesium carbonate, (289 mg, 0.886 mmol) and dry molecular sieve (150 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.60 mL) and benzaldehyde (18 μL, 0.18 mmol) were added along with bis(diethylamino)cyclopropenylidene

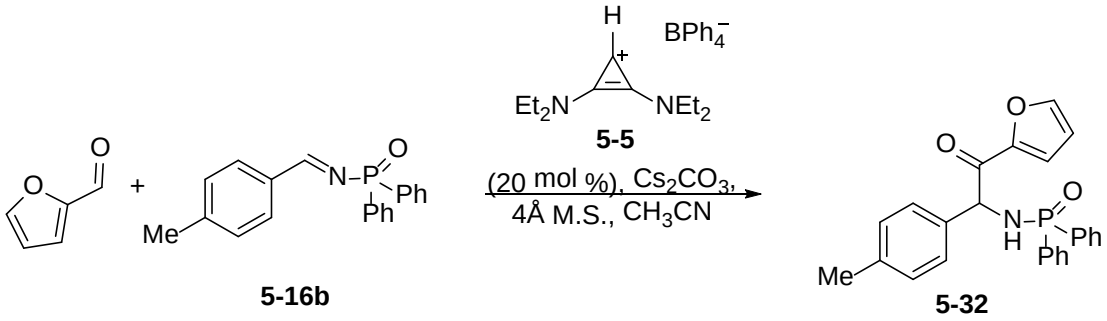
tetraphenylborate (15.7mg, 0.031 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated and product was purified via column chromatography (30% EtOAc : hexanes) to give 10.1 mg (~13%) of **5-31** as an off white solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.93 (dd, *J*=13.0, 7.2 Hz, 2H), 7.85 (d, *J*=7.2 Hz, 2H), 7.82 (dd, *J*=5.0, 1.2 Hz, 2H), 7.667 (dd, *J*=12.3, 7.2 Hz, 2H), 7.56 (dd, *J*= 6.3, 6.3 Hz, 1H), 7.50-7.45 (m, 4H), 7.34 (t, *J*=7.9 Hz, 2H), 7.23-7.14 (m, 5H), 5.95 (dd, *J*=10.2, 8.2 Hz, 1H), 4.93 (dd, *J*=8.3, 8.3 Hz, 1H). All spectra are consistent with what has been reported previously.[83]

2-(Diphenylphosphinamide)-1-(2-furyl)-2-p-tolylethanone (5-32)



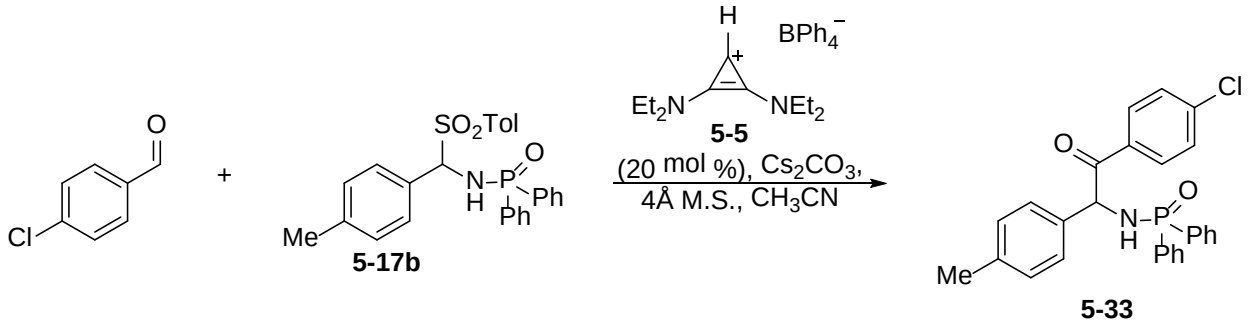
In a test tube with Schlenk takeoff **5-17b** was added (75 mg, 0.15 mmol) as well as cesium carbonate, (248 mg, 0.761 mmol) and dry molecular sieve (124 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.52 mL) and furfural (19 μL, 0.23 mmol) were added. Pre-catalyst **5-5** (15.7 mg, 0.031 mmol) was added in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (6:4 EtOAc to

toluene+1%MeOH) to afford 41.3 mg (63%) of **5-32** as an amber colored solid. R_f = 0.3 (6:4 EtOAc to Hex + 2% MeOH); **m.p.** (^oC): 139-142; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.81 (dd, *J*=12.1, 7.4 Hz, 2H), 7.67 (dd, *J*=12.3, 7.4 Hz, 2H), 7.48-7.42 (m, 2H), 7.42-7.36 (m, 3H), 7.25 (m, 2H), 7.11 (d, *J*=3.6 Hz, 1H), 7.09 (d, *J*=8.0 Hz, 2H), 7.00 (d, *J*=8.1 Hz, 2H), 6.39 (dd, *J*=3.1, 1.1Hz, 1H), 5.67 (dd, *J*=9.1, 9.0 Hz, 1H), 4.78 (dd, *J*=8.1, 8.1 Hz, 1H), 2.33 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 185.4, 150.5, 147.2, 138.0, 135.7, 135.6, 133.3, 132.7, 132.6. 132.3, 132.1, 132.1, 132.0, 131.9, 131.8, 131.8, 131.6, 129.6, 128.7, 128.6, 128.3, 128.2, 128.0, 119.6, 112.6, 59.0, 21.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3328, 3147, 3057, 2922, 2863, 1675, 1567, 1512, 1464, 1200, 1110, 726; **HRMS** (EI^+) m/z calculated for $C_{25}H_{22}NO_3P$ $[M]^+$: 415.1337; found: 415.1327.



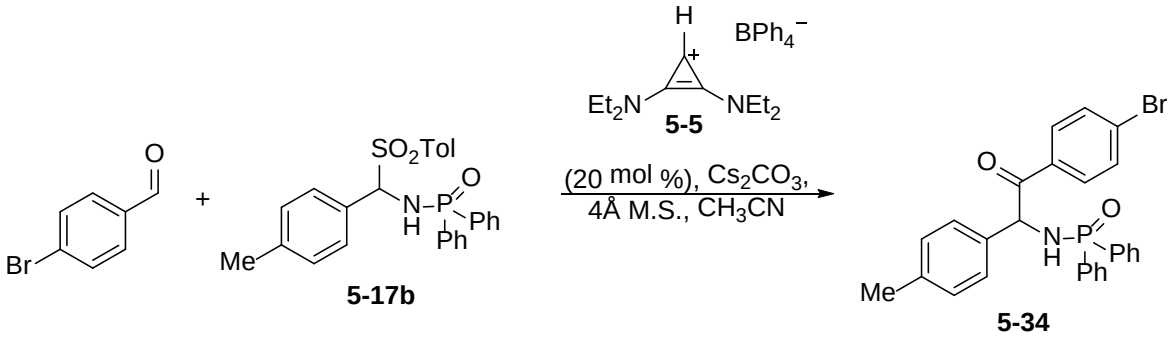
In a test tube with Schlenk takeoff imine **5-16b** was added (100 mg, 0.31 mmol) as well as cesium carbonate, (305 mg, 0.93 mmol) and dry molecular sieve (300 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (1.0 mL) and furfural (78 μL, 0.94 mmol) were added. Pre-catalyst **5-5** (24 mg, 0.046 mmol) was added in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column as above to afford 123 mg (96%) of **5-32** as an amber colored solid. Material was in all ways consistent with the reported above.

2-(Diphenylphosphinamide)-1-(p-chloro-phenyl)-2-p-tolylethanone (5-33)



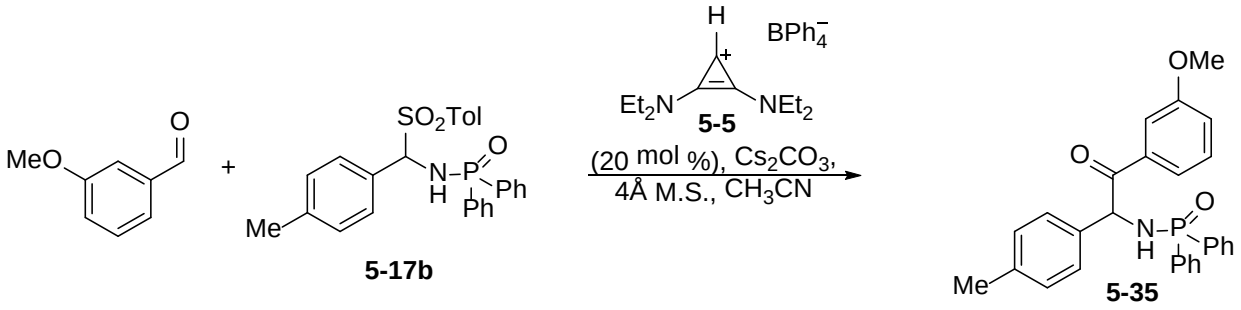
In a test tube with Schlenk takeoff acceptor **5-17b** was added (75 mg, 0.16 mmol) as well as cesium carbonate, (257 mg, 0.788 mmol), dry molecular sieve (124 mg) and 4-chloro-benzaldehyde (24 mg, 0.17 mmol). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.52 mL) was added along with pre-catalyst **5-5** (15.8 mg, 0.032 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (1:1 EtOAc to hexanes +1% MeOH) to afford 54.3 mg (75%) of compound **5-33** as a white solid. R_f = 0.3 (50%EtOAc: hexanes); **m.p.** (^oC): 144-147; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.81 (dd, *J*=12.0, 7.2 Hz, 2H), 7.77 (d, *J*=8.6 Hz, 2H), 7.68 (dd, *J*=12.2, 7.3Hz, 2H), 7.47 (t, *J*=14.7 Hz, 1H), 7.42-7.37 (m, 3H), 7.30-7.25 (m, 3H), 6.98 (d, *J*=17.6 Hz, 2H), 6.96 (d, *J*=17.5 Hz, 2H), 5.86 (dd, *J*=8.5, 8.5 Hz, 1H), 4.86 (dd, *J*=8.1, 8.1 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 195.6, 140.1, 138.1, 135.6, 135.6, 133.4, 132.7, 132.7, 132.6, 132.2, 132.2, 131.8, 131.7, 131.6, 130.6, 129.9, 129.0, 128.8, 128.7, 128.3, 128.2, 128.0, 59.1, 21.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3330, 3165, 3057, 1686, 1590, 1438, 1202, 1124, 1093, 728; **HRMS** (EI^+) m/z calculated for $C_{27}H_{23}NO_2PCl$ $[M]^+$: 459.1155; found: 459.1161.

2-(Diphenylphosphinamide)-1-(p-bromo-phenyl)-2-p-tolylethanone (5-34)



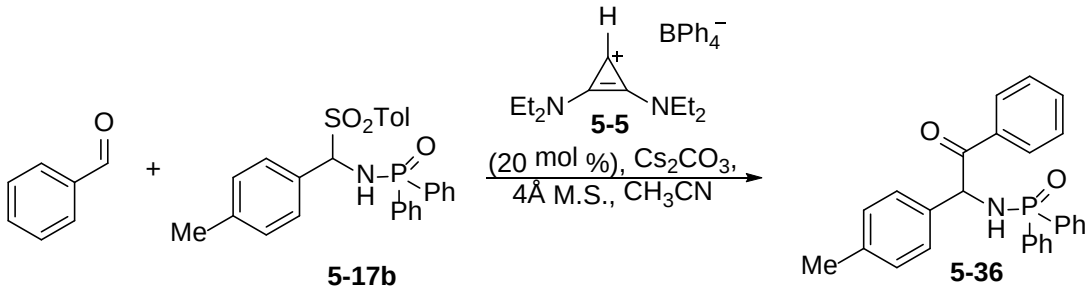
In a test tube with Schlenk takeoff **5-17b** was added (90 mg, 0.19 mmol) as well as cesium carbonate, (308 mg, 0.945 mmol), dry molecular sieve (150 mg) and 4-bromo-benzaldehyde (42 mg, 0.23 mmol). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.63 mL) was added along with pre-catalyst **5-5** (19 mg, 0.038 mmol) was added in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (1:5 EtOAc to CH_2Cl_2) to afford 71.8 mg (75%) of **5-34** as a white solid. R_f = 0.3 (20%EtOAc, DCM); **m.p.** (^oC): 149-151; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.81 (dd, *J*=11.9, 7.9 Hz, 2H), 7.70-7.64 (m, 4H), 7.48-7.34 (m, 6H), 7.28-7.24 (m, 2H), 6.98 (d, *J*=17.7 Hz, 2H), 6.95 (d, *J*=17.8 Hz, 2H), 5.85 (dd, *J*=9.9, 8.9 Hz, 1H), 4.85 (dd, *J*=8.1, 8.1 Hz, 1H), 2.21 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 195.9, 195.8, 138.1, 135.6, 135.5, 133.4, 133.2, 132.7, 132.6, 132.5, 132.1, 132.1, 132.0, 131.8, 131.8, 131.7, 130.7, 129.9, 128.9, 128.8, 128.7, 128.3, 128.2, 128.0, 59.1, 21.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3331, 3149, 3057, 2886, 1686, 1586, 1484, 1247, 1021, 990, 909, 727, 533; **HRMS** (EI^+) m/z calculated for $C_{27}H_{23}NO_2PBr$ $[M]^+$: 503.0650; found: 503.0658.

2-(Diphenylphosphinamide)-1-(m-methoxy-phenyl)-2-p-tolylethanone (5-35)



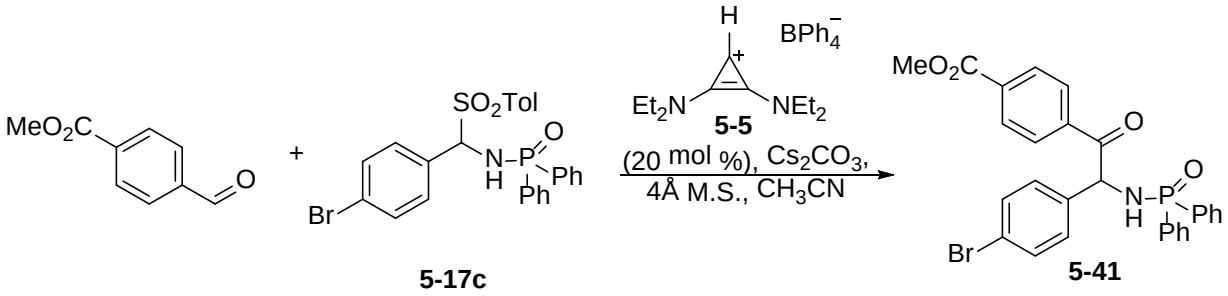
In a test tube with Schlenk takeoff **5-17b** was added (75 mg, 0.16 mmol) along with cesium carbonate, (256 mg, 0.788 mmol) and dry molecular sieve (199 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.52 mL) and 3-methoxy-benzaldehyde (96 μL, 0.79 mmol) was added as well as pre-catalyst **5-5** (15.8 mg, 0.031 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction is quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product is purified via column (3:7 EtOAc to hexanes+2%MeOH) to afford 64.4 mg (89.7%) of **5-35** as a white solid. R_f =0.3 (7:3 hexanes: EtOAc); **m.p.** (^oC): 147-147; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.81 (dd, *J*=12.1, 7.1 Hz, 2H), 7.68 (dd, *J*=12.2, 7.0 Hz, 2H), 7.50-7.36 (m, 6H), 7.31-7.25 (m, 2H), 7.20 (t, *J*= 8.1 Hz, 1H), 7.20-7.15 (m, 5H), 5.87 (dd, *J*=9.7, 8.6 Hz, 1H), 4.86 (dd, *J*=8.5, 8.3 Hz, 1H), 3.74 (s, 3H), 2.22 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 196.7, 196.6, 160.0, 138.0, 136.0, 136.0, 135.8, 133.6, 132.9, 132.7, 132.6, 132.5, 132.1, 132.1, 131.9, 131.9, 131.7, 131.7, 129.8, 129.7, 128.8, 128.7, 128.4, 128.3, 128.0, 121.9, 120.3, 113.5, 59.2, 55.5, 21.3; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3328, 3176, 3.56, 2921, 1685, 1597, 1582,1438,1287, 1200,1110; **HRMS** (EI^+) m/z calculated for $C_{28}H_{26}NO_3P$ $[M]^+$: 455.1650; found: 455.1665.

2-(Diphenylphosphinamide)-1-phenyl-2-p-tolylethanone (5-36)



In a test tube with Schlenk takeoff **5-17b** was added (75 mg, 0.16 mmol) as well as cesium carbonate, (257 mg, 0.785 mmol) and dry molecular sieve (124 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.52 mL) and benzaldehyde (80 μL, 0.79 mmol) were added along with pre-catalyst **5-5** (15.7 mg, 0.031 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent is evaporated *in vacuo* and product is purified via column (6:4 EtOAc to hexanes) to afford 60 mg (90%) of **5-36** as a white solid. All spectra are in general agreement with what has been established previously.[10] **m.p.** (^{o}C): 146-148; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.84 (d, *J*=7.2 Hz, 2H) 7.83-7.80 (m, 2H), 7.68 (dd, *J*=12.3, 7.1 Hz, 2H), 7.48-7.39 (m, 5H), 7.36-7.25 (m, 4H), 7.02 (d, *J*=7.6 Hz, 2H), 6.96 (d, *J*=7.8 Hz, 2H), 5.91 (dd, *J*=9.6, 8.7Hz, 1H), 4.89 (dd, *J*=8.3, 8.2 Hz, 1H), 2.22 (s, 3H); All spectra are consistent with what is reported in the literature.[83]

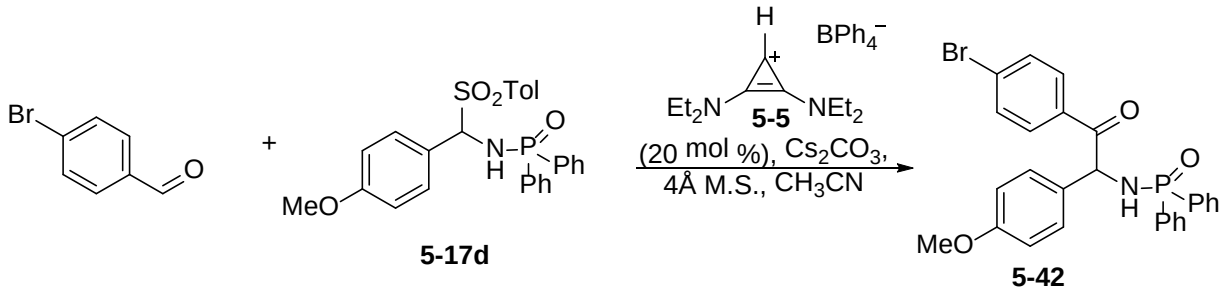
Methyl 4-(2-(4-bromophenyl)-2-((diphenylphosphoryl)amino)acetyl)benzoate (5-41)



In a test tube with Schlenk takeoff acceptor **5-17c** was added (106 mg, 0.20 mmol) along with cesium carbonate, (292 mg, 0.90 mmol) and dry molecular sieve (150 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.6 mL) and methyl-4-formyl benzoate (30 mg, 0.18 mmol) were added along with pre-catalyst **5-5** (18 mg, 0.035 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react for 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (gradient 3:7 EtOAc to toluene, to 1:1 EtOAc to toluene) to afford 17.1 mg (17%) of **5-41** as a white solid. **m.p.** (^{o}C): 168-172; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.98 (d, *J*=7.9 Hz, 2H) 7.86 (d, *J*=8.3 Hz, 2H), 7.82 (dd, *J*=12.0, 7.8 Hz, 2H), 7.65 (dd, *J*=12.2, 7.8 Hz, 2H), 7.55-7.46 (m, 1H), 7.44-7.38 (m, 3H), 7.29 (dt, *J*=7.5, 2.5 Hz, 2H) 7.28-7.24 (m, 2H), 6.97 (d, *J*=8.3 Hz, 2H), 5.94 (dd, *J*=7.9, 7.9 Hz, 1H), 4.89 (dd, *J*=8.1, 7.9 Hz, 1H), 3.89 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 196.0, 196.0, 166.0, 137.5, 137.4, 134.6, 133.1, 132.6, 132.4, 132.6, 132.1, 132.0, 131.8, 131.7, 131.4, 130.0, 129.9, 129.2, 128.9, 128.8, 128.5, 128.4, 122.6, 59.1, 52.7; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3328, 3148, 3058, 2952, 1726, 1690, 1438, 1279, 1195; **HRMS** (EI^+) m/z calculated for $C_{28}H_{23}NO_4P^{81}Br$ $[M]^+$: 549.0528; found: 549.0529; m/z calculated for $C_{28}H_{23}NO_4P^{79}Br$ $[M]^+$: 549.0548; found: 547.0523.

N-(2-(4-Bromophenyl)-1-(4-methoxyphenyl)-2-oxoethyl)-P, P-diphenylphosphinic amide

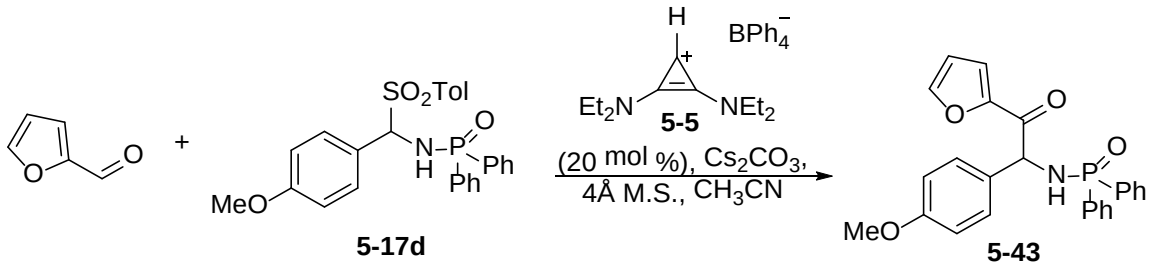
(5-42)



In a test tube with Schlenk takeoff acceptor **5-17d** was added (77 mg, 0.16 mmol) along with cesium carbonate, (257 mg, 0.79 mmol) and dry molecular sieve (124 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.52 mL) and p-bromobenzaldehyde (32 mg, 0.17 mmol) were added along with pre-catalyst **5-5** (16 mg, 0.030 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react for 12 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (1:1 EtOAc to hexanes +1% MeOH) to afford 56.7 mg (70%) of **5-42** as a white solid. **m.p.** (^{o}C): 134-135; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.81 (dd, *J*=12.1, 8.4 Hz, 2H), 7.70-7.64 (m, 4H), 7.55-7.44 (m, 3H), 7.44-7.40 (m, 3H), 7.28 (dt, *J*=7.7, 4.5 Hz, 2H), 7.01 (d, *J*=8.7 Hz, 2H), 6.67 (d, *J*=8.7 Hz, 2H), 5.84 (dd, *J*=9.9, 8.1 Hz, 1H), 4.83 (dd, *J*=8.2, 8.1 Hz, 1H), 3.70 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 195.8, 159.6, 133.5, 133.2, 132.7, 132.7, 132.5, 132.2, 132.2, 132.1, 131.9, 131.8, 131.8, 130.7, 130.6, 130.6, 129.4, 129.0, 128.8, 128.7, 128.4, 128.3, 114.7, 58.8, 55.4; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3331, 3167, 3058, 2933, 2790, 1687, 1609, 1512, 1396, 1255, 1178; **HRMS** (EI^+) m/z calculated for $C_{27}H_{23}NO_3P^{81}Br$ $[M]^+$: 521.0578; found: 521.0583; calculated for $C_{27}H_{23}NO_3P^{79}Br$ $[M]^+$: 519.0599; found: 519.0601.

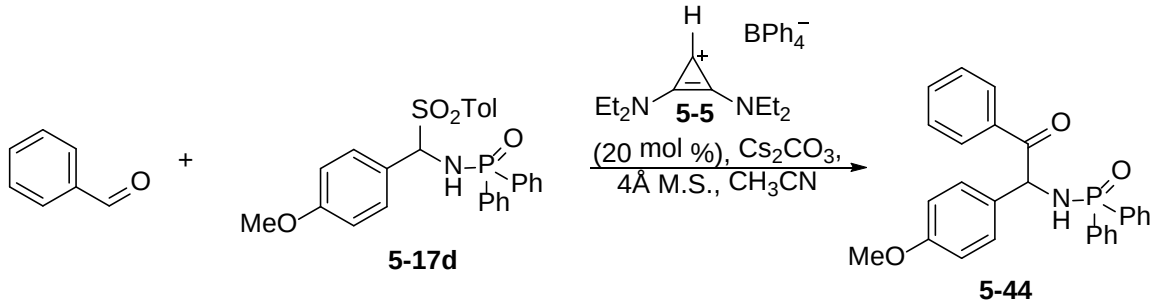
N-(2-(Furan-2-yl)-1-(4-methoxyphenyl)-2-oxoethyl)-P, P-diphenylphosphinic amide

(5-43)



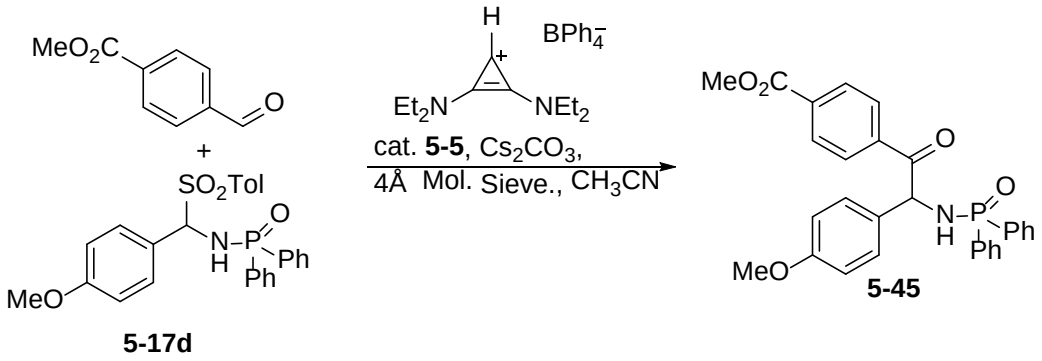
In a test tube with Schlenk takeoff acceptor **5-17d** was added (75 mg, 0.15 mmol) along with cesium carbonate, (248 mg, 0.76 mmol) and dry molecular sieve (200 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.5 mL) and furfural (38 μL, 0.46 mmol) were added along with pre-catalyst **5-5** (15 mg, 0.030 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react for 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (7:3 hexanes to acetone, followed by 100% EtOAc) to afford 60 mg (90%) of **5-43** as a white solid. **m.p.** (^{o}C): 151-152; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.82 (dd, *J*=12.0, 8.3 Hz, 2H), 7.67 (dd, *J*=12.2, 8.2 Hz, 2H), 7.50-7.43 (m, 2H), 7.43-7.38 (m, 3H), 7.29 (dt, *J*=7.6, 3.2 Hz, 2H), 7.12 (s, 1H), 7.11 (d, *J*=6.3 Hz, 2H), 6.72 (d, *J*=8.7 Hz, 2H), 6.41 (dd, *J*=3.5, 1.5 Hz, 1H), 5.67 (dd, *J*=8.7, 8.6 Hz, 1H), 4.78 (dd, *J*=8.1, 8.0 Hz, 1H), 3.73 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 185.5, 185.4, 159.5, 150.6, 147.2, 133.3, 132.7, 132.7, 132.7, 132.3, 132.2, 132.2, 132.0, 131.9, 131.8, 131.8, 131.7, 130.8, 130.8, 129.4, 128.8, 128.7, 128.4, 128.3, 119.6, 114.4, 112.7, 58.7, 55.4; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3329, 3103, 3058, 2956, 2837, 1675, 1609, 1567, 1511, 1465, 1250; **HRMS** (EI^+) m/z calculated for $C_{25}H_{22}NO_4P$ $[M]^+$: 431.1286; found: 431.1300.

N-(1-(4-Methoxyphenyl)-2-oxo-2-phenylethyl)-P, P-diphenylphosphinic amide (5-44)



In a test tube with Schlenk takeoff acceptor **5-17d** was added (75 mg, 0.15 mmol) along with cesium carbonate, (247 mg, 0.76 mmol) and dry molecular sieve (120 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.51 mL) and benzaldehyde (78 μL, 0.76 mmol) were added along with pre-catalyst **5-5** (15 mg, 0.030 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (4:6 EtOAc to hexanes +2% MeOH) to afford 46.6 mg (69%) of **5-44** as a white solid. **m.p.** (^{o}C): 157-158; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.83 (d, *J*=7.6 Hz, 2H), 7.82-7.76 (m, 2H), 7.68 (dd, *J*=12.0, 7.5 Hz, 2H), 7.50-7.34 (m, 5H), 7.32-7.26 (m, 4H), 7.04 (d, *J*=8.5 Hz, 2H), 6.66 (d, *J*=8.60 Hz, 2H), 5.91 (dd, *J*=9.3, 9.3 Hz, 1H), 4.89 (dd, *J*=8.2, 8.2 Hz, 1H), 3.76 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 196.7, 196.7, 159.4, 134.4, 133.6, 133.5, 132.9, 132.7, 132.6, 132.5, 132.1, 132.1, 131.9, 131.8, 131.7, 131.7, 131.0, 131.0, 129.4, 129.2, 128.8, 128.7, 128.7, 128.3, 128.2, 114.5, 58.7, 55.3; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3330, 3178, 3058, 2933, 2766, 1685, 1609, 1597, 1439, 1287, 1202, 1124; **HRMS** (EI^+) m/z calculated for $C_{27}H_{24}NO_3P$ $[M]^+$: 441.1494; found: 441.1512.

Methyl-4-(2-((diphenylphosphoryl)amino)-2-(4-methoxyphenyl)acetyl)-benzoate (5-45)

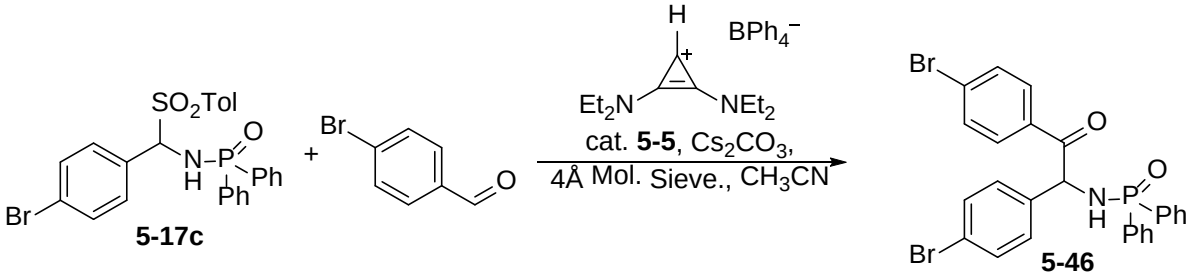


5-17d **5-45**

In a test tube with Schlenk takeoff acceptor **5-17d** was added (70 mg, 0.14 mmol) along with cesium carbonate, (232 mg, 0.71 mmol) and dry molecular sieve (180 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.47 mL) and methyl-4-formylbenzoate (29 mg, 0.17 mmol) were added along with bis(diethylamino)-cyclopropenylidene tetraphenylborate (14.2 mg, 0.028 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react for 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated and product was purified via column chromatography (7:3 EtOAc to hexanes +2% MeOH) to give 20.2 mg (28%) of **5-45** as a white solid. **m.p.** (^{o}C): 117-119; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.98 (d, *J*=7.4 Hz, 2H), 7.86 (d, *J*=8.4 Hz, 2H), 7.82 (dd, *J*=11.1, 8.2 Hz, 2H), 7.68 (dd, *J*=11.4, 8.0 Hz, 2H), 7.50-7.43 (m, 1H), 7.43-7.38 (m, 3H), 7.29 (dt, *J*=7.6, 3.0 Hz, 2H), 7.01 (d, *J*=7.2 Hz, 2H), 6.68 (d, *J*=8.6 Hz, 2H), 5.90 (dd, *J*=9.2, 8.8 Hz, 1H), 4.82 (dd, *J*=8.1, 8.0 Hz, 1H), 3.88 (s, 3H), 3.70 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 196.5, 196.4, 166.2, 159.6, 153.0, 137.9,134.3, 133.4, 132.7, 132.7, 132.5, 132.4, 132.3, 132.3, 131.9, 131.8, 131.7, 131.7, 131.6, 131.5, 130.3, 130.3, 129.9, 129.5, 129.3, 129.1, 128.9, 128.8, 128.7, 128.7, 128.6, 128.4, 128.3, 114.7, 59.2, 55.4, 52.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3331, 3183, 2953,

2838, 1725, 1688, 1512, 1438, 1280; **HRMS** (EI^+) m/z calculated for $C_{29}H_{27}NO_5P$ $[M]^+$: 500.1627; found: 500.1613.

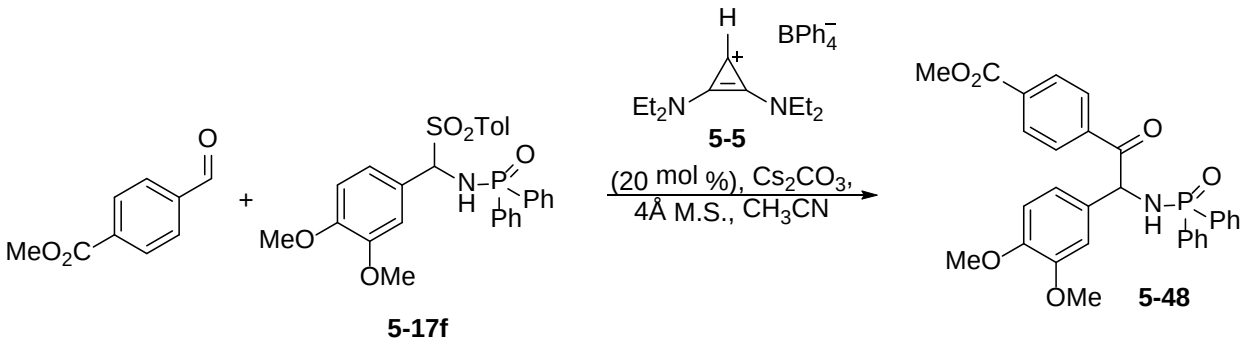
N-(1, 2-Bis(4-bromophenyl)-2-oxoethyl)-P,P-diphenylphosphinic amide (5-46)



In a test tube with Schlenk takeoff acceptor **5-17c** was added (90 mg, 0.27 mmol) along with cesium carbonate, (271 mg, 0.83 mmol) and dry molecular sieve (139 mg). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.56 mL) and *p*-bromobenzaldehyde (34 mg, 0.18 mmol) were added along with bis(diethylamino)-cyclopropenylidene tetraphenylborate (16.7 mg, 0.033 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react for 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated and product was purified via column chromatography (2:8 EtOAc to CH_2Cl_2) to give 16.2 mg (17%) of compound **5-46** as a white solid. **m.p.** (^oC): 158-161; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.80 (dd, *J*=12.1, 7.1 Hz, 2H), 7.68 (d, *J*=8.6, 2H), 7.63 (dd, *J*=12.3, 7.1 Hz, 2H), 7.53-7.43 (m, 3H), 7.43-7.38 (m, 3H), 7.29 (dt, *J*=7.5, 3.0 Hz, 2H), *7*.29-7.23 (m, 2H), 6.96 (d, *J*=8.4, 2H), 5.86 (dd, *J*=7.9, 7.8 Hz, 1H), 4.88 (dd, *J*=8.1, 8.0 Hz, 1H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 195.4, 137.7, 137.7, 133.2, 132.9, 132.6, 132.6, 132.4, 132.3, 132.2, 132.0, 132.0, 131.8, 131.8, 131.5, 130.7, 129.8, 129.4, 128.9, 128.8, 128.5, 128.4, 122.6, 58.8; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3331, 3149, 3058, 3012, 1686, 1586, 1487, 1438, 1199, 1124; **HRMS** (EI^+) m/z calculated for $C_{26}H_{20}NO_2P^{81}Br_2$ $[M]^+$: 570.9557; found: 570.9558; m/z calculated for

$C_{26}H_{20}NO_2P^{81}Br^{79}Br$ $[M]^+$: 568.9578; found: 568.9585; m/z calculated for $C_{26}H_{20}NO_2P^{79}Br_2$ $[M]^+$: 566.9598; found: 566.9606.

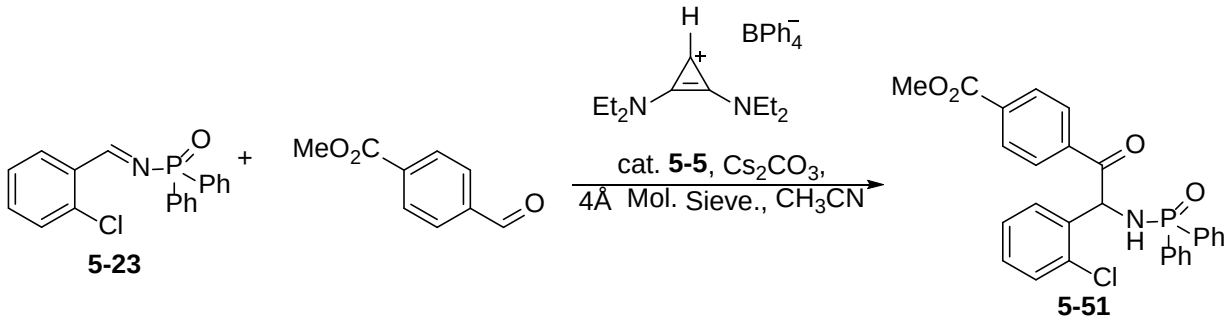
Methyl 4-(2-(3, 4-dimethoxyphenyl)-2-((diphenylphosphoryl)amino)acetyl)benzoate (5-48)



In a test tube with Schlenk takeoff acceptor **5-17f** was added (87 mg, 0.17 mmol) along with cesium carbonate, (162 mg, 0.501 mmol), dry molecular sieve (150 mg), methyl-4-formyl benzoate (41 mg, 0.25 mmol) were added along with pre-catalyst **5-5** (12.6 mg, 0.025 mmol). A stir bar was added along with a septum and the test tube was put under inert atmosphere. Acetonitrile (0.56 mL) was added and the mixture was sealed, parafilmed and allowed to react for 16 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (gradient 4:6 EtOAc to hexanes+ 2% MeOH, to 100% EtOAc) to afford 24.1 mg (27%) of **5-48** as a white solid. **m.p.** (^{o}C): 74-75; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.98 (d, *J*=7.9 Hz, 2H) 7.86 (d, *J*=8.0 Hz, 2H), 7.80 (dd, *J*=12.0, 8.0 Hz, 2H), 7.68 (dd, *J*=12.0, 8.0 Hz, 2H), 7.53-7.46 (m, 1H), 7.44-7.38 (m, 3H), 7.29 (dt, *J*=7.5, 2.0 Hz, 2H), 6.62 (s, 1H), 6.61 (d, *J*=15 Hz, 2H), 5.92 (dd, *J*=9.0, 9.0 Hz, 1H), 4.83 (dd, *J*=8.5, 8.0 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.69 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 196.4, 196.4, 166.1, 149.6, 149.2, 137.9, 134.4, 133.4, 132.8, 132.7, 132.4, 132.3, 132.3, 131.9, 131.9, 131.8, 131.7, 130.7, 130.7, 129.9,

129.1, 128.9, 128.8, 128.4, 128.3, 120.8, 111.7, 111.3, 59.5, 56.0, 56.0, 52.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}):3332. 3180, 3057, 3002, 2953, 2837, 2254, 2221, 1725, 1689, 1592, 1515, 1463, 1421, 1280, 1241, 1143, 1027, 993, 726, 699; **HRMS** (EI^+) m/z calculated for $C_{30}H_{28}NO_6P^{81}$ $[M]^+$: 529.1654; found: 529.1630.

Methyl 4-(2-(2-chlorophenyl)-2-((diphenylphosphoryl)amino)acetyl)benzoate (5-51)

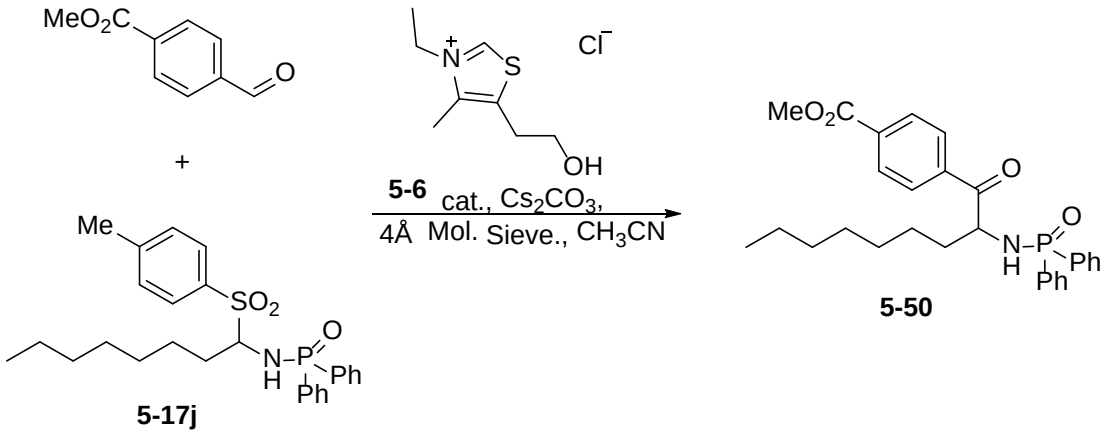


5-23 **5-51**

In a test tube with Schlenk takeoff acceptor the imine was added (121.3 mg, 0.357 mmol) along with cesium carbonate, (348 mg, 1.07 mmol), dry molecular sieve (150 mg), methyl-4-formylbenzoate (88 mg, 0.535 mmol) were added along with bis(diethylamino)-cyclopropenylidene tetraphenylborate (27 mg, 0.053 mmol). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (1.2 mL) and in one portion and the mixture was sealed, parafilmed and allowed to react for 16 hours. The reaction was quenched with acetic acid, filtered through a short plug of silica (washed with 100% EtOAc). Solvent was evaporated and product was purified via column chromatography (7:3 EtOAc to CH_2Cl_2, 4:6 acetone: hexanes). One final impurity was removed with a basic wash in a separatory funnel, (1N NaOH, CH_2Cl_2) dried over sodium sulfate and solvent removed *in vacuo* to give 12.0 mg (6.6%) of the

α-amino ketone as a white solid. **m.p.** (°C): 66-68; **^{1}H NMR** (600 MHz, $CHCl_3$) δ 7.97 (d, *J*=8.4 Hz, 2H), 7.91 (d, *J*=8.3 Hz, 2H), 7.86 (dd, *J*=11.9, 7.5 Hz, 2H), 7.67 (dd, *J*=12.3, 7.7 Hz, 2H), 7.49 (t, *J*=7.27 Hz, 1H), 7.43 (dt, *J*=7.6, 2.7 Hz, 2H), 7.39 (t, *J*=7.4 Hz, 1H), 7.24 (dt, *J*=7.32, 2.6 Hz, 2H), 7.20 (d, *J*=7.2 Hz, 1H), 7.11-7.06 (m, 3H), 6.34 (dd, *J*=10.2, 7.8 Hz, 1H), 4.82 (dd, *J*=6.6, 6.6 Hz, 1H), 3.88 (s, 3H); **^{13}C NMR** (150 MHz, $CHCl_3$) δ 196.1, 196.1, 166.2, 137.7, 136.3, 136.3, 134.5, 133.7, 133.4, 133.4, 132.8, 132.8, 132.5, 132.3, 132.3, 132.2, 131.9, 131.9, 131.7, 131.7, 130.4, 129.9, 129.8, 128.9, 128.9, 128.8, 128.3, 128.3, 127.8, 57.0, 52.6; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3316, 3146, 2924, 2223, 1726, 1695, 1475, 1438, 1406, 1279, 1240, 1193, 1124, 1109, 1036, 1019, 992.8, 914.8, 771.2, 752.9, 727.8, 695.1; **HRMS** (EI^+) m/z calculated for $C_{28}H_{23}{}^{35}ClNO_4P$ $[M]^+$: 503.1073; found: 503.1053; $C_{28}H_{23}{}^{37}ClNO_4P$ $[M]^+$: 505.1024; found: 505.1083.

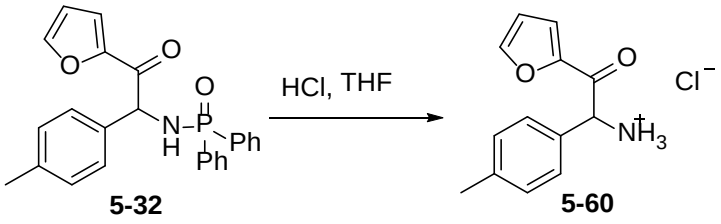
Methyl 4-(2-((diphenylphosphoryl)amino)nonanoyl)benzoate (5-50)



In a Schlenk test tube acceptor (50 mg, 0.11 mmol), methyl-4-formyl benzoate (21 mg, 0.13 mmol), thiazolium (5.3 mg, 0.021 mmol), cesium carbonate (172 mg, 0.53 mmol), and molecular sieves (82 mg) were added. The flask was put under argon and acetonitrile (0.7 mL) was added. After 16 hours the flask was quenched with acetic acid and passed through silica. The

crude product was purified via column chromatography (7:3 CH_2CH_2: EtOAc) to give 23.4 mg (45%) yield of the aza-benzoin product. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 8.07 (d, *J*=8.3 Hz, 2H), 7.90 (dd, *J*=12.1, 7.0 Hz, 2H), 7.81 (d, *J*=8.3 Hz, 2H), 7.79 (dd, *J*=12.2, 7.1 Hz, 2H), 7.53 (dt, *J*=7.4, 1.1 Hz, 1H), 7.51-7.43 (m, 3H), 7.36 (dt, *J*=7.7, 3.1 Hz, 2H), 4.87 (ddd, *J*=9.3, 5.2, 3.7 Hz, 1H), 4.12 (dd, *J*=9.6, 9.5 Hz, 1H), 3.93 (s, 3H), 1.79-1.73 (m, 1H), 1.62-1.57 (m, 1H), 1.42-1.34 (br. s, 1H), 1.26-1.10 (m, 9H), 0.82 (t, *J*=7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 200.6, 166.2, 138.3, 134.6, 133.1, 132.6, 132.3, 132.2, 132.2, 132.2, 132.1, 132.1, 130.2, 128.9, 128.8, 128.8, 128.7, 128.5, 55.3, 52.7, 35.5, 31.9, 29.4, 29.1, 24.7, 22.8, 14.2; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3380, 3173, 2927, 2855, 1727, 1690, 1592, 1438, 1405, 129, 1191, 1109; **HRMS** (ESI^+) m/z calculated for $C_{29}H_{34}NO_4P$+H $[M]^+$: 492.2298; found: 492.2321.

2-(Furan-2-yl)-2-oxo-1-(p-tolyl)ethanaminium chloride (5-60)

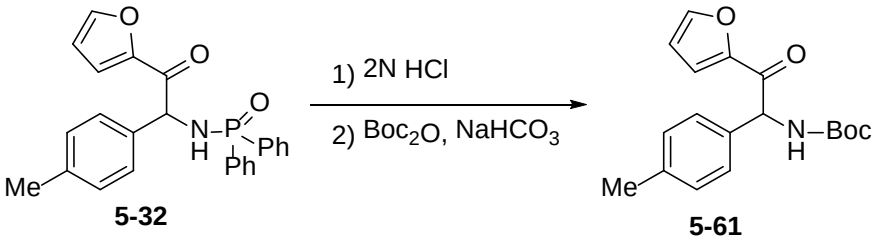


5-32 **5-60**

To the aza-benzoin acceptor (40mg, 0.096 mmol) was added an aqueous hydrochloric acid solution (0.5 mL, 2N), and THF (0.5 mL) under argon. The reaction was stirred for 15 hrs at room temperature. Reaction was quenched with dil. NaOH and the crude reaction mixture extracted into ether. The ether layer was dried over sodium sulfate and HCl (2.0 M in diethyl ether) was added until precipitation stopped to afford 9.6 mg (40%) of the ammonium salt as a white solid. **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.79 (d, *J*=1.4 Hz, 1H), 7.42 (d, *J*=8.6 Hz, 2H), 7.41 (s, 1H), 7.29 (d, *J*=8.1 Hz, 2H), 6.63 (dd, *J*=3.7, 1.6 Hz, 1H), 5.84 (s, 1H), 4.86 (br. s, 3H), 2.34 (s, 3H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 182.5, 151.1, 150.2, 142.0, 131.5, 130.5, 129.9, 122.2,

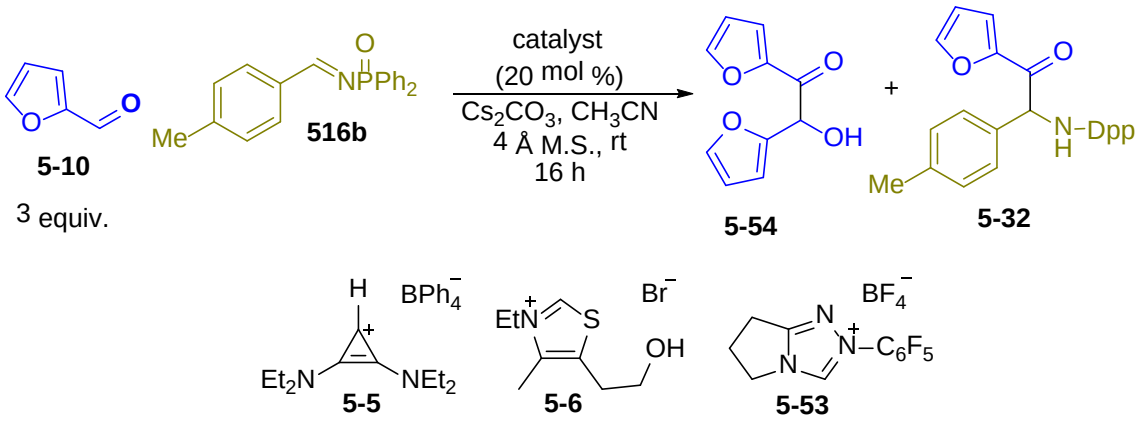
114.2, 60.4, 21.3; **HRMS** (ESI^+) m/z calculated for $C_{13}H_{14}NO_2$ $[M]^+$: 216.1019; found: 216.1026.

t*ert*-Butyl-(2-(furan-2-yl)-2-oxo-1-(p-tolyl)-ethyl)-carbonate (5-61)



The starting α-keto amine (40 mg, 0.096 mmol) **5-32** was dissolved in THF (0.5 mL) at room temperature under inert atmosphere and 2 M hydrochloric acid was added (0.5 mL). The mixture was stirred at room temperature for 15 hours. Once the reaction completion was assessed by TLC, THF (4 mL) was added as well as solid powdered bicarbonate until litmus paper tested slightly basic. Then Boc anhydride was added (90 μL, 0.41 mmol), once the protection was complete by TLC (<8 hrs) the material was extracted into diethyl ether, washed with 1 M NaOH, water and dried by passing through a tube packed with sodium sulfate. The crude oil was then purified by column chromatography (10% EtOAc: hexanes to 30% EtOAc: hexanes) to afford 27 mg of pure product **5-61** as a white solid (88% yield). **m.p.** (^oC): 128-130; **^{1}H NMR** (500 MHz, $CHCl_3$) δ 7.53 (s, 1H), 7.28 (d, *J*=7.8 Hz, 2H), 7.22 (d, *J*=3.6 Hz, 1H), 7.12 (d, *J*=7.9 Hz, 2H), 6.46 (d, *J*=2.0 Hz, 1H), 6.01 (d, *J*=7.5 Hz, 1H), 5.87 (d, *J*= 6.9 Hz, 1H), 2.29 (s, 3H), 1.41 (s, 9H); **^{13}C NMR** (125 MHz, $CHCl_3$) δ 185.1, 155.1, 150.9, 147.2, 138.4, 134.3, 129.9, 128.1, 119.4, 112.7, 59.8, 28.5, 21.3; **FTIR** (KBr thin film) ν_{max} (cm^{-1}): 3426, 3362, 3133, 2978, 2930, 1714, 1675, 1569, 1490, 1465, 1249; **HRMS** (ESI^+) m/z calculated for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543; found: 316.1556.

Benzoin Aza-benzoin Comparison Experiment



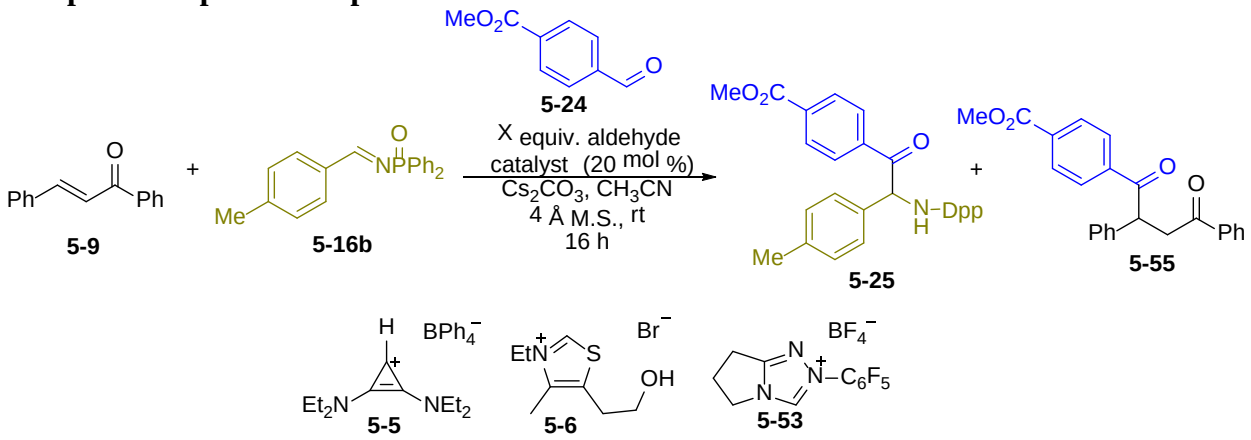
Three Schlenk tubes were each loaded with imine **5-16b** (30 mg, 0.093 mmol), furfural (27 mg, 0.28 mmol), cesium carbonate (92 mg, 0.28 mmol) and activated 4 Å molecular sieves (100 mg). The appropriate catalyst was added to each Schlenk tube (0.014 mmol) (7.1 mg for bisdiethylaminocyclopropenium **5-5**, 3.6 mg for thiazolium **5-6**, and 5.1 mg for triazolium **5-53**). Exact amounts of bibenzyl were added to each flask as an internal standard (7.0 mg, 13.2 mg and 8.0 mg respectively). All Schlenk tubes were evacuated under high vacuum for 15 minutes and an argon atmosphere was established. Acetonitrile was added (0.31 mL) and after 16 hours all reactions were quenched with acetic acid and passed through a plug of silica with 100% ethyl acetate. They were then evaporated down *in vacuo*, co-evaporated twice with chloroform and reaction spectra were recorded.

For bis(diethylamino)cyclopropenium **5-5** NMR yield values: Aza-benzoin product 79%, residual imine 8% and residual aldehyde 1.05 equiv (35%).

For thiazolium **5-6** isolated values: NMR yield values: Aza-benzoin product 91%, residual aldehyde 1% and benzoin product (67%).

For triazolium **5-53** isolated values: NMR yield values: Aza-benzoin product 70%, and benzoin product (47%)

Acceptor Competition Experiment



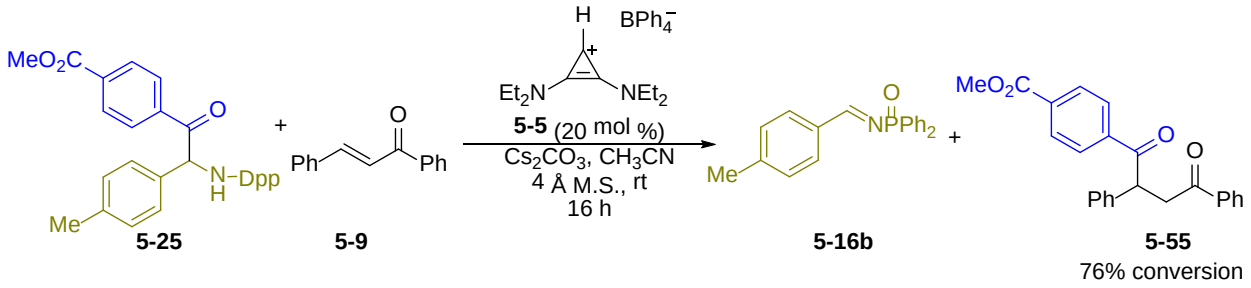
Three Schlenk test tubes were each loaded with imine **5-16b** (51 mg, 0.16 mmol), methyl-4-formyl benzoate **5-24** (27 mg, 0.16 mmol), chalcone **5-9** (33 mg, 0.16 mmol), cesium carbonate (260 mg, 0.8 mmol) and activated molecular sieve (125 mg). The appropriate catalyst was added to each Schlenk test tube (0.032 mmol) (16 mg for bisdiethylaminocyclopropenium **5-5**, 8.0 mg for thiazolium **5-6**, and 12 mg for triazolium **5-53**). All Schlenks were evacuated under high vacuum for 15 minutes and a nitrogen atmosphere was established. Acetonitrile was added (0.53 mL) and after 16 hours all reactions were quenched with acetic acid and passed through a plug of silica with 100% ethyl acetate. They were then evaporated down *in vacuo* and spectra (shown) were recorded. The reported purification was accomplished via column and p-TLC where appropriate. A solvent system of 5% EtOAc : hexanes was effective for purifying the Stetter product and 30% EtOAc : hexanes with 2% methanol was used for the aza-benzoin product. All purified substances were consistent with what has been reported previously or above.

For bis(diethylamino)cyclopropenium **5-5** isolated values: Stetter product (29.4 mg, 50% yield with respect to aldehyde). Aza-benzoin product (7.5 mg, 10% yield with respect to aldehyde).

For thiazolium **5-6** isolated values: Stetter product (2.8 mg, 4% yield with respect to aldehyde). Aza-benzoin product (13.5 mg, 18% yield with respect to aldehyde).

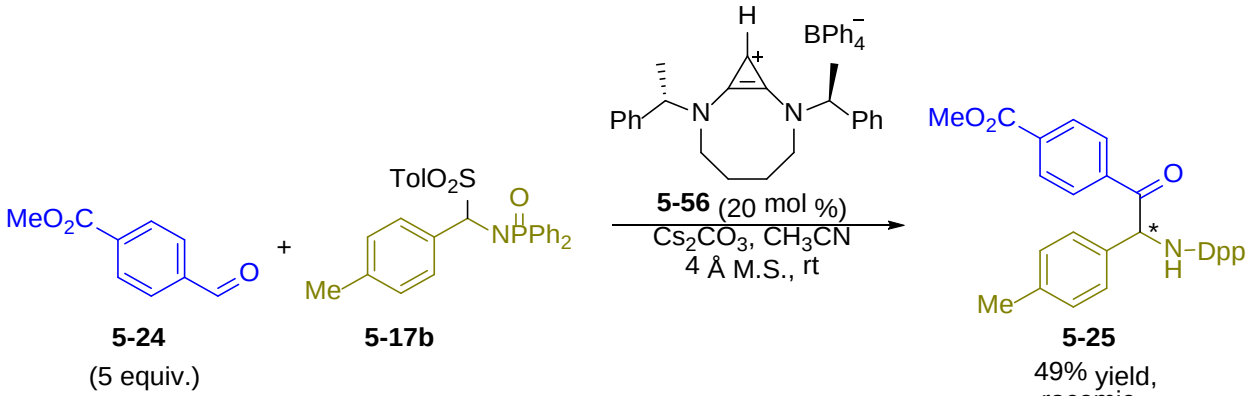
For triazolium **5-23** isolated values: Stetter product (none detected). Aza-benzoin product (6.5 mg, 8% yield with respect to aldehyde).

Retro-Aza-Benzoin Stetter Reaction



A Schlenk test tube was charged with aza-benzoin product **5-25** (38.3 mg, 0.079 mmol), chalcone (16.5 mg, 0.079 mmol) and bis(diethylamino)cyclopropenium **5-5** (8 mg, 0.016), cesium carbonate (127 mg, 0.39 mmol), activated molecular sieves (62 mg) and acetonitrile (0.26 mL). After 16 hours it was quenched with acetic acid and passed through a plug of silica with 100% ethyl acetate. Solvent was evaporated *in vacuo* and NMR spectrum recorded (see paper).

Aza-Benzoin Reaction using Chiral Catalyst 5-56



5-24
(5 equiv.)

5-17b

5-25
49% yield,

In a test tube with Schlenk takeoff adduct **5-17b** was added (75 mg, 0.16 mmol) along with cesium carbonate, (257 mg, 0.79 mmol), dry molecular sieve (200 mg) and methyl-4-formyl-benzoate **5-24** (132 mg, 0.79 mmol). The test tube was put under inert atmosphere and a septum was added. Acetonitrile (0.53 mL) was added along with pre-catalyst **5-56** (21 mg, 0.032 mmol) in one portion and the mixture was sealed, parafilmed and allowed to react for 8 hours. The reaction was quenched with acetic acid, filtered through fritted glass and a short plug of silica (washed with 100% EtOAc). Solvent was evaporated *in vacuo* and product was purified via column (4:6 EtOAc to hexanes) to afford 37 mg (49%) of **5-25** as a white solid, ^{1}H NMR consistent with **10** above. Enantiomeric excess was determined by chiral HPLC, and the material was found to be racemic (not show).

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