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Organocatalyzed Enantioselective Rauhut-Currier Reaction and Formal [3+2] Cycloaddition: Their Application to the Synthesis of α-Alkylidene-γ-butyrolactones and Benzofuranones

A Doctoral Thesis
Submitted to the Department of Chemistry
Graduate School of Science
Osaka University

By

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Department of Synthetic Organic Chemistry

Osaka University

August, 2014

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To MEXT, for accepting me and allowing me to study in Japan.

And to my friends, for making this journey a little bit easier.

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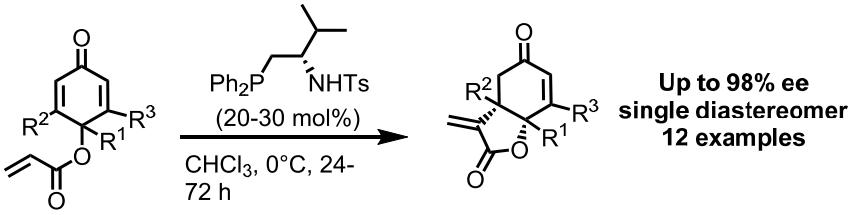
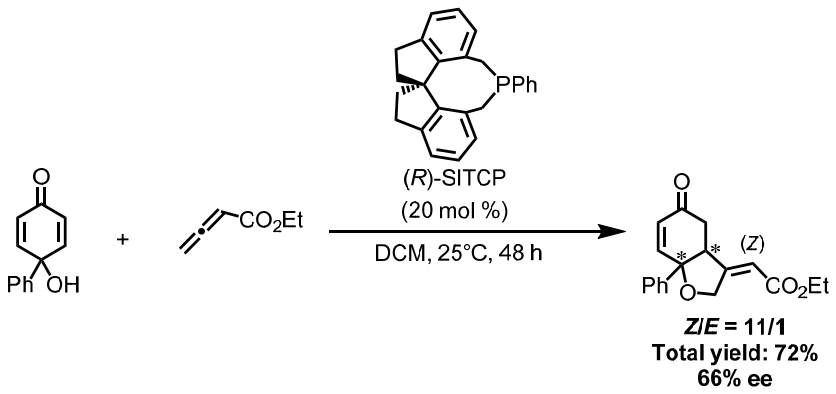
Abstract



Chapter 1:

The Rauhut–Currier (RC) reaction is known to be a readily access synthetic pathway to α -substituted enones The acid–base organocatalyzed intramolecular RC reaction of the dienone enolates has been developed. The enantioselective RC process produces the highly functionalized α -methylidene- γ -butyrolactones as a single diastereomer with up to 98% ee.[1]



Chapter 2:

Enantioselective cycloaddition of allenoates is a useful strategy for the synthesis of heterocycles containing adjacent chiral centers.[2] Formal [3+2] cycloaddition reaction of allenoate through a unique mechanistic pathway has been discovered. SPINOL derived monophosphine catalyst furnishes the benzofuranone product in high diastereomeric ratios, good yields, and enantioselectivity up to 66% ee.

[1] (a) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders, H. Sasai, *Angew. Chem. Int. Ed.*, **2012**, *51*, 5423. (b) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, M. Suzuki, D. Enders, H. Sasai, *Tetrahedron*, **2013**, *69,* 1202.

[2] (a) S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, H. Sasai, *Org. Lett.,* **2013**, *15*, 4142; (b) S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, H. Sasai*, Asian J. Org. Chem.*, **2014**, *3*, 412

Abbreviations

α	alpha
Ac	acetyl
acac	acetylacetonate
Ar	aryl
atm	atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
t-Bu	*tert*-butyl
˚C	degrees Celsius
CN	Nitrile
COD	1,5-cyclooctadiene
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
ee	enantiomeric excess
Eq.	equation
equiv.	equivalent
Et	ethyl
Fig	figure
G or FG	functional group
h	hour
HPLC	high performance liquid chromatography
LAH	lithium aluminium hydride
LB	Lewis Base
MBH	Morita–Baylis–Hillman
Me	methyl
MeDuPhos	1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene
min	minute
MS	molecular sieves
Ph	phenyl
p	*para*-substitution
i-Pr	isopropyl
quant.	quantitative

Abbreviations

R	Any atom or group except hydrogen
rac	racemic
RC	Rauhut-Currier
rt	room temperature
temp.	temperature
THF	tetrahydrofuran
Ts	*para*-toluenesulfonyl

INTRODUCTION:

MacMillan defined the word organocatalysis as the usage of organic molecules with low molecular weight as catalysts in organic reactions.[1] However, in the literatures before this, a large number of publications regarding the use of an organic molecule in a catalytic amount were mentioned. In 1912, Bredig and Fiske reported the addition of HCN to aldehyde in the presence of cinchona alkaloids resulting in low ee.[2] Later in 1960, Pracejus reported the addition of methanol to ketenes with ee up to 74%.[3,4] One of the cornerstones in organocatalysis is the intramolecular aldol reaction catalyzed by proline that was discovered by the pharmaceutical companies Hoffman-La Roche[5] and Schering.[6] This reaction was also known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction. It allows the preparation of intermediates for the synthesis of steroids and other enantiomerically pure molecules.

Today, asymmetric organocatalysis is known as a synthetic tool, besides asymmetric metallic catalysis and enzymatic catalysis, for the synthesis of chiral organic molecules. Several advantages compared with the other two catalytic methods have caused the fast growth and acceptance of organocatalysis. Generally, organocatalysts are non-toxic and sturdy compounds with a large number commercially available and easily synthesized. They are quite stable under aerobic conditions, and the reactions do not require extremely dry conditions, hence inert-equipment such as vacuum lines or gloveboxes are not necessary. In most cases, the reactions are conducted under mild conditions and in high concentrations to avoid the use of large amounts of solvents and minimize waste. Furthermore, thanks to these characteristics, organocatalysts are tolerant of various functional groups and prevent time-consuming and protecting-group manipulations.

Organocatalysts generally have two functions. Firstly, they can activate the electrophile or the nucleophile, or both in the case of bifunctional catalysis; Secondly, they make up an asymmetric environment that can induce the chirality of the product. The organocatalysts can be classified by its interaction with the substrate as covalent or non-covalent catalysts. In covalent catalysis, a covalent bond between the organocatalyst and the substrate is formed, increasing the interaction between the substrate and the reagent in the reaction. In this area, aminocatalysts[7] and carbenes[8] are included. Regarding non-covalent interactions between the substrate and the catalyst, the activation of the substrate occurs by hydrogen, for example

thioureas,[9,10] squaramides[11,12] and phosphoric acids[13–15], or ionic interactions, such as chiral bases such as cinchona alkaloids[16] and phase-transfer catalysts. These catalysts represent the extensive and vast collection of organocatalysts currently available.

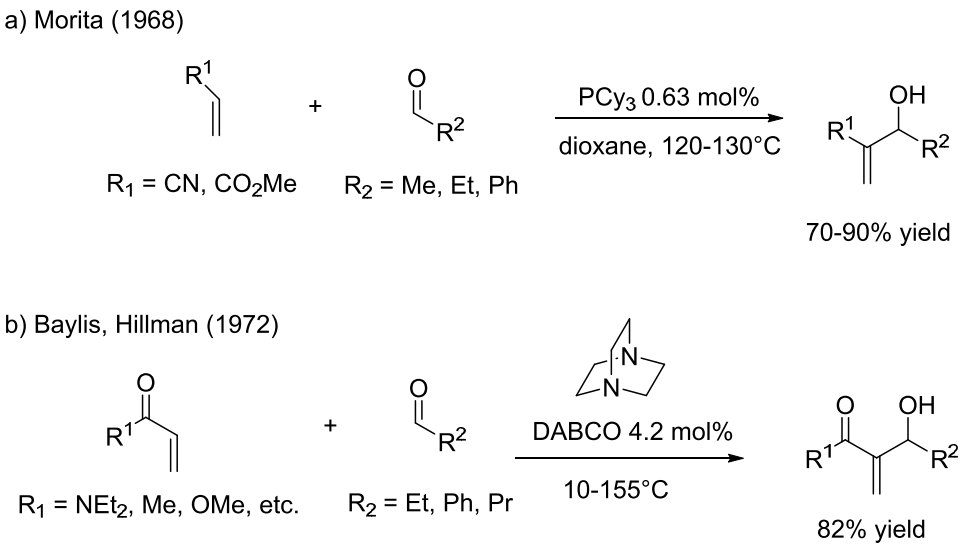
Reference:

1. K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc*., **2000**, *2*. 122, 4243.
2. G. Bredig, W. S. Fiske, *Biochem. Z.*, **1912**, 7
3. H. Pracejus, J. L. Ann. *Chem. Pharm*., **1960***, 634*, 9
4. H. Pracejus, H. Mätje, J. Prakt. *Chem./Chem.-Ztg*., **1964**, *24*, 195
5. Z. G. Hajos, D. R. Parrish, *J. Org. Chem*., **1974**, *39*, 1615
6. U. Eder, G. Sauer, R. Wiechert*, Angew. Chem., Int. Ed. Engl*., **1971***, 10*, 496
7. M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun*., **2011**, *47*, 632
8. A. Grossmann, D. Enders, *Angew. Chem., Int. Ed.*, **2012**, *51*, 314
9. A. G. Doyle, E. N. Jacobsen, *Chem. Rev***., 2007**, *107*, 5713
10. P. R. Schreiner*, Chem. Soc. Rev*., **2003***, 32*, 289
11. J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.,* **2011**, *17*, 6890
12. R. I. Storer, C. Aciro, L. H. Jone, *Chem. Soc. Rev.,* **2011**, *40*, 2330
13. T. Akiyama, *Chem. Rev*., **2007**, *107*, 5744
14. M. Terada*, Curr. Org. Chem***., 2011***, 15*, 2227
15. M. Terada, K. Kanomata, *Synlett*, **2011**, 1255
16. T. Marcelli, H. Hiemstra*, Synthesis*, **2010**, 1229

Chapter 1: Enantioselective Intramolecular Rauhut-Currier Reaction

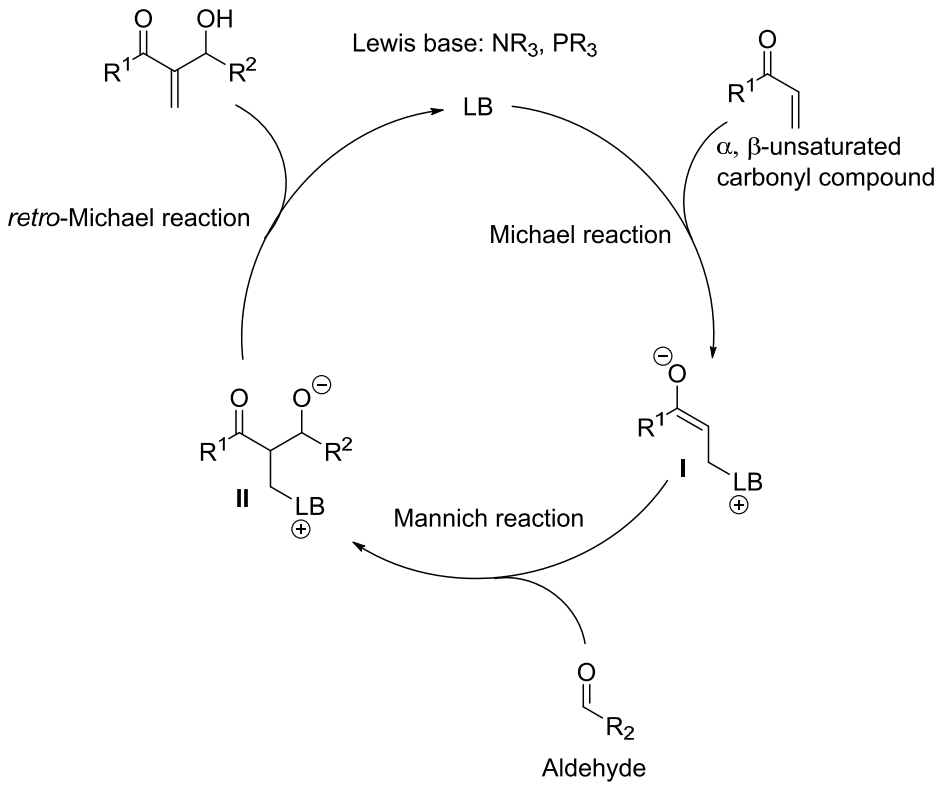
1.1 The Morita-Baylis-Hillman (MBH) and Rauhut-Currier (RC) reaction

1.1.1 Brief history of the MBH reaction



Scheme 1: Early examples of MBH reaction

Upon its discovery, the Morita-Baylis-Hillman (MBH) reaction, has provided an atom-economic method of carbon-carbon bond-formation between the α-position of α,β-unsaturated carbonyls and aldehydes to form allylic alcohols. The MBH reactions are primary catalyzed by organic Lewis-base compounds such as tertiary amines and alkyl/aryl phosphines. In 1968, Morita and co-workers discovered the first example of this type of reaction when using tricyclohexylphosphine as a catalyst to conduct a reaction between various aldehydes and activated alkenes.[1] A few years later, Baylis and Hillman were able to carry out a similar reaction by utilizing DABCO (**Scheme 1**).[2]

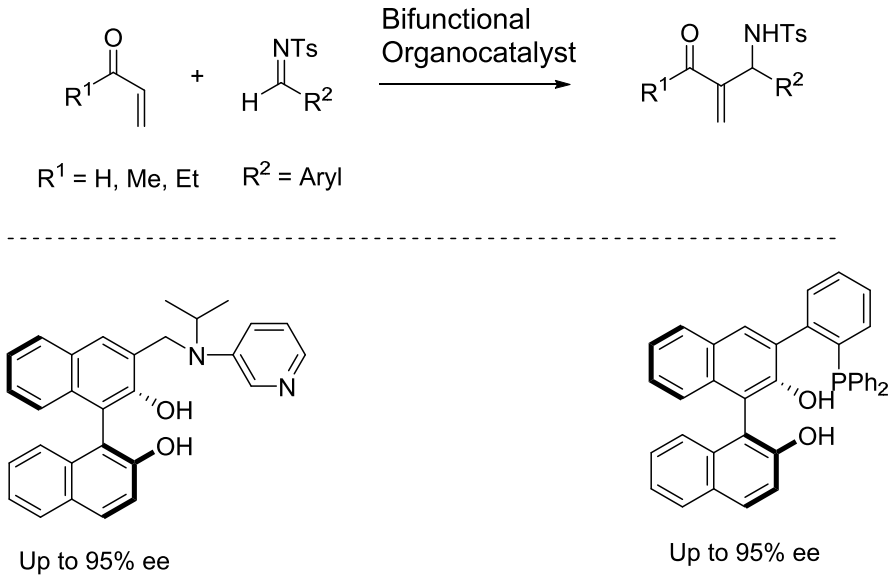


Scheme 2: Mechanism of the MBH reaction

The transformation proceeds first by Michael addition of the Lewis-base to an activated alkene to form a Zwitterionic intermediate **I** (**Scheme 2**). The nucleophilicity of the α-position carbon then adds to an electrophilic aldehyde producing coupling intermediate **II**. Proton transfer takes place from II followed by the release of the Lewis base catalyst finally generating the MBH coupling product. Slow reaction rates often limit the value of MBH reactions in organic synthesis. It is not uncommon for DABCO or trialkylphosphine catalyzed MBH reaction to require days or week, depending on the subtrates.[3] Mild or harsh reaction conditions are often applied to increase the reaction rate.

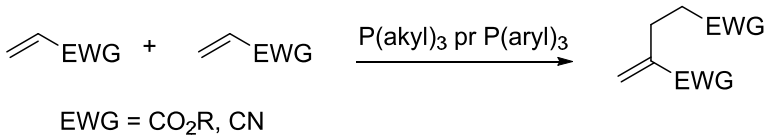
The aza analogue of the MBH reaction, aptly named the aza-MBH reaction, is one of the research topic of the Sasai group. Specifically, the development of asymmetric bifunctional catalyst for the aza-MBH reaction. Within the recent years, we have developed several acid-base organocatalyst to promote the enantioselective aza-MBH reaction. In many cases, binol was selected as the chiral backbone and its dual proton donating group was utilized as to activate substrates or intermediates in cooperation with an attached Lewis base arm. Successful

catalyst such as those in **scheme 3**, containing amine or phosphine as the acting Lewis-base respectively, were able to afford aza-MBH products in high yields and high enantioselectivity of up to 95%. [4]



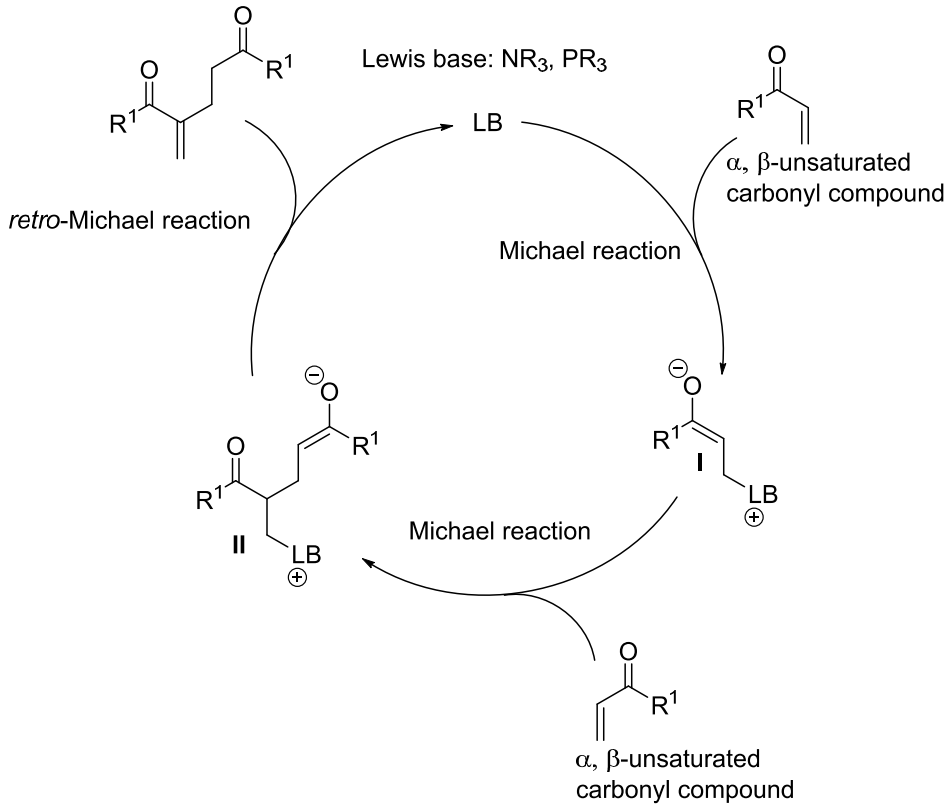
Scheme 3: Our novel bifunctional catalysts

1.1.2 Brief history of the RC reaction



Scheme 4: Earliest example of the RC reaction

The Rauhut-Currier (RC) reaction is similar to the MBH reaction and coincidently also known as the vinylogous MBH reaction. It involves the coupling of an active alkene with a second active alkene, as compared to an aldehyde for MBH reactions, by Michael addition creating a new carbon-carbon bond between the α-position of one activated alkene and the β-position of a second. In 1963, Rauhut and Currier reported the dimerization of active alkenes when under the influence of phosphine catalysts (**Scheme 4**).[5]

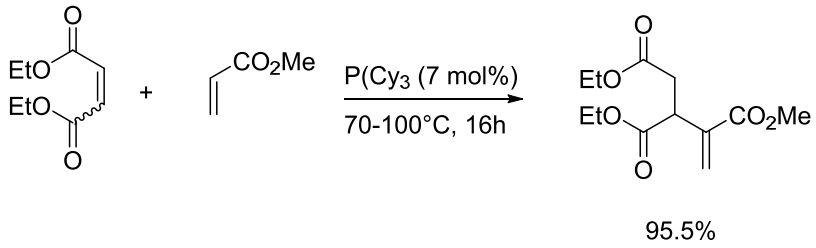


Scheme 5: Mechanism of the RC reaction

The reaction mechanism follows that of MBH with the attack of the LB to the activated alkene forming the common zwitterionic species **I**. This enolate then performs a Michael addition to a second activated alkene to generate a second zwitterionic intermediate **II**. Then a proton shift occurs followed by the release of the LB catalyst to give the RC coupling product (**Scheme 5**).

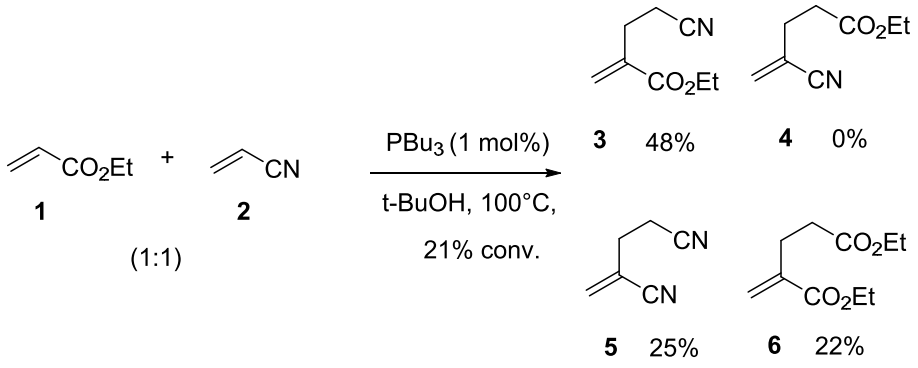
1.2 Methods for regioselectivity, activation and enantioselectivity

1.2.1 Solutions for regioselectivity



Scheme 6: First cross coupling of the RC reaction

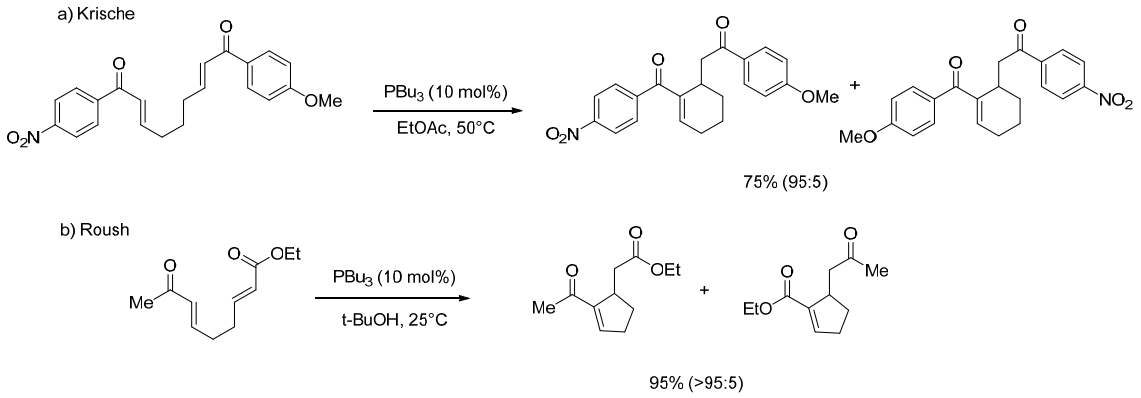
In 1969, Morita and Kobayashi reported the first cross coupling of the RC reaction of activated alkenes (**Scheme 6**).[6] They were able to receive high yields in the coupling of the substrates and avoid any homodimerization. This is quite fortunate and is most likely due to the electronic or steric differences of the substrate. In the case of similar electronic groups and low steric effects however, there are often difficulties in controlling selectivity due to the possibility of two cross-coupling product and homodimerization.



Scheme 7: Undesired homodimerization

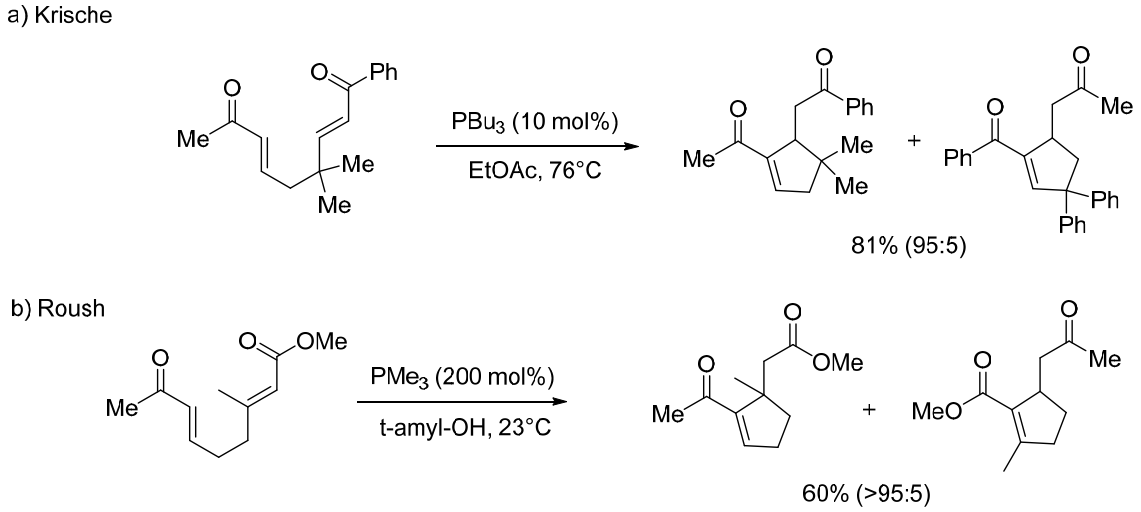
In 1970, McClure experimented with the RC reaction using acrylonitrile and ethyl acrylate, both compounds known to dimerize in presents of phosphine catalyst.[7] Reaction of equal molar amounts of both substrates affords homodimerization product **5** and **6** in 25% and 22% yield respectively, and only one of the cross coupling product **3** in 48% yield (**Scheme 7**).

The other cross-coupling product, **4**, was not observed showing that the intermediates in the pathway to **4** is less favorable.



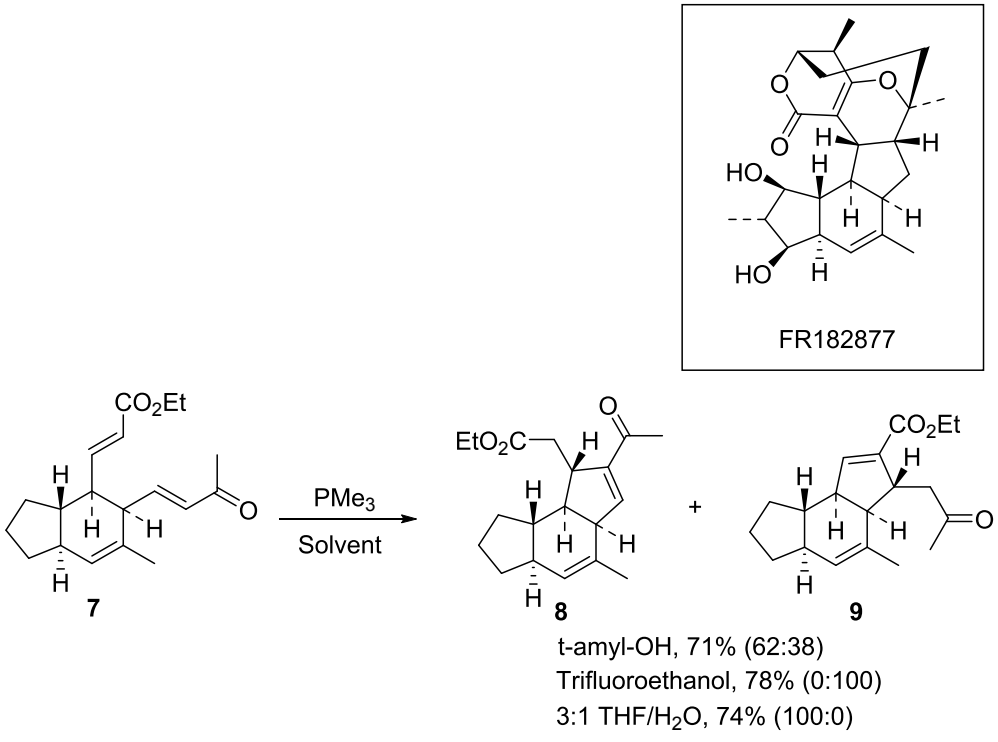
Scheme 8: Electronic control of product distribution

In 2002, Krische[8] and Roush[9] were able to reduce the problems of selectivity by tethering the coupling partners. They were also able to demonstrate that regioselectivity could be achieve through the differing electrophilicity of the groups (**Scheme 8**). For instance, Krische and co-workers were able to produce six-member ring regioisomeric product as the sole product in 75% yield. Roush observed a parallel electronic effect receive their desired five-member ring product in 95% yield. The major product reflects a chemoselective nucleophilic addition of the phosphine catalyst to the more electrophilic enone, then cyclization to the less reactive Michael acceptor.



Scheme 9: Effects of substitution in the RC reaction

Both authors were able to demonstrate the steric effects of the reaction (**Scheme 9**). Basically, the less hindered enone accepts the first Michael addition of the catalyst while the hindered serves as the second Michael acceptor during cyclization.



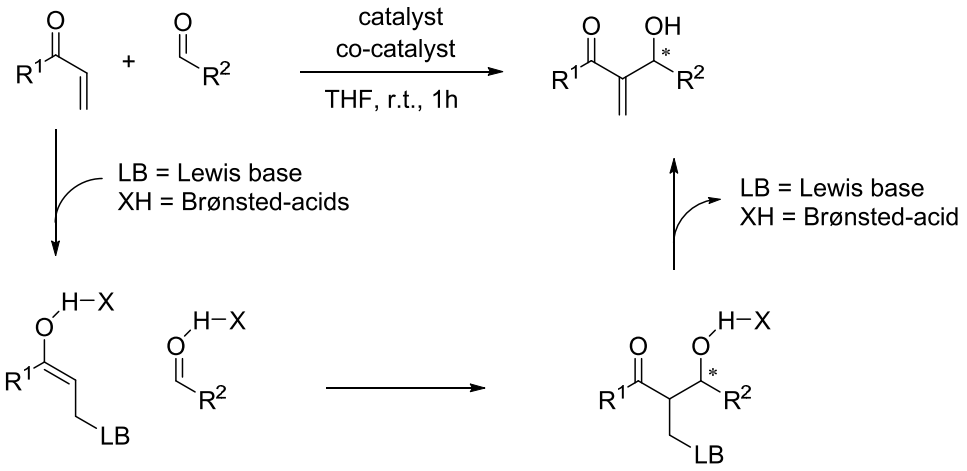
Scheme 10: Regioselectivity of the RC reaction with solvents

Roush and co-workers attempted to access the central cylclopentane ring of FR182877 by intramolecular RC reaction (**Scheme 10**).[10] Intramolecular RC cross coupling of **7** can give rise to two possible RC product. In the process of trying to obtain desired product **8**, they noticed the formation of by-product **9**. It has been mentioned that the reaction solvent can dramatically affect selectivity in the MBH reaction due to the proton donating group of the solvent.[11] Therefore to increase selectivity as well as efficiency, the sampling of various solvents was carried out. Fortunately, they were able to obtain either product exclusively by using trifluoroethanol for **9** and 3:1 of THF and H_2O for their desired product **8**.

1.2.2 Brønsted-acid additives

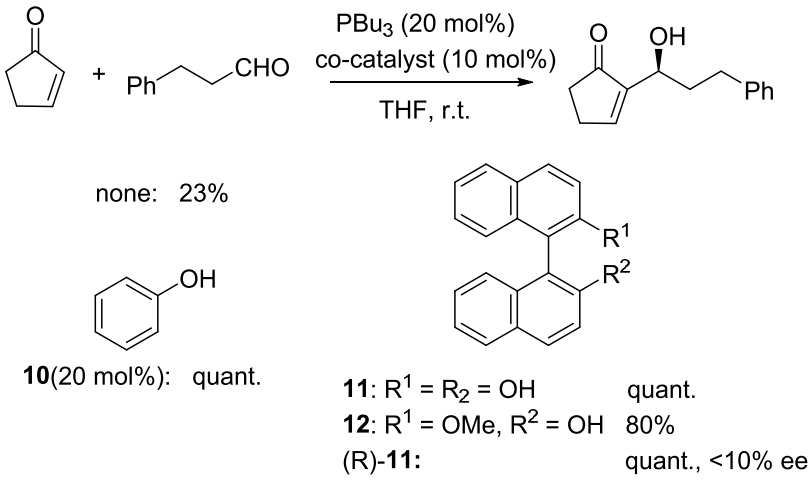
While this research focuses on the RC reaction, the initial introduction of the Lewis-base to α,β-unsaturated carbonyls occurs in both MBH and RC reaction, hence acid additive studies for both reactions have shown similar affects and most likely occurs through similar mechanisms.

In some cases, the MBH reaction becomes limited due to slow reaction rates thus requires excessive reaction times or heat to achieve completion of the reaction.[3] One way researchers have attempted to accelerate the reaction rate is with the use of Brønsted-acids. This is achieved through hydrogen bonding of the Brønsted-acid to the zwitterionic intermediates (**Scheme 11**).



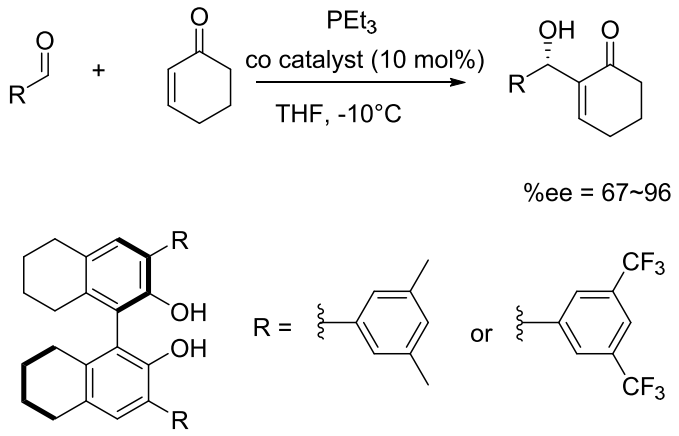
Scheme 11: Plausible mechanism for Brønsted-acid co-catalyzed MBH reaction

In 2000, Ikegami and co-workers were able to promote the MBH reaction with phenol and phenol type acids.[12] In the absence of an additive, MBH reaction between unsaturated carbonyls and aldehyde occurs slowly and provides the product in 23% yield. Upon addition of phenol (**10**), the reaction is clearly accelerated furnishing the product at quantitative yields. Phenol type Brønsted-acids **11** and **12** were also screened. **11** was also able to provide the product in quantitative yields at lower catalyst loading of 10 mol%. **12**, similar to **11** but with one hydroxyl group, gave the product in lower yields, 80%, showing that the hydroxyl groups of **11** work cooperatively. They deduced that the activation of the substrate occurs via complex of the substrate and Brønsted-acid and therefore chiral Brønsted-acids could be used to induce enantioselectivity (**Scheme 12**). Unfortunately, using asymmetric **R-(11)**, though yields were excellent, could only give low ee's.



Scheme 12. Mildly acidic phenol type Brønsted-acid co-catalyzed MBH reaction

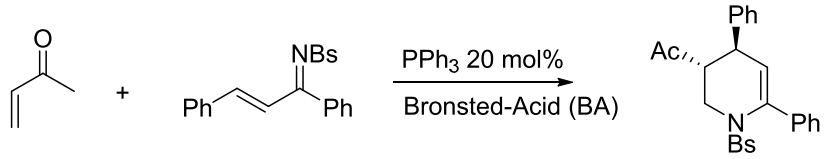
Schaus and co-workers continued the search for a suitable Brønsted-acid that can be used effectively in an asymmetric MBH reaction.[13] After screening a variety of binaphthol-derived Brønsted acids, they noticed two structural features of the catalyst were necessary to obtain high enantioselectivity (**Scheme 13**). Partial saturation and substitution at the 3,3'-postion of the binol derivative led to higher enantioselectivity.



Scheme 13. Binaphthol derivative co-catalyzed MBH reaction

In 2012, Zhong and co-workers published an aza-RC type [4+2] annulation between vinyl ketones and azadienes (**Table 1**).[14] During their research, they noticed that proton donating additive, similar to MBH literatures, could be used to increase reactivity as well as diastereomeric ratios. Upon the addition of phenol, d.r. was increased from 10:1 to 17:1, though yield seemed unaffected. However, after testing various other acid additives, particularly phenol derivatives, 4-methoxy phenol provided them with their best results, at 95% yield and >20:1 dr. Furthermore, the reaction was able to complete significantly faster, in 6h compared to 24h. It is interesting to note that the addition electron donating effect of 3,5 dimethoxy phenol were not able to improve results.

Table 1. Effects of acid additive on the RC reaction



Entry	BA (mol%)	Time (h)	Yield (%)	dr
1	none	24	87	10:1
2	C_6H_5OH (20)	22	88	17:1
3	4-NO_2-C_6H_4OH (20)	17	57	15:1
4	4-MeO-C_6H_4OH (20)	8	91	16:1
5	4-MeO-C_6H_4OH (30)	6	95	>20:1
6	3,5$(MeO)_2$-C_6H_3OH (20)	12	73	18:1

1.2.3 Asymmetric MBH/RC catalyst

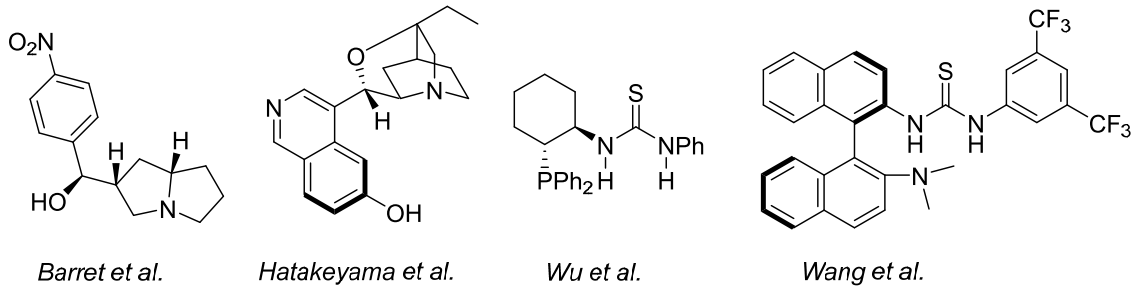
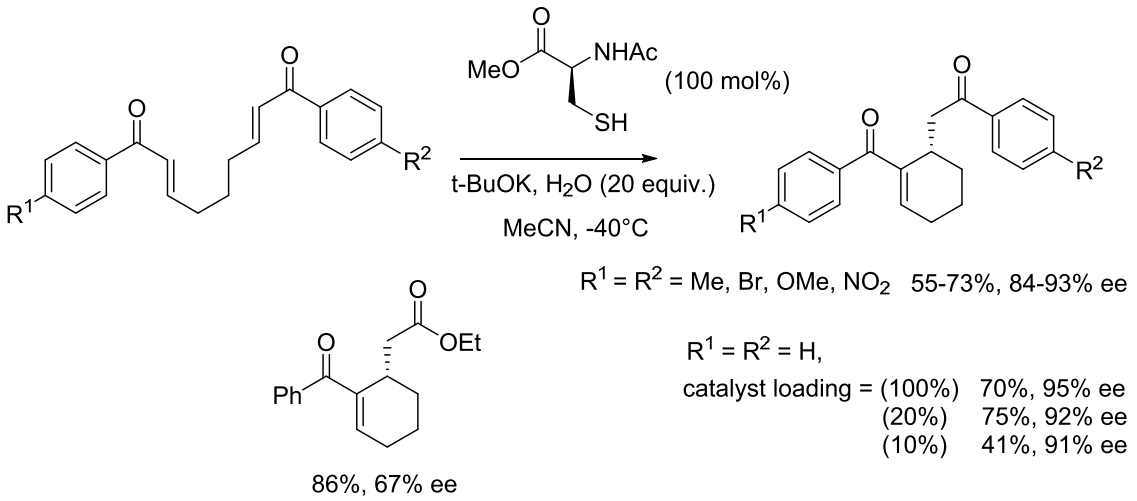


Figure 1. Asymmetric bifunctional MBH catalyst

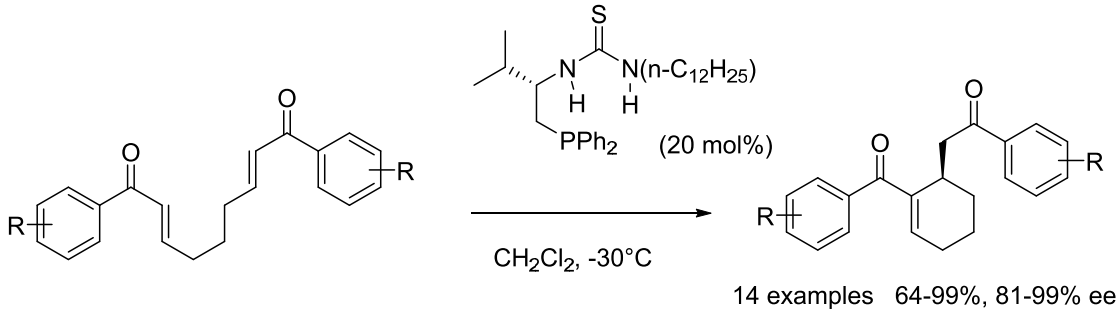
Researchers have been able to incorporate both Lewis-base and Brønsted-acid into an individual catalyst. In addition to exhibiting catalytic activity and increased reaction rate, the chiral structure of the catalyst allows for the production of optically active compounds. Some of the more notable enantioselective bi-functional MBH catalysts are illustrated in **Figure 1**. Barret[15] and Hatakeyama[16] utilized a hydroxyl group as the hydrogen donor whereas Wu[17] and Wang[18] used thiourea.

Due to the lack of selectivity, the enantioselective RC reaction did not gain as much attention as the similar MBH reaction. The first example of enantioselective intramolecular RC reaction occurred in 2007 when Miller's group used N-acetyl cysteine as a catalyst.[19] With the addition of potassium tert-butoxide and a protic donor, water, they were able to achieve modest yields and high enantioselectivity (**Scheme 14**). In the case of cross coupling however, lower enantioselectivity was observed, 67% ee. Catalyst loading could be lowered from 100% to 20% with only a small loss of enantioselectivity. At 10%, a large drop in yield is observed.



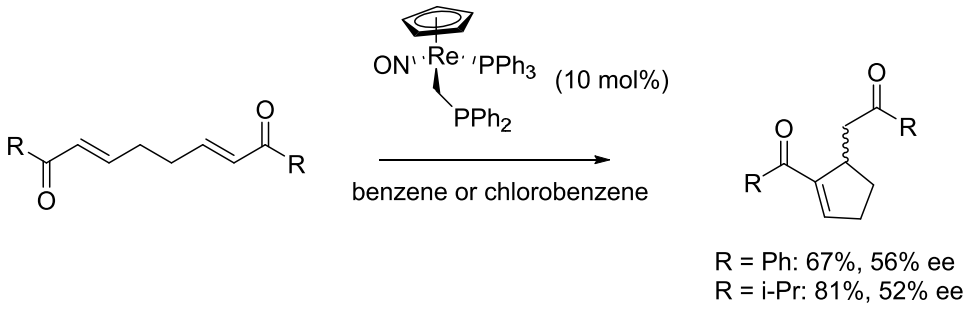
Scheme 14. Asymmetric bifunctional MBH catalyst

The Wu group reported the first use of chiral organophosphine to catalyze enantioselective RC reaction.[20] They have previously reported highly efficient asymmetric MBH using amino acid-derived phosphinoureas[21] and were able to apply such catalyst to the RC reaction of bis(enones). Such phosphinothioureas not only contain a Lewis-base group to initiate the reaction, phosphine, but also a Brønsted-acid group to increase the reaction rate and induce enantioselectivity. With these bi-functional, they were able to achieve very high yields as well as very high enantioselectivity (**Scheme 15**)



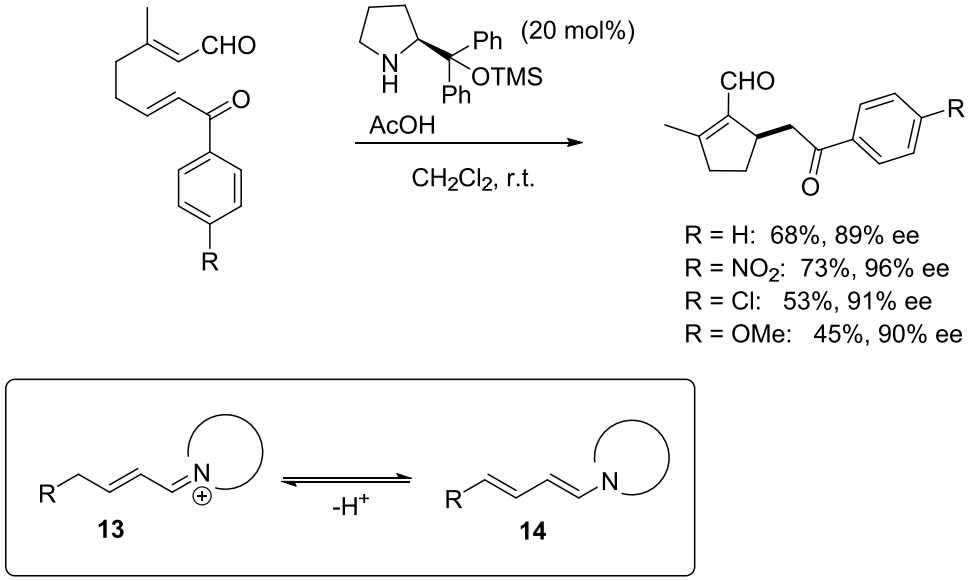
Scheme 15. Intramolecular RC reaction using amino phosphine catalyst

Gladysz and co-workers were also able to carry out enantioselective RC reaction by using chiral rhenium complex including phosphine.[22] It was proposed that the rhenium increased the nucleophilicity of the phosphine. They obtained cyclization product in good yield and modest enantioselectivity (**Scheme 16**).



Scheme 16. Asymmetric RC catalyst

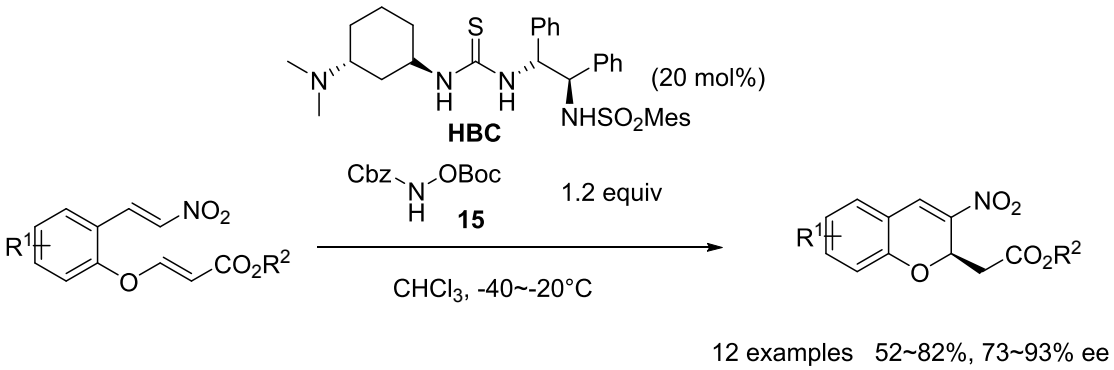
A mechanistically distinct RC-type reaction was discovered by Christmann and co-workers in 2009.[23] By utilizing secondary amines, an α,β-unsaturated carbonyl can be converted to iminium ion **13**, which can further conjugate to electron-rich dienamines **14**. This key intermediate renders the alpha position sufficiently nucleophilic enough to perform a Michael-addition producing an RC coupling product. With this method, they could obtain their desired products in moderate yields and high enantioselectivity (**Scheme 17**). It is important to note that regioselectivity was due to the catalyst's specificity towards aldehydes.



Scheme 17. Intramolecular RC reaction via dienamine activation

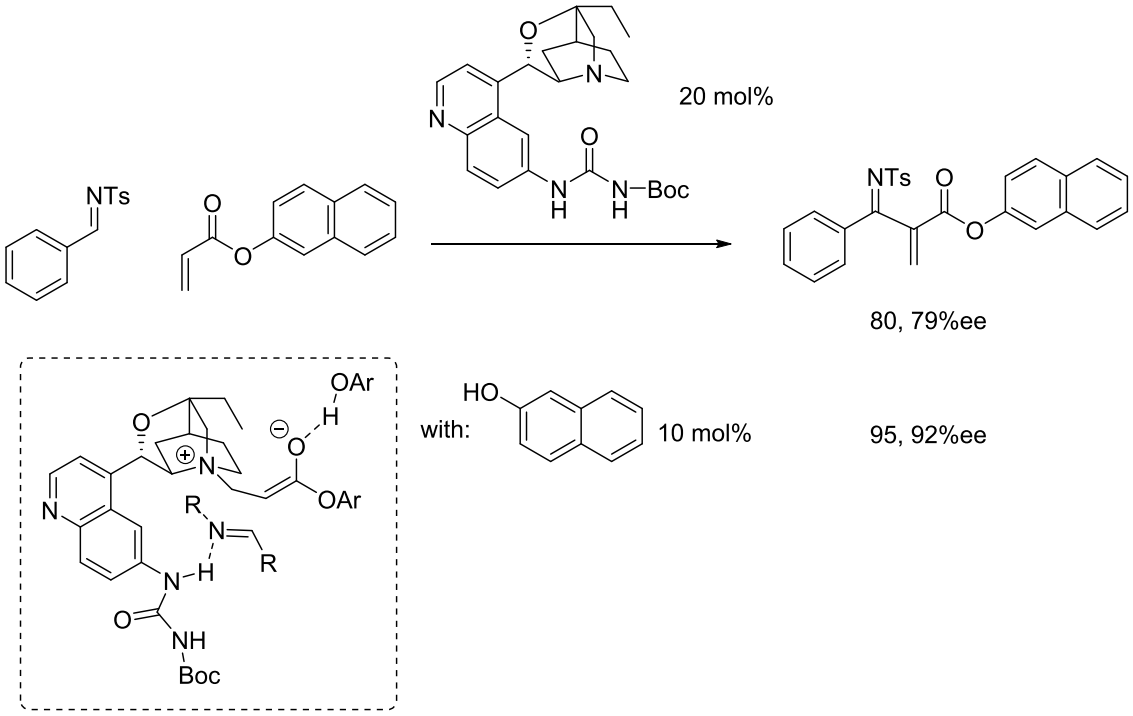
The Gu and Xiao group conducted intramolecular enantioselective RC reaction via cooperative nucleophilic activation.[24] Hydrogen-bonding catalyst (**HBC**) were used to activate substrates successfully converting it to a nucleophilic promoter. With **15** as the Lewis-base, a

typical RC reaction cycle takes place as **HBC** continue to stabilize each intermediate through a series of H-bonding interaction and producing an optically active RC product.



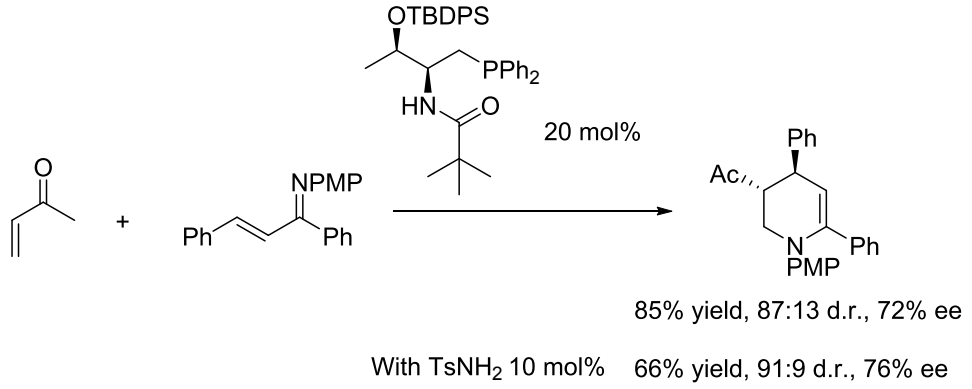
Scheme 18. Intramolecular RC reaction via cooperative nucleophilic activation

Zhu and Masson searched for an appropriate bifunctional catalyst for their asymmetric aza-MBH reaction between imines and β-naphthyl acrylate (**Scheme 19**).[25] During the course of their studies, they realize possibility of β-naphthyl contaminant and its potential effect on the reaction. Thus, they investigated the effects of acid additives at differing pKa and observed an increase in not only yield, but also enantioselectivities. Of course, the acid additive being achiral could not have induced enantioselectivity alone. They suggested the acid additive plays a role in the reaction by assisting the chiral catalyst during the course of the reaction. The catalyst, bearing its own proton donating group, can potentially interact with the resulting enolate or the imine, for activation. The author's state that the acid additive protonates the enolate group, therefore allowing the catalyst to freely interact with the imine substrate, providing a less constrained intermediate structure and increasing its effectiveness.



Scheme 19. Bifunctional catalysis with acid additive

A similar effect was observed in Zhong and Loh's research regarding the aza-RC reaction between vinyl ketones and azadienes (**Scheme 20**).[26] The addition of benzenesulfonamide resulted in a clear increase of enantioselectivity. It is likely that the acid additive plays a similar role in cooperation of a chiral bifunctional catalyst both aza-MBH reaction and aza-RC reaction.



Scheme 20. Bifunctional catalyst with acid additive

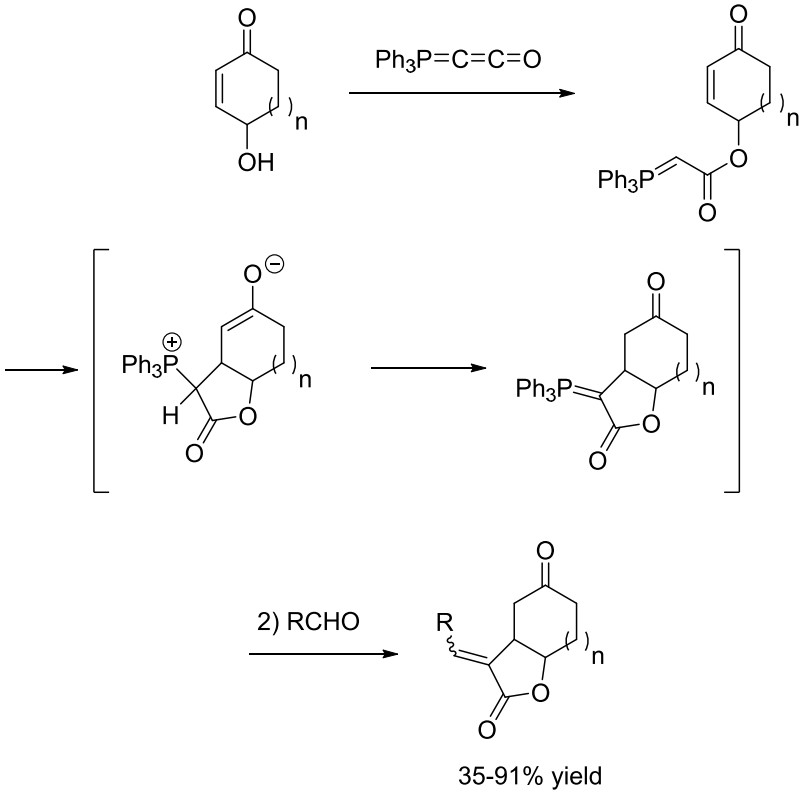
1.2.4 Cyclichexadienone reactions

Enantioselective desymmetrization of cyclohexadienone has been a strategy employed in the recent decade for the synthesis of bicyclic or tricyclic compounds. Rovis and co-workers published some of the earliest, conducting the intramolecular Stetter reaction to afford hydrobenzofurans in high yields and enantioselectivities.[27] The Stetter reaction allows the aldehyde group on the 4 position to act as a nucleophile and perform a Michael addition to the cyclohexadienone functional group. They were the only group to stretch their substrate scope to substrates containing functional groups at the 2,6 and 3,5 position. Particularly for 2,6 position functional groups containing substrates, they were able to receive standard reactivity. As you will see later in this text, such substrates presented us with no reactivity for our research. You's group published several examples including intramolecular enantioselective Michael reaction, oxo-Michael reaction, and aza-Michael reaction[28]. In each case, they used acid type chiral catalyst to activate the dienone group to initiate it as a Michael acceptor. Later, Ye's group demonstrate that amine type chiral catalyst may also be used to catalyze the reaction via iminium-based activation of the dienone.[29] In these articles, including others published up to now, any special reactivities from the cyclohexadienone moiety group were not addressed. That is, whether or not the presence of both double bonds play a role in reactivity, and also whether or not the cyclic structure is important. Our research establishes the importance of both. Comparing the substrate reactivities from these publications to our own results, it appears as if the reaction in our research is much more sensitive to alkyl versus aryl substituents in additional to their electronic effects.

1.3 Research: Results and Discussion

1.3.1 Introduction

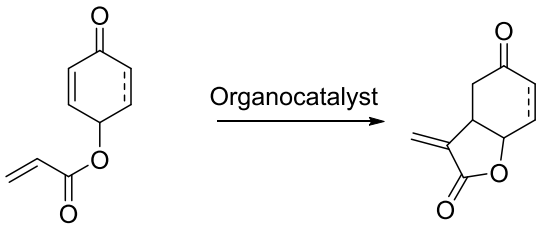
We also employed the tethering strategy for the intramolecular Rauhut-Currier reaction. The most recent method towards the synthesis of paeonilactone-B derivatives by Taylor[30,31] involves the use of Bestmann's ylide to undergo Wittigs cyclization and produce α-alkylidene-γ-butyrolactones. We hypothesize that by replacing the Bestmann's ylide group with an α,β-unsaturated carbonyl group, the compound could undergo an intramolecular RC reaction in presence of a Lewis-base (**Scheme 21**).



Scheme 21. Cyclization by Bestmann ylide

What differentiates our substrate from that of previous literature is the asymmetric structure of the two enone groups (**Scheme 22**). The first enone group is an unsaturated, unsubstituted acrylate group. As the more reactive of the two enone, the acrylate group will most likely act as the first Michael acceptor. Hence, the regioselectivity problems in the previous intramolecular RC reactions is solved by simply steric hindrance, rendering electronic

control unnecessary. As for the second enone group, we believe the dienone group could adequately play the role of the second Michael acceptor. Once again, its lower reactivity due to the cyclic structure will prevent its participation as the first Michael acceptor. Enantioselective desymmetrization of hexacyclicdienone is a known strategy capable of resulting in high yields and enantioselective. In the presence of a Lewis base, such as phosphine or tertiary amines, we hypothesized the formation of bicyclic lactone product through the RC mechanistic pathway.

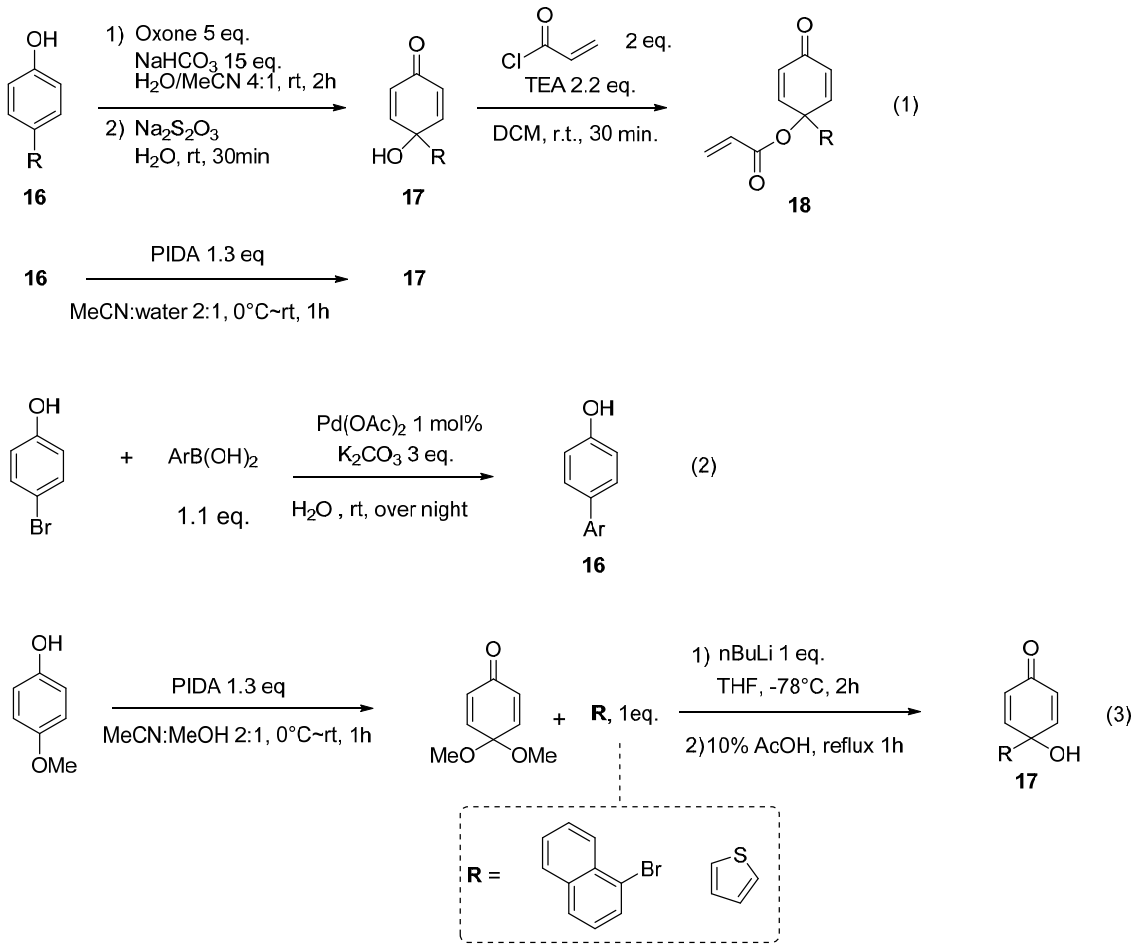


Scheme 22. Our model substrate

1.3.2 Preliminary screening and optimization

Compound **18** was chosen as a model substrate for the intramolecular RC reaction. As mentioned in the introduction **18** contains two non-symmetric α,β-unsaturated carbonyl groups, selectivity should not be a problem due to the sterically hindered of cyclic dienone. Though this does not guarantee the participation of the cyclidienone group as the first Michael acceptor, this should at least significantly decrease its probability.

Substrate **18** was synthesized from common chemicals by first using Carreno's[32] method of alkyl phenol oxidation and later replaced by PIDA oxidation for the synthesis of further substrates due to ease. Subsequently, the addition of the acrylate group by simple replacement reaction with acryloyl chloride. More complex substrates can be synthesis by the creation of phenol derivative via Suzuki coupling of 4-bromophenol. Other method include first the synthesis of protected dienone followed by nucleophilic addition of Grinard like reagents and subsequent deprotection (**Scheme 23**).

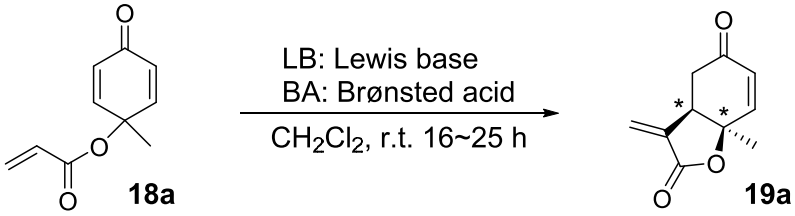


Scheme 23. Synthesis of substrate

Upon screening several Lewis-base catalyst, we were pleased to observe that PPh_3 could carry out the reaction and produce 16% of our desired product (**Table 2, entry 1**), however, it is unfortunate that 100% catalyst loading was require to see such low yield. It should be possible to improve reactivity by using alkyl phosphines in place of aryl phosphine due to their higher Lewis basicity, but the goal of this research is to ultimately find or develop a bifunctional catalyst. Alkyl phosphine related bifunctional catalyst are rarely seen, strongly prone to oxidation, and require difficult synthetic procedures. Hence, searching for optimal conditions with triphenylphosphine is advantageous. The MBH reaction has been known to accelerate in presence of a Brønsted-acid,[33] therefore, we attempted to apply this strategy to the RC reaction in order to increase the reactivity rate, as well as decrease the catalyst loading. To our delight, in presence of phenol the yield was increased significantly to 77%, confirming that a Brønsted-acids can be used to accelerate the reaction (**Table 2, entry 2**). After further

testing, we were able to lower the catalyst loading to 20 mol% while still maintaining a moderate yield of 63% (**Table 2, entry 4**).

Table 2. Preliminary testing



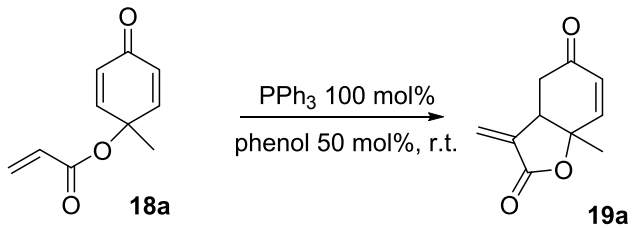
18a **19a**

Entry	LB (mol%)	BA (mol%)	Yield %
1	PPh_3 (100)	-	16
2	PPh_3 (100)	phenol (100)	57
3	PPh_3 (100)	phenol (50)	81
4	PPh_3 (20)	phenol (50)	60
5	PPh_3 (100)	(*S*)-BINOL (50)	37 (racemic)
6	DMAP, DBU or DABCO (100)	phenol (50)	<10

Tertiary amine, such as DMAP, DBU, or DABCO (**Table 2, entry 6**), did not catalyze cycloisomerization as efficiently as phosphine even at 100 mol% catalyst loading in the presence of phenol and provided low or no yield of the desired product. These results closely resemble those of previous literature dealing with intramolecular RC reactions.[13, 14]

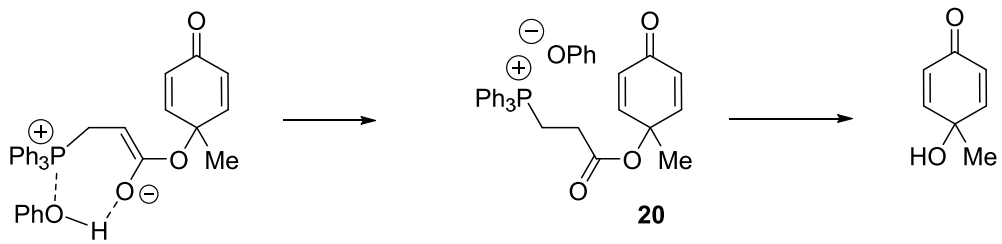
The effects of differentiating solvents were examined. Aprotic solvents, such as halogens and aromatic solvent, were able to provide the product in moderate to good yields with the exception of tetrahydrofuran (THF). The high coordination strength of THF may affect the necessary formation of anion during the course of the reaction pathway. Protic solvent provided very little or no reactivity, methanol and water (**Table 3**), most likely due to its interference with the several proton transfer steps.

Table 3. Solvent screening



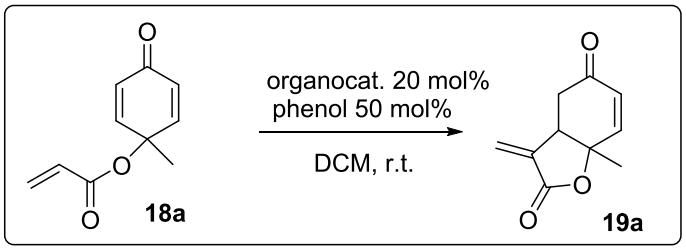
Entry	Solvent	Time (h)	% Yield
1	$CHCl_3$	23	53
2	EDC	24	60
3	chlorobenzene	23	80
4	toluene	24	83
5	MeCN	23	65
6	THF	17	trace
7	MeOH	18	0
8	water	19	trace

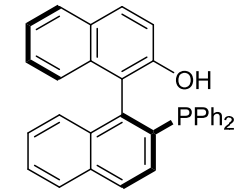
During the course of our Brønsted-acid studies, we noticed that in excessive concentrations of phenol, not only is the reaction halted completely, but the presence of an intermediate can be observed. Indeed, in 10 eq. of phenol, we were able to isolate intermediate **20**, in which the phosphonium cation is stabilized by the phenoxide anion (**Scheme 24**). If this solution is allowed to sit for an extended period of time, >24 hours, decomposition product is observed. There are cases in which the completion of the reaction does not occur despite long reaction times and remaining substrate. We can conclude that decomposition is accompanied by the removal of the acrylate group as well as the loss of phosphine catalyst.



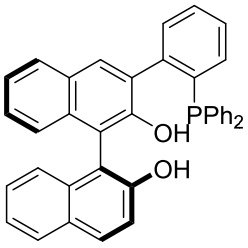
Scheme 24. Possible intermediates

1.3.3 Asymmetric catalyst screening and optimization

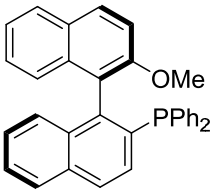




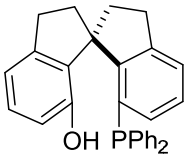
(*S*)-**21**, no reaction



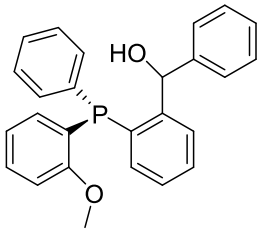
(*S*)-**22**, no reaction



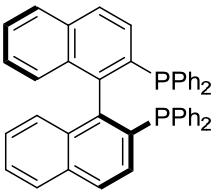
(*R*)-**23**, no reaction



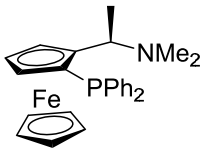
(*S*)-**24**, no reaction



25, no reaction

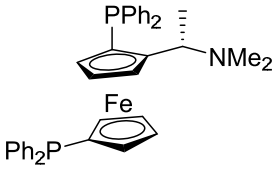


(*S*)-**binap**,6% yield, 20% ee



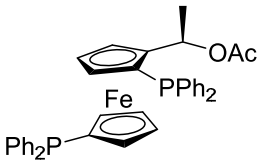
(*R*)(*S*)-**PPFA**

72% yield, 20% ee



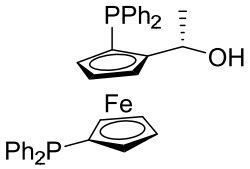
(*S*)(*R*)-**BPPFA**

13% yield, 9% ee



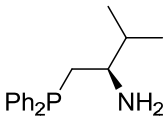
(*R*)(*S*)-**PPFOAc**

8% yield, racemic

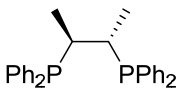


(*S*)(*R*)-**BPPFOH**

3% yield, 9% ee



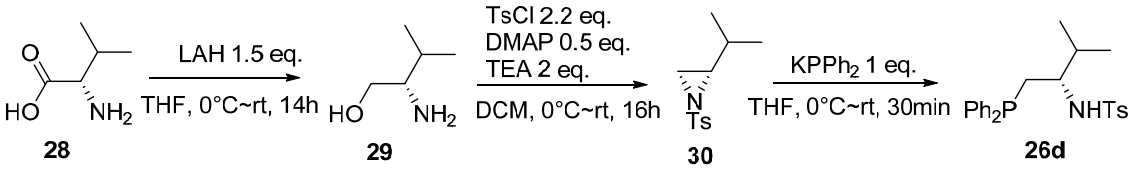
26a, 52% yield, 60% ee



27, no reaction

Scheme 25. Screening of chiral organocatalyst

Next, we tested an array of available chiral organocatalyst (**Scheme 25**). Chiral catalyst containing phosphine and acid group showed no reactivity (catalyst **21**, **22**, **24**, and **25**). Diphosphine **(*S*)-binap** was able to catalyze the reaction but in very low yield and with low selectivity. Ferrocenyl phosphine **PPFA** promoted the reaction in modest yields and low enantioselectivity of 20%. However, ferrocenyl diphosphine derivatives **BPPFA**, **PPFOAc**, and **BPPFOH** gave worse results, less than 13% yield and a high of 9% ee. Amino acid based phosphine catalyst **26a** caught much of our attention when it provided moderate yield and ee of the product, 52% yield and 60% ee. In comparison to the previously tested catalysts, **26a** is considerably less bulky and therefore could provide less steric hindrance in the course of the reaction. Diphosphine **27**, despite its size being comparable to amino phosphine catalyst **26a**, showed no reactivity.



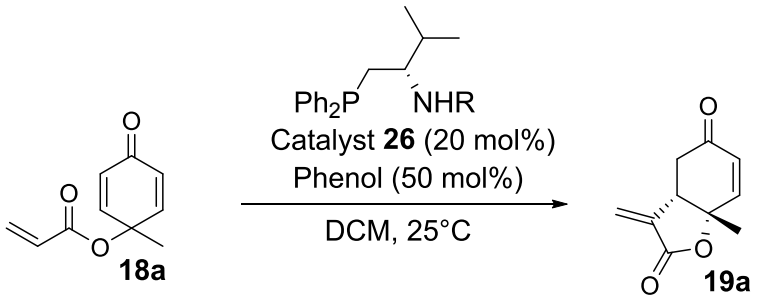
Scheme 26. Synthesis of protected amino-acid derived phosphine

Pleased with the results, we proceeded to synthesize derivatives of **26a** in order to improve the yield and enantioselectivity further. Previous literatures have shown that the amine group can assist the reaction by activating the enone by proton donation and also take part in the transition intermediate to induce stereoselectivity.[34] We reasoned that by increasing, or decreasing, the acidity of the amine group, it would be possible to increase the enantioselectivity. Initially following the synthetic pathway to **26d** by Hayashi's lab,[35] we discovered a one step cyclization method from **29** to **30**. Ring opening synthesis with potassium diphenyl phosphine provides a tosyl protected amino phosphine **26d** (**Scheme 26**).

After synthesizing **26d**, we subjected the catalyst to our reaction conditions and observe improved results to 77% yields and 80% ee (**Table 4**). We also manage to synthesize other catalyst of differing protective groups, such as thiourea (**26b**) or triflate (**26c**) groups. However, these catalyst only produced trace amounts of products. We deduce that, much like the inactivity in the presence of excess phenol, the proton donation strength of these groups are

much too high and over stabilizes the intermediates. Next, by simply lowering the reaction temperature to 0°C, the enantioselectivity could be increased further to 93% ee, although with longer reaction times. Surprisingly, conducting the reaction without phenol afforded similar results but in lower reaction times. Most likely, the proton donating group of the catalyst is adequate to provide high enantioselectivity while the additional proton donating group of the acid additive only acts to over stabilize the intermediate. Finally, by switching the solvent to chloroform, we were able receive our best results yet, at 99% yield and 98% ee.

Table 4. Protective groups

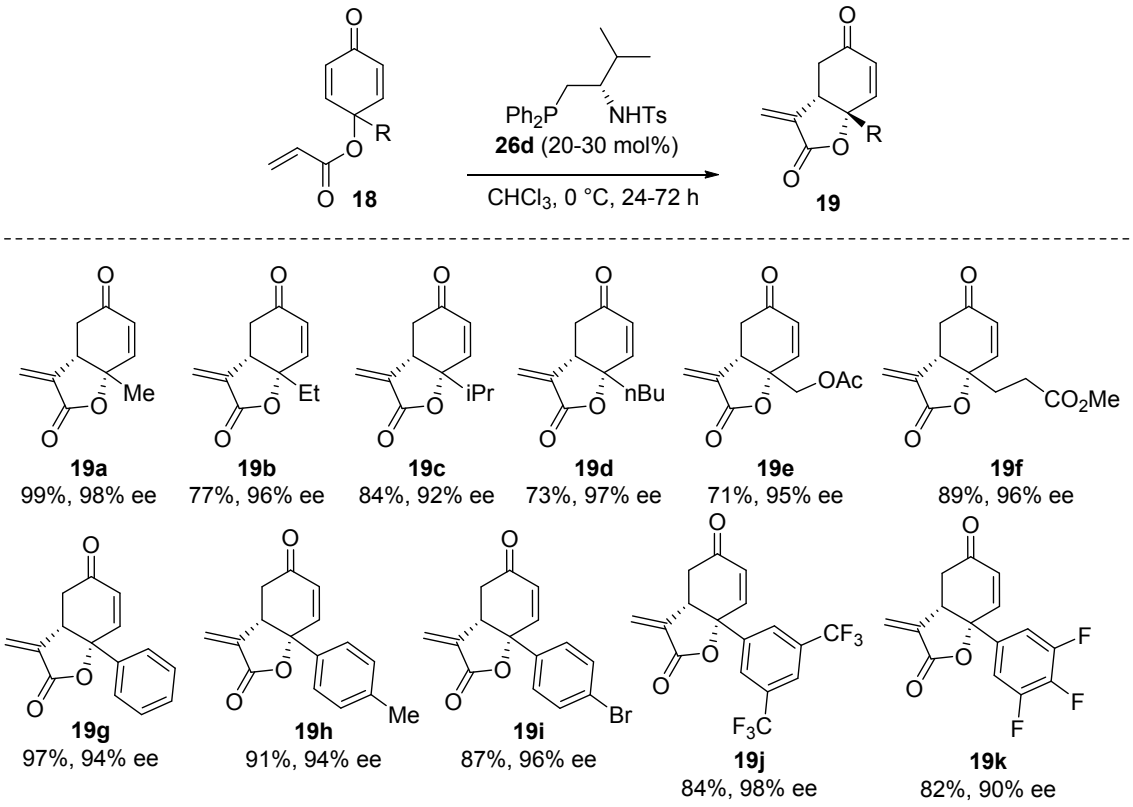


Entry	R (catalyst)	Time (h)	Yield (%)	Ee (%)	Conditions
1	H (**26a**)	18	52	60	
2	CSNHPh (**26b**)	19	trace	-	
3	Tf (**26c**)	19	trace	-	
4	Ts (**26d**)	19	77	80	
5	Ts (**26d**)	48	80	93	0°C
6	Ts (**26d**)	24	87	93	0°C, w/o phenol
7	Ts (**26d**)	24	99	98	0°C, w/o phenol, in $CHCl_3$

1.3.4 Substrate Scope

With our optimized condition in hand as well as a highly adequate catalyst, we continued to substrate scope (**Scheme 27**). We were able to synthesize and provide good result for up to 11 substrates bearing different substituents at the 4 position of the cyclicdienone. Compared to the simple methyl group, longer chains of alkyl groups sustained increasing instability and required increasing of catalyst loading to 30 mol% and longer reaction time, up

to 72 hours. Overall, the ee for the alkyl substrates were generally high, the lowest being 92% ee of the isopropyl group. Aryl substituents provided much more stable reactivity and did not require changes from the optimal conditions. Good yields and high enantioselectivities were observed with both electron withdrawing and electron donating aromatic groups.

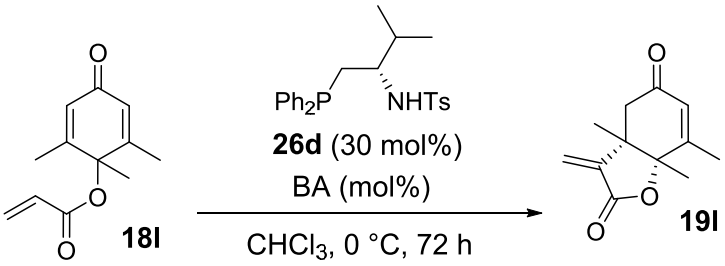


Scheme 27. Substrate scope

Though our previous substrate screening provided us with good results, some substrates were more stubborn. For example, 3,4,5 trimethyl substrate **18l**, under optimized conditions, suffered from a significant amount of decomposition providing a final yield of 56% in addition to 70% ee (**Table 5, entry 1**). The addition of the methyl groups at the 3 and 5 position on the aromatic ring seem to destabilize the intermediate by increasing polymerization reactivity. The additional steric hindrances at point of the new carbon bond formation provided by these group can explain the large drop in enantioselectivity. Though previous data has shown that the catalyst is able to achieve good result without the acid additive, we decided to see its effect on this particular substrate. At 30 mol% of phenol, there is a clear increase enantioselectivity, to

81% ee. This is most likely due to the same factors as in previous literatures[25,26] involving chiral Lewis-base and Brønsted-acid catalyst in combination with achiral acids. The protonation from the acid additive stabilizes the acrylate anion, allowing the proton donor of the catalyst to freely activate the carbonyl group of the dienone. This releases steric constraints as well as increases the rigidness of the catalyst. Enantioselectivity can be increase farther with increase concentration of the phenol, up to 96% ee, however this is with the loss of reactivity. The increasing concentration acid additive seems to over stabilize the reaction intermediate causing low yields of product and loss of substrate. Other acids of differing pKa were also tested and a trend can be seen. 4-nitro phenol, having a pKa of 7.2 stopped reactivity completely leaving the substrate unreacted. Other phenol derivatives, such as 4-methoxy phenol (pKa = 10.2) having similar pKa to that of phenol (pKa = ~10), displayed improved ee at the same concentration. Higher pKa values, such as 2,4,6 trimethyl phenol (pKa = 10.8) displayed lower ee, at 74%, almost similar to results in the absence of acid additive. In the end, 2-naphthol, having a pKa of 9.5 and a bulky structure gave us the best results considering yield and enantioselectivities. It is not clear as to whether or not the bulky structure of the naphthol acid plays a role in enantioselectivity.

Table 5. Acid additives with chiral catalyst

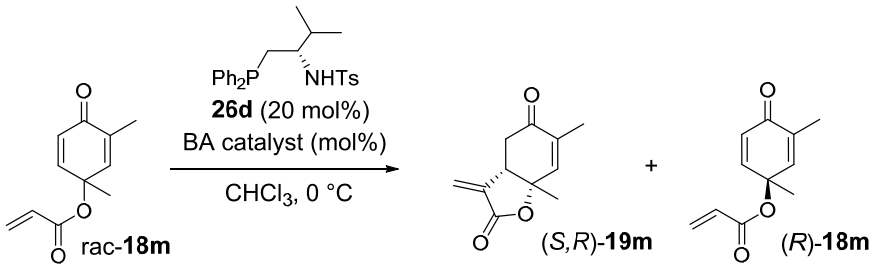


Entry	BA (mol%)	Yield (%)	Ee (%)
1	none	56	70
2	C_6H_5OH (30)	42	81
3	C_6H_5OH (50)	5	96
4	4-MeO-C_6H_4OH (30)	36	90
5	2,4,6-Me_3-C_6H_2OH (30)	47	74
6	4-NO_2-C_6H_4OH (30)	trace	-
7	2-Naphthol (30)	38	93

1.3.5 Kinetic Resolution Studies

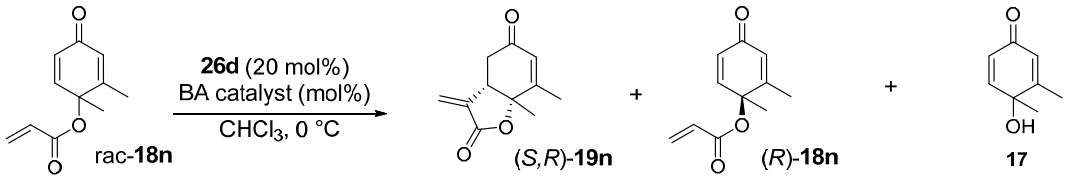
We attempted kinetic resolution studies with substrates **18m** and **18n**, containing an additional individual methyl group at the 2 or 3 position of the cyclic dienone (**Table 6** and **7**). Interestingly, products in which the carbon bond formation occurs on the same side as the additional methyl group is never observed in both cases. Bond formation occurs at the least sterically hindered side. Even so, these substrates suffered from the same instability as the 3,4,5 trimethyl substrate **18l**. The conjugation of the both double bonds during the generation of the intermediate plays an important role in the activation of the dienone group. Therefore, though bond formation occur on one side, substituent on the opposing side appears to affect the overall stability of the substrate. This results in low yields and loss of starting material for both substrates. Both enantioselectivity of the product and substrate were analyzed. With the catalyst alone, the result were poor for both substrates and finding an adequate stop time for best results proved very difficult. Using the same strategy as our previous substrate, acid additives can be used to improve results. By increasing the concentration of the phenol acid additive to 30 mol%, we observed much improved kinetic resolution and were able to achieve 86% ee with a product and substrate ratio near 50:50. Results can be improved further with the use of naphthol, 94% ee. Results for substrate **18n** was also improved with similar conditions. If the yield of product and substrate and its comparison to its corresponding enantioselectivity is considered carefully, it is apparent that decomposition must be selective also. Indeed, small amounts of decomposition products were observed and analyzed, displaying large amount of ee (**Table 7**). Decomposition of the substrates appears to be selective as well.

Table 6. Kinetic resolution studies with compound 18m



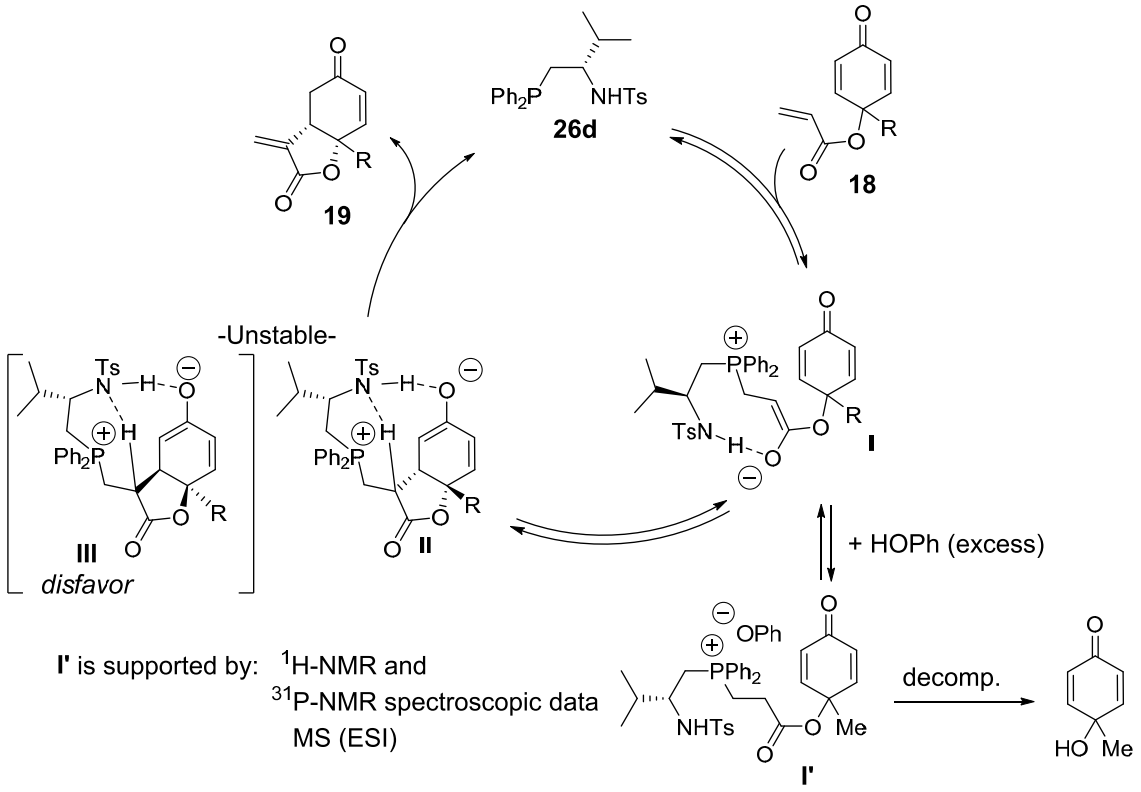
Entry	BA catalyst (mol%)	Ratio **19m**:**18m**	% Total yields of **19m**, **18m**	% ee of (*S,R*)-**19m**, (R)-**18m**
1	none	73:27	64	54, 70
2	C_6H_5OH (10)	71:29	62	56, 88
3	C_6H_5OH (20)	52:48	68	86. 60
4	C_6H_5OH (30)	50:50	73	86, 62
5	2-Naphthol (30)	40:60	76	94, 50

Table 7. Kinetic resolution studies with compound 18n



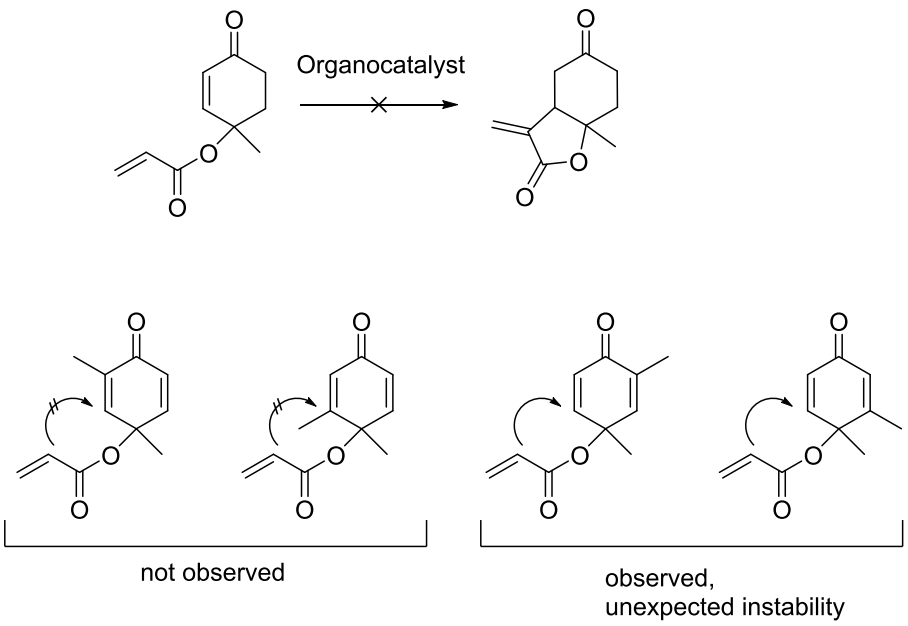
Entry	BA catalyst (mol%)	Ratio **19n**:**18n**	% Total yields of **19n, 18n**	% ee of (*S,R*)-**19n,** (R)-**18n**	% ee of **17**
1	C_6H_5OH (30)	40:60	66	87, 76	69
2	2-Naphthol (30)	64:36	64	88, 72	65

1.3.6 Proposed Reaction Mechanism



Scheme 28. Proposed Mechanism

The reaction mechanism follows closely to that of typical RC reaction pathway. Michael addition of phosphine forms intermediate **I**. The proton donating group of the bifunctional catalyst can further stabilize this enolate. The role of the acid additive in enantioselectivity also spurns from its ability to stabilize this enolate intermediate. This would allow the proton donating group of the catalyst to proceed to intermediate **II** through the stabilization of the formation of the second enolate. Once again, the formation of this enolate/diene structure is the source of instability due to its reactivity toward over Micahel intermolecular RC reaction.



Scheme 29. Additional observations

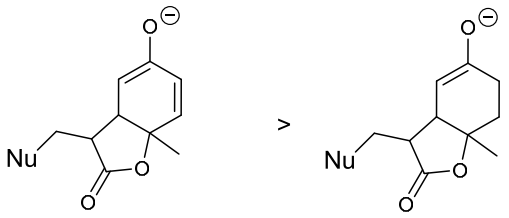
A few observations from the last few substrates allowed us to add an important detail to the proposed reaction mechanism (**Scheme 29**).

1: The absences of one double bond halts the reaction.

2: Substrates **18m** and **18n** only yields bond formation on the less hindered side.

3: Instability of despite bond formation away from hindered side.

With these observation, we can conclude that the electrophilicity of the dienone, as well as its instability, is in part due to the cross conjugation of the carbon double bonds. Meaning one of the carbon double bond is individually conjugated with the oxygen anion or that of the second double bond. Previous literatures containing examples of Michael-addition to cyclichexadiene substrates involve strong nucleophiles and the need for both carbon double bonds is not apparent. The Rauhut-Currier reaction however, involves a weaker nucleophilic conjugate addition.

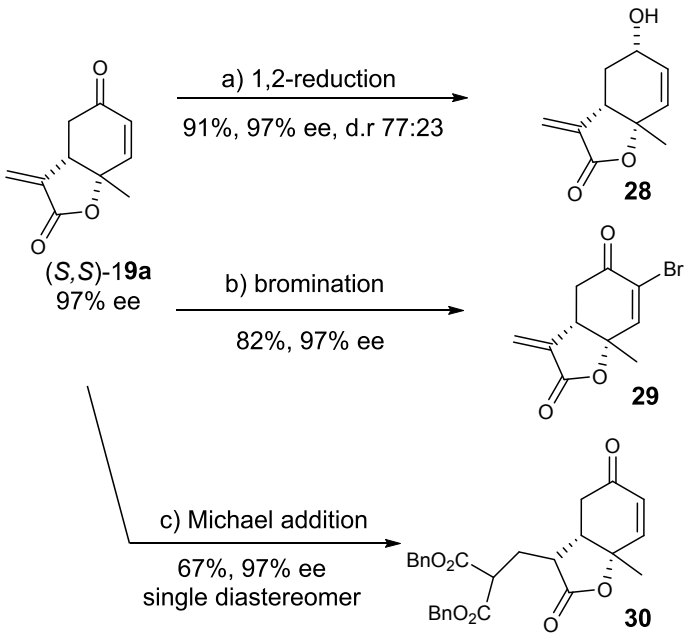


Scheme 30. Reactivity of the second conjugate addition

The enhance electrophilicity stems from the simultaneous formation of diene/enolate functional group upon conjugate addition as compared to the lone enolate (**Scheme 30**). The formation of the conjugated diene intermediate however, garners with it instability due to over Michael intermolecular RC reaction, instead of the desired enolate type reaction, with both dienone and acrylic group of a second substrate. This is apparent when using substrates **18m** and **18n**. The electron donating property of the methyl groups enhance diene reactivity, which explains the significant loss of substrate in these reactions despite carbon bond formation taking place away from the methyl substituents. Additionally, bulky substituents at the 4 position, particularly the aromatic groups, are much less susceptible to overreaction perhaps due to the negative effect of steric hindrance to the diene reactivity.

1.3.7 Transformations

We were able to take advantage of the functional groups of the product and perform a few transformation reactions. Selective reduction of an individual carbonyl group was achieved affording product **28** in high yields while maintaining enantioselectivity. Selective bromination of α-carbon on an individual enone group was also possible with the addition of bromide. A second Michael addition could be performed with malonate. The β-unsubstituted enone is favor as the acceptor (**Scheme 30**).



Scheme 30. Examples of transformationConclusion:

Conclusion:

The enantioselective intramolecular RC reaction of compound **18**, containing two structurally different enone groups, was made possible with bifunctional amino acid derived phosphine catalyst **26d**. We have demonstrate that an additional acid co-catalyst could be utilized to cooperate with the chiral catalyst to increased enantioselectivity. With our optimized conditions, we produced up to 11 different RC type substrates in high yields and high enantioselectivities.

Reference:

1. K. Morita, Z. Suzuki, Z. H. Hirose, *Bull. Chem. Soc. Jpn*., **1968**, *41*, 2815
2. (a) A. B. Baylis, M. E. D. Hillman, *German Patent* 2,155,113, **1972** *Chem. Abstr.*, **1972**, 77, 34174. (b) M. E. D. Hillman, A. B. Baylis U. S. *Patent* 3,743,669, **1973**
3. (a) S. Rafel, W. Leahy, *J. Org. Chem*., **1997**, *62*, 1521; b) S. E. Drewes, M. B. Rohwer, *Synthetic Commun*. **1997**, *27*, 415
4. (a) K. Matsui, S. Takizawa , H. Sasai, *J. Am. Chem. Soc.*, **2005**, *127*, 3680; (b) K. Matsui, K. Tanaka, A. Horii, S. Takizawa, H. Sasai, *Tetrahedron: Asymmetry,* **2006** *17,* 578; (c) K. Matsui, S. Takizawa, H. Sasai, *Synlett*,, **2006**, 761-765.
5. M. M. Rauhut, H. Currier, (American Cyanamid Co.), U.S. Patent 3 07,499,919,630,122, **1963**; *Chem Abstr*., **1963**, *58*, 11224a
6. K. Morita, T. Kobayashi, *Bull. Chem. Soc. Jpn*., **1969**, *42*, 2732
7. J. D. McClure, *J. Org. Chem*. **1970**, *35*, 3045
8. M. J. Krische, L. C. Wang, A. L. Luis, K. Agapiou, H. Y. Jang*, J. Am. Chem. Soc.,* **2002,** *124*, 2402
9. W. R. Roush, S. A. Frank, D. J. Mergott, *J. Am. Chem. Soc*., **2002**, *124*, 2404
10. W. R. Roush, J. L. Methot, *Org. Lett*., **2003**, *5*, 4223
11. V. K. Aggarwal, I. Emme, S. Y. Fulford, *J. Org. Chem*., **2003**, *68*, 692
12. S. Ikegami, Y. M. A. Yamada, *Tetrahedron Lett.,* **2000**, *41*, 2165
13. S. E. Schaus, N. T. McDougal, W. L. Trevellini, S. A. Rodgen, L. T. Kliman, *Adv. Synth. Catal.,* **2004**, *346*, 1231
14. Z. Shi, Q. Tong, W. W. Y. Leong, G. Zhong, *Chem. Eur. J*., **2012**, *18*, 9802
15. A. G M. Barret, A. S. Cook, A. Kamimura, *Chem. Commun*., **1998**, 2533
16. Y. Ibawuchi, M. Nakatani, N. Yokoyama, S. Hatakeyama*, J. Am. Chem. Soc*., **1999**, *121*, 10219
17. K. Yuan, L. Zhang, H. L. Song, Y. Hu, X. Y. Wu, *Tetrahedron Lett*., **2008**, *49*, 6262
18. J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett*., **2005**, *7*, 4293
19. S. J. Miller, C. E. Aroyan, *J. Am. Chem. Soc*., **2007**, *129*, 256
20. X. Y. Wu, J. J. Gong, T. Z. Li, K. Pan. *Chem. Commun*., **2011**, *47*, 1491
21. a) X. Y. Wu, J. J. Gong, K. Yuan, *Tetrahedron: Asymmetry*, **2009**, *20*, 2117; b) X. Y. Wu, J. J. Gong, K. Yuan, H. L. Song, *Tetrahedron*, **2010**, *66*, 2439

22. J. A. Gladysz, F. O. Siedel, *Synlett,* **2007**, 986

23. M. Christmann, E. Marques-Lopez, R. P. Herrera, T. Marks, W. C. Jacobs, D. Konning, *Org. Lett.,* **2009**, *11*, 4116

24. F. L. Gu, W. J. Xiao, W. F. Wang, L. Peng, J. An, C. Li, Q. Q. Yang, L. Q. Lu, *Chem. Eur. J.,* **2011**, *17*, 6484.

25. N. Abermil, G.Masson, J. Zhu, *J. Am. Chem. Soc*., **2008**, *130*, 12596

26. Z. Shi, P. Yu, T.-P. Loh, G. Zhong, *Angew. Chem. Int. Ed*., 2**012**, *51*, 7825

27. Q. Liu, T. Rovis*, J. Am. Chem. Soc.,* **2006**, *128*, 2552

28. M.-Q. Jia, S.-L. You*, Chem Commun*., **2012**, *48*, 6363

29. W. Wu, X. Li, H. Huang, X. Yuan, J. Lu, K. Zhu, J. Ye, *Angew. Chem. Int. Ed.,* **2013***, 52*, 1743

30. J. K. Taylor, M. G. Edwars, M. N. Kenworthy, R. R. A. Kitson, M. S. Scott, *Angew Chem*., **2008**, *120*, 1961

31. J. K. Taylor, R. R. A. Kitson, J. L. Wood, *Org. Lett*., **2009**, *11*, 5338

32. M. C Carreno. M. Gonzalez-Lopez. A. Urbano, *Angew. Chem. Int. Ed*., **2006**, *45*, 2737

33. a) K. Matsui, S. Takizawa, H. Sasai, *Tetrahedron Lett*., **2005**, *45*, 1943; b) K. Matsui, S. Takizawa, H. Sasai, *J. Synth. Org. Chem. Jpn*., **2007**, *65*, 1089; c) S. Takizawa, N. Inoue, S. Hirata, H. Sasai, *Angew. Chem. Int. Ed*., **2010**, *49* 9725

34. F. Zhong, Y. Wang, X. Han, K-W. Huang, Y. Lu, *Org. Lett*., **2011**, *13*, 1310

35. K. Kawamura, H. Fukuzawa, M. Hayashi, *Org. Lett.,* **2009**, *10*, 3509

Chapter 2: Formal [3+2] Cycloaddition of Allenes

2.1 Background to Allenoate Reactions

2.1.1 Allenes

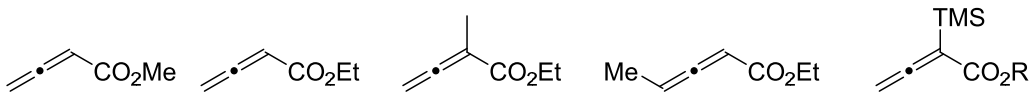
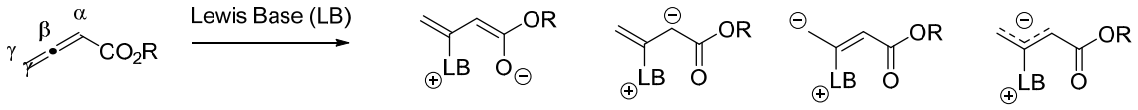


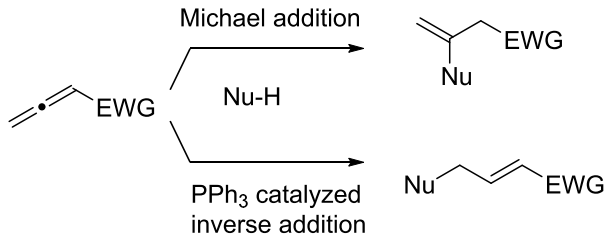
Figure 1. Examples of allenes

Allenes are an attractive type of substrate when combined with Lewis bases due to their range of reactivity[1] and simple preparation procedures (**Figure 1**).[2] In the presence of a Lewis-base, the β-carbon of an allene undergoes a Michael addition resulting in the formation of a zwitterion enolate like intermediate. The diverse reactivity of this intermediate can be demonstrated in several ways. Most literature examples include anion localization at the α–carbon or γ–carbon, delocalized as a 1,3 dipole, or the formation of an enolate (**Scheme 1**). The mode of reactivity is dependent on the Lewis base as well as the electrophilic coupling partner, which can lead to a wide range of structurally diverse products.



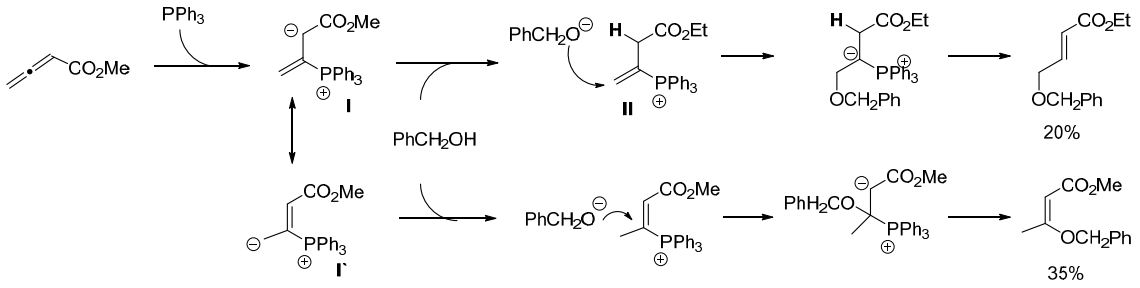
Scheme 1. Anion delocalization

Allenes bearing electron with-drawing groups generally exhibit differing reactivity for each carbon-carbon double bond: the α,β-double bond is electron-deficient while the β,γ- bond is relatively electron-rich. Therefore, in the case of a simple nucleophilic addition, a Michael type adduct is generally produced. In 1985, Cristau *et al*. reported an umpolung inversion γ-addition of nucleophiles in electron deficient allenes via multistep transformation in presence of triphenylphosphine catalyst (**Scheme 2**).[3]



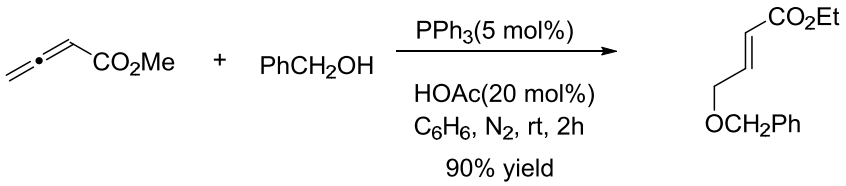
Scheme 2. Inverse addition

Initiated by Trost and co-workers, this reaction has been expanded to a larger set of nucleophiles.[3] A more detailed study on the reaction mechanism of the reaction shows a similar pathways to that of annulation reactions with the formations of phosphonium α-anion, **I**. However, instead of acting as a Lewis-base nucleophile, this intermediate plays the role of Brønsted-base and subsequently attracts a proton from the nucleophile, thereby activating it. The resulting vinylphosphonium salt then undergoes a nucleophilic attack from said activated nucleophile, followed by proton exchange, affords the inversion addition adduct with the elimination of the triphenylphospine catalyst, finishing the cycle. A year later, Lu et al. demonstrated the possibility of Michael-addition products albeit via branching mechanistic pathways.[5] If intermediate **I** is not protonized quickly enough, it can undergo delocalization forming intermediate **I`**, which then receives a second Michael addition at the β-position with release of the catalyst. The rate of formation of intermediate **II** is dependent on the acidity of the nucleophile (**Scheme 3**).



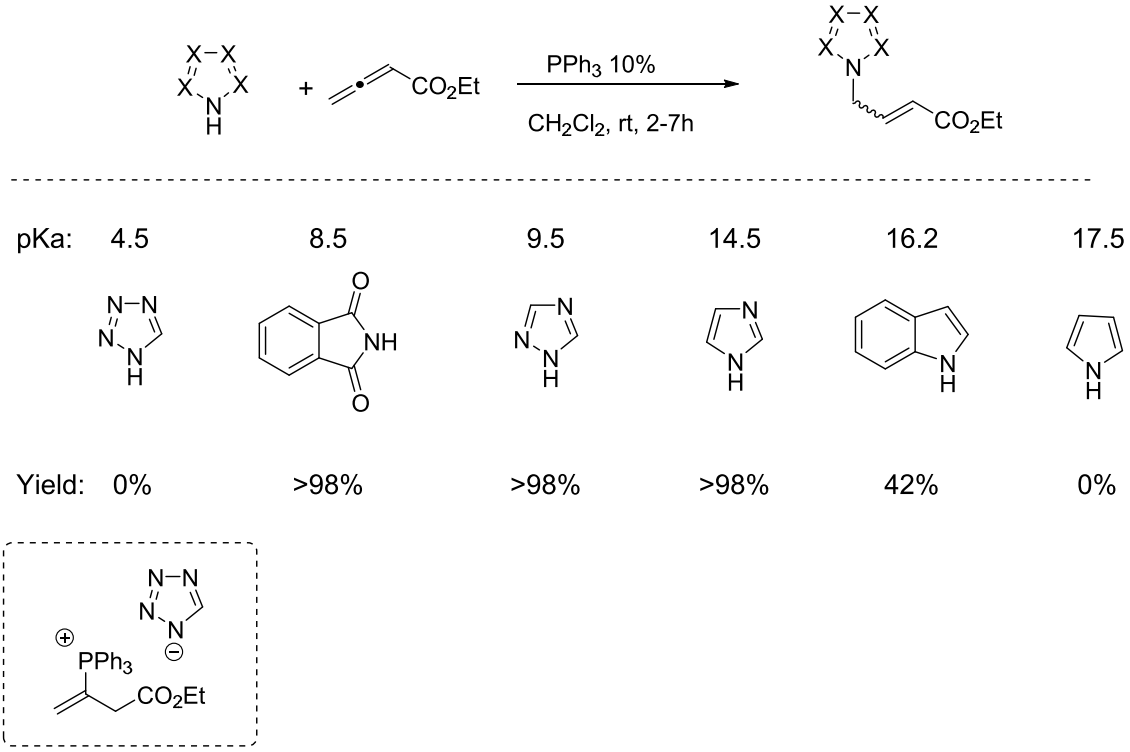
Scheme 3. Mechanism inverse addition with pronucleophile

A catalytic amount of acid could be added to the reaction to force the quick protonation of intermediate **I** and prohibit the localization of the anion. Indeed, in the presence 20 mol% of acetic acid, the trapping of anion **I** was successful, affording the inverse addition product as the sole product in 90% yield (**Scheme 4**).



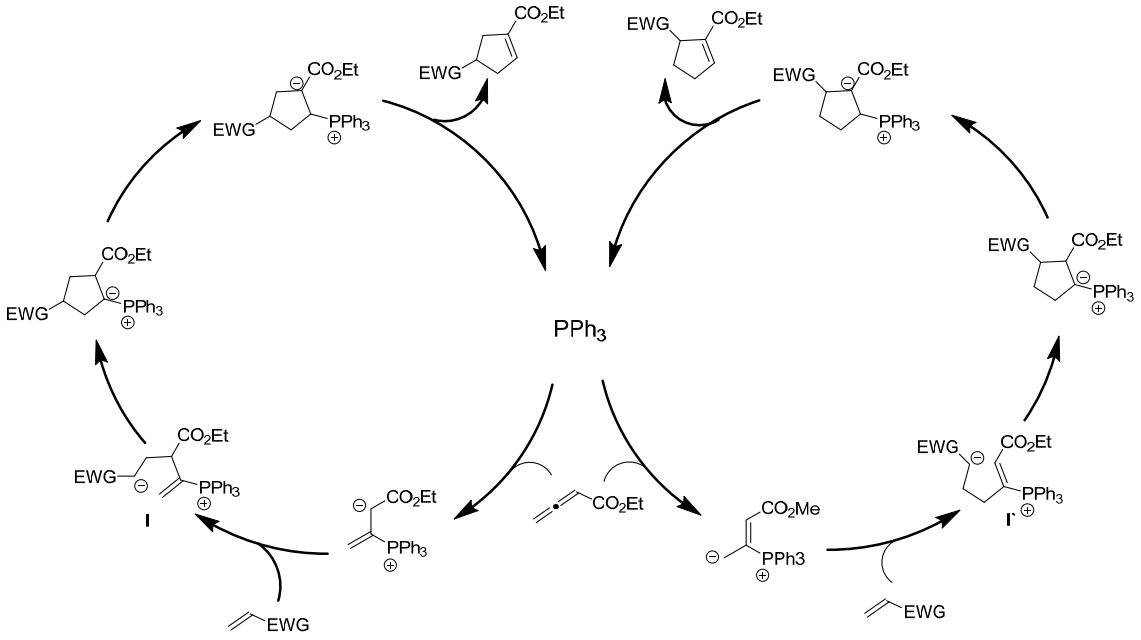
Scheme 4. Mechanism of inverse addition with pronucleophiles

In more recent studies, Cristau group determined the pKa range in which a nucleophile will react with the phosphonium intermediate (**Scheme 5**).[6] They concluded that pronucleophiles with too low of a pKa, <8.5, are able to protonate the phosphonium intermediate quickly, however, the resulting conjugate base is much too weak to perform the nucleophilic attack. As a result, will remain as the phosphonium substrate salt, completely halting the reaction. Pronucleophiles that are too high of pKa, >16.2, are not able to protonate the intermediate and are therefore unreactive in the solution.



Scheme 5. pKa range of umpolung reaction

2.1.2 Phosphine catalyzed annulation:



Scheme 6. First example of annulation products

One of the first examples of phosphine catalyzed annulations of allenes was presented by Lu's group in 1995 (**Scheme 6**).[7] The coupling of 2,3 butadienoate with electron deficient olefins to form cyclopentene derivatives is initiated by the nucleophilic attack of the triphenylphosphine catalyst to the butyldienoate and resulted in two products due to the possible localization of the anion on either the α-carbon or γ-carbon. These resonance stabilized phosphonium dienolates can conduct a Michael-addition to electron deficient olefins to form intermediates **I** or **I`**. This is followed by intramolecular cyclization, proton transfer, and phosphine elimination. In all substrate cases, the major product implies the reaction is more likely to take the α addition pathway due to the additional stabilization of the α-carbon anion adjacent to the electron withdrawing groups. Although regioselectivities were not great(d.r. = 75:25), Lu's pioneering work on this [3+2] annulation of allenes spurned further investigation in several research groups.

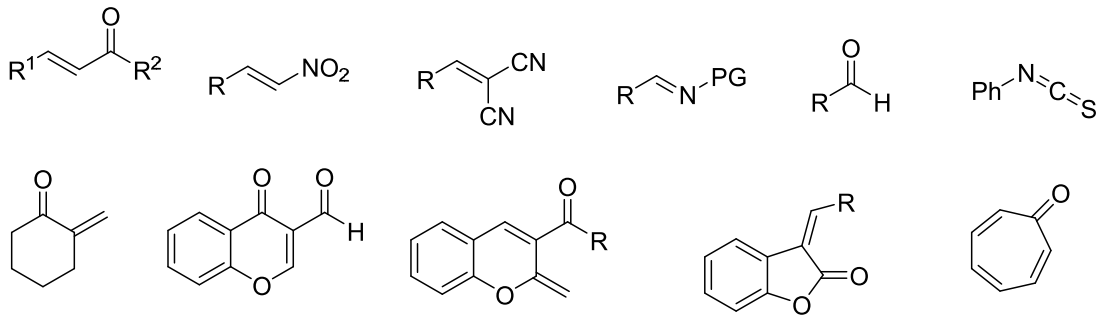


Figure 2. Examples of compatible electrophiles

And so, over 20 different research groups began investigating the combination of allene and electrophiles that can be used in the catalytic reaction. **Figure 2** shows the diverse range of allene and electrophile combination for the synthesis of a variety of chemical structures with application for medicinally important compounds and biologically active natural products. Along with the [3+2] annulation of electron deficient olefins,[8] unprecedented [4+2] annulation with electron-deficient olefins[9] was discovered in which delocalization occurs further onto the α-methyl group of substrates, allowing for six member ring formation. The initial γ -addition or β`-addition step could be selective through the utilization of electron-donating phosphine hexamethylphosphorous triamine, or electron-withdrawing triarylphosphine such as tris(p-fluorophenyl)phosphine, respectively. The [3+2] annulation of imine[10] and ketones[11] occur in a similar mechanistic pathway as that of allene-alkenes. However, due to the strong nucleophilic nature of the nitrogen atom, reactions mainly occur through the α-addition pathway to generate solely α-addition products. [4+2] annulation of imine[12] and ketones[13] is also possible by exploiting, again, α-substituted allenoates.

2.1.3 Enatioselective Catalyst

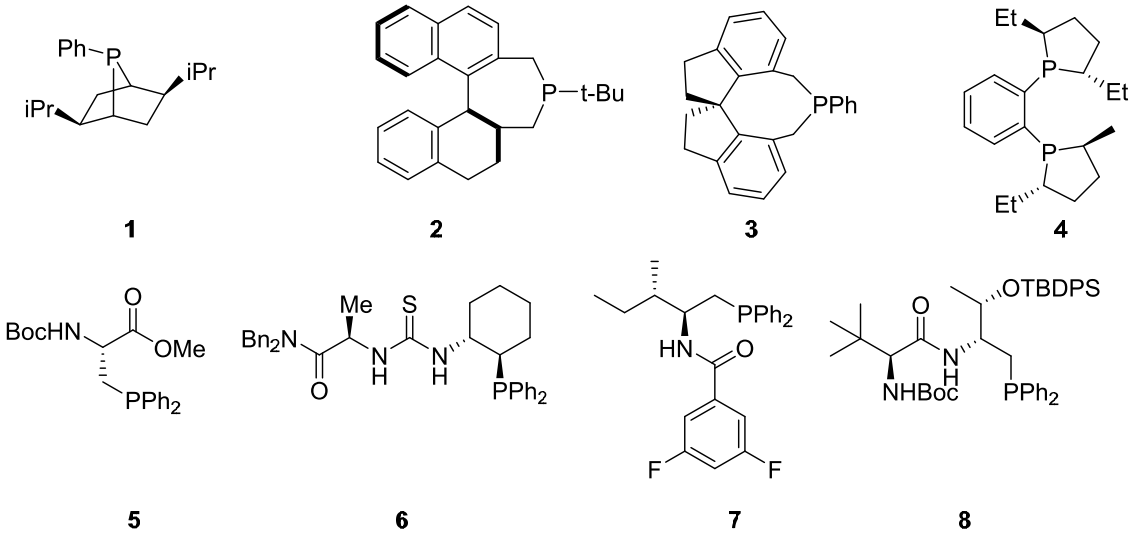


Figure 3. Chiral phosphine catalyst

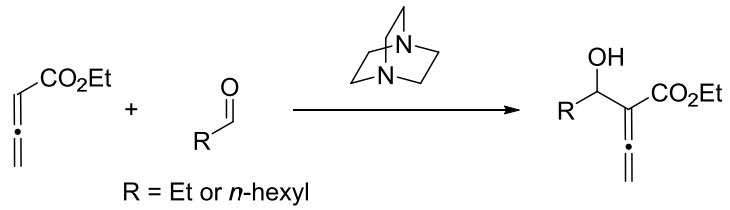
A handful of chiral phosphine organocatalyst exist to be compatible with these types of reactions. They can be divided into two category depending on whether or not they contain additional functional groups, specifically proton donor groups (**Figure 3**).

The first group are phosphine catalyst that do not have additional functional groups. Chirality is induce completely though the chiral backbone of the catalyst. The first enantioselective phosphine catalyze annulation reaction, [3+2], was reported by Zhang and co. workers[14] with catalyst **1**. Eight years later, the [4+2] annulation of allenes and imines was demonstrated by employing Gladiali's catalyst **2**.[15] Additionally, Fu's group later reported that **2**, along with a similar catalyst **3** are both able to promote the asymmetric γ-addition of pronucleophiles to allenes.[16]

The second group are phosphine catalyst with proton donating groups. Miller in 2007 reported [3+2] annulation of allenes and olefins through hydrogen-bond interaction with catalyst **5**.[17] Triggered by Millers pioneer work, other research groups begin developing amino acid derived bifunctional chiral phosphines. Zhao demonstrated [4+2] annulation of allenoates with alkylidene cyanoacetate with catalyst **6**.[18] Lu described the enantioselective [3+2] annulation of allenoates and imines using catalyst **7**[19] as did Jacobsen's group with **8**.[20]

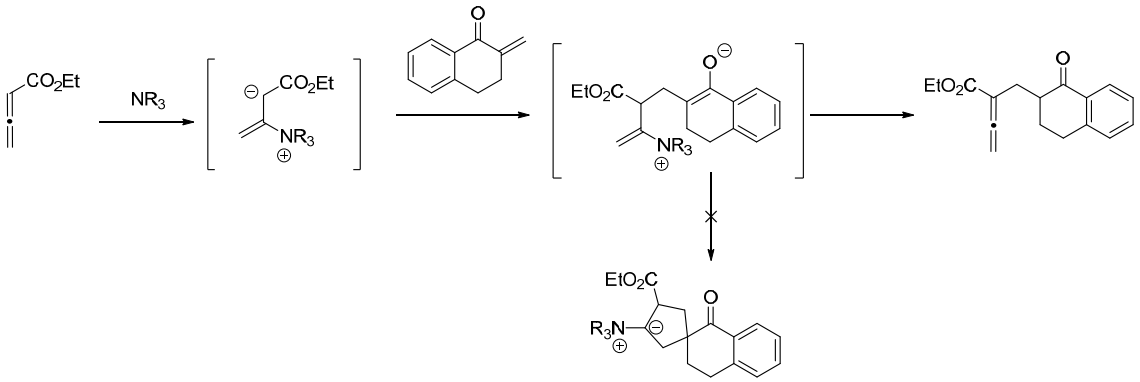
2.1.4 Amine catalyst

Amines are also effective Lewis Base catalyst when paired with allenoates albeit displaying different reactivity and transformation compared to phosphine. The first reported amine catalyzed reaction was provided by Tsuboi et al. in 1993 with the coupling of allenoates and aldehydes in the presence of DABCO (**Scheme 7**).[21] Each product rose from a Morita-Baylis-Hillman type reaction mechanism.



Scheme 7. First example of amine catalyzed allenoate reaction

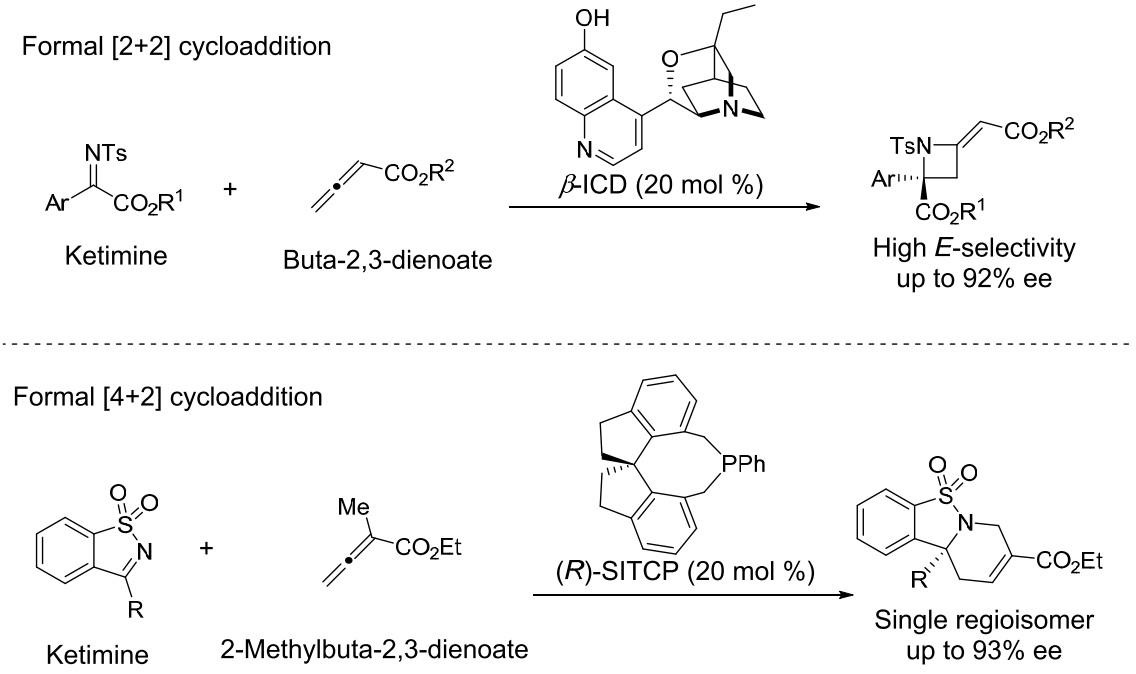
Additionally, Millers group demonstrated Rauhut-Currier type reactions are possible when coupled with α,β-unsaturated carbonyl compounds (**Scheme 8**).[22] Phosphine catalyst are known to provide [3+2] cycloadducts with these types of substrates, which were not observed in the case of amine catalyst. They presented a clear difference in reaction mechanism when either catalyst is employed. After the addition of phosphine, a 1,3 dipole intermediate is formed subsequent cycloaddition occurs to generate ylide type intermediate, which is stabilized by the adjacent phosphonium moiety. Amine catalyst however, are unable to form such ylide structure and instead begins with an enolate type intermediate and undergoes a Rauhut-Currier type reaction.



Scheme 8. RC type allenoate reactivity with amine catayst

2.1.6 Our Previous Research

In the recent years, our lab has begun entering the field of allenoate reactivity with electrophiles. In particular, we have paired ketamine with unsubstituted dienes for the formal [2+2] cycloaddition reaction in the presences of bifunctional catalyst β-ICD.[23] The tertiary amine allows for aza-MBH type reactivity as the hydroxyl assist in the close proximity activation of the ketimine to afford high enantioselectivity of the desire product. The following year, we presented formal [4+2] cycloaddition reaction of ketimine with α-substituted allenoate (**Scheme 9**).[24] In both cases, mechanistic pathway followed that of previous literatures.



Scheme 9. Chiral catalyst

2.2 Enantioselective formal [3+2] Cycloaddition

2.2.1 Hypothesized Reaction

Our research regarding the intramolecular Rauhut-Currier reaction has given us a better understanding of the cyclicdienone group and its ability as a Michael acceptor. After several attempts to expand the research to other substrate, we realize two double bond as well as the cyclic structure plays an important role in its electrophilic activation.

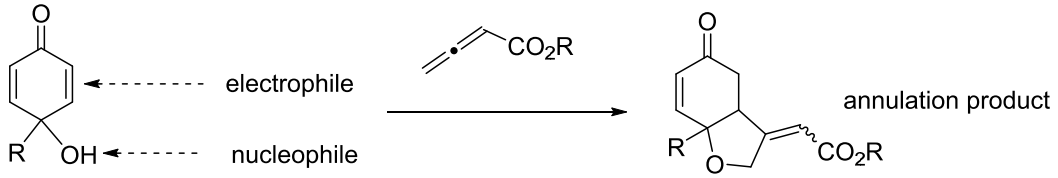
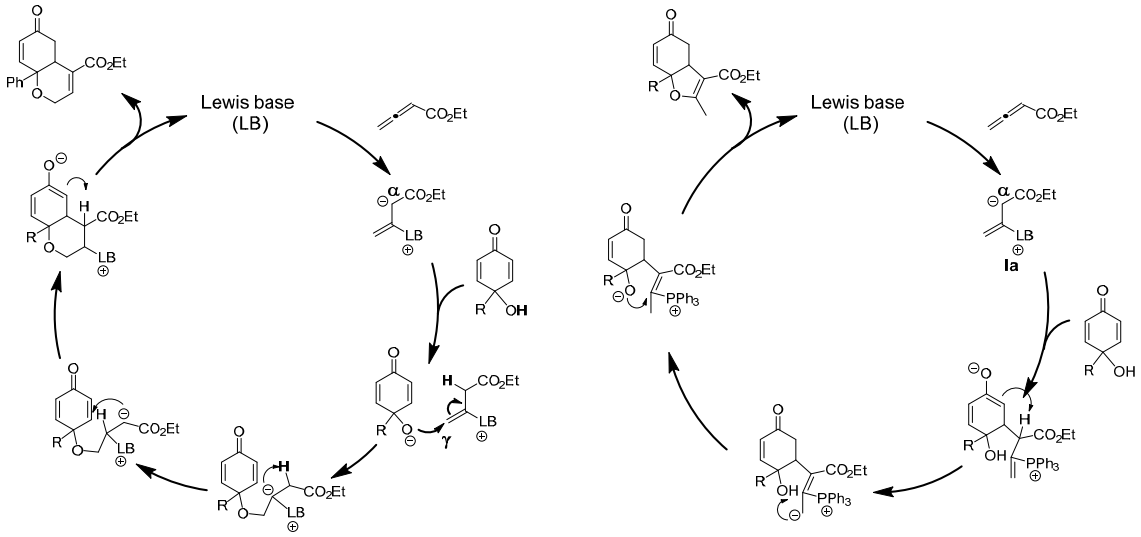


Figure 4. Chiral phosphine catalyst

We reason that cyclic dienones containing a hydroxy group would be able to couple with the phosphine catalyzed allenoate system (**Figure 4**). Specifically, the hydroxy group to act as a nucleophile and the dienone group as the electrophile to form a cyclization product as shown in previous examples. **Scheme 10** represent a few hypothesized possible products following currently known mechanistic pathways.

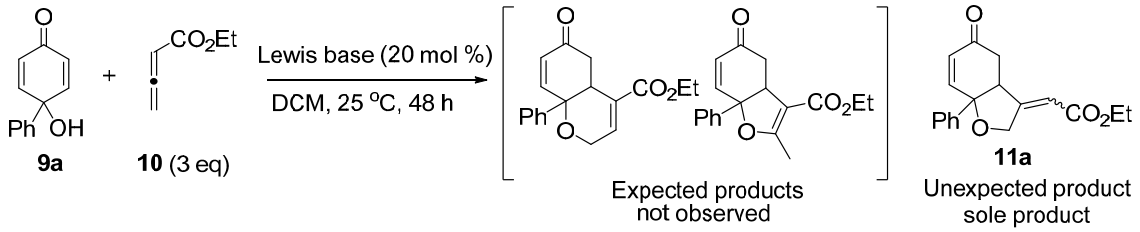


Scheme 10. Possible pathways and products

2.2.2 Preliminary Testing

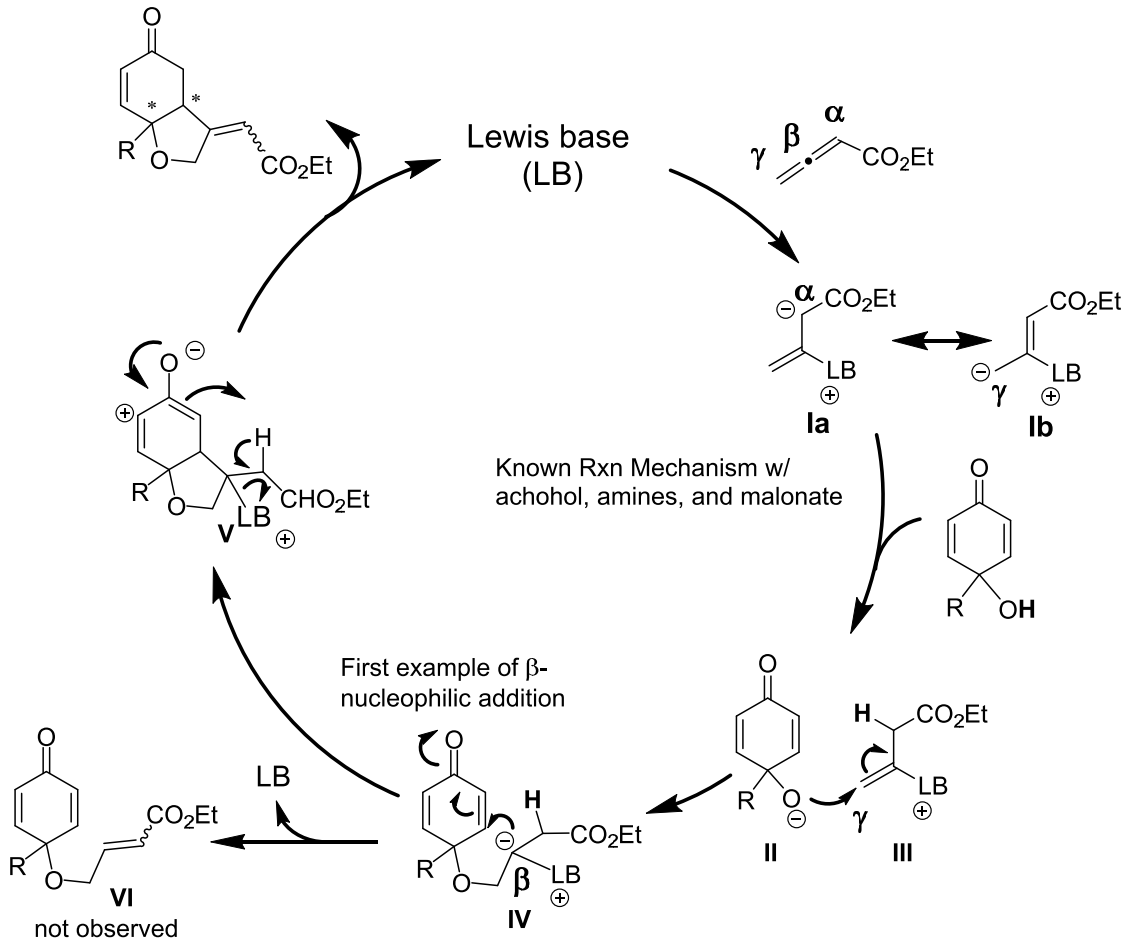
Assuming that the reaction will follow the common mechanistic pathways shown in previous literatures, we hypothesized the reaction will produce annulation products in **Scheme 10** via nucleophilic addition of the α– or γ–anion to the dienone and subsequent nucleophilic addition of the hydroxy group. During preliminary testing however, neither product was observed (**Table 1**). Certainly, starting material **9a** and allenoate **10** in the presence of triphenylphosphine did undergo a reaction to give two similar products in high yield. After further analysis, we concluded that the products are **11a** in equal ratio diastereomers. If so, this product could not be obtain with the current common literature mechanism as well as any of the less common ones. If indeed the dienone group act as the electrophile, then it is apparent that a nucleophilic attack occurred at the β-position, never before seen in allenoate chemistry.

Table 1. Preliminary testing



Entry	Lewis base	*Z*:*E*	NMR yield of **11a** (%)
1	PPh_3	1:1	72
2	DABCO	—	N.R.
3	DMAP	—	N.R.
4	DBU	—	N.R.
5	none	—	N.R.

The localization of anion onto the β-carbon is expected after the annulation or umpolung inversion addition, however, its lifetime is short due to the subsequent adjacent proton transfer to form the more stable conjugating double bond. Thus, a nucleophilic attack from the β-position has never been reported. We suspect the reaction mechanism does follow the standard umpolung mechanistic pathway up to a point (**Scheme 1**). Following the addition of the phosphine catalyst and the formation of the phosphonium α-anion intermediate **Ia**, the hydrogen atom of the hydroxy group is extracted. This activated oxygen anion **II** performs a nucleophilic attack to the γ-carbon of **III** to form the stable ylide phosphonium intermediate **IV**. If the reaction were allowed to continue the generally pathway, a hydrogen transfer would occur to form the final umpolung product **VI**. However, this product is never observed. We hypothesize that the β-anion instead is quickly absorbed by the dienone group via Michael-addition and finally release of the catalyst by hydrogen transfer to produce the observed product in equal diastereomeric ratio. If our proposed mechanism is correct, this would represent the first example of a β-nucleophilic attack in the library of allenoate reactivities.



Scheme 11. Proposed mechanistic pathway

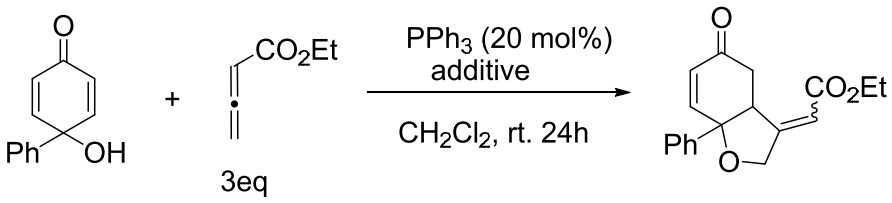
No other by products are observed beside polymerization. Much like in our previous Rauhut-Currier research, the generation of conjugating double bond intermediate **V** may undergo polymerization via over Michael reaction. The allenoate also suffers from polymerization in presence of the catalyst. The catalyst substrate intermediate **Ia** competes for reactivity with not only substrate **9a**, but also allenoate starting substrate **10**. Thus the presence of three equivalent of allenoate is require for high yields of products.

The reactivity does appear to slow down over time. This is most likely due to the competing substrates. As the concentration of substrate **9a** decreases over time, the allenoate is more likely to polymerize with itself. Additionally, polymerization also causes loss of catalyst. 20 mol% of catalyst must be used to obtain high yields.

Tertiary amine have been known to catalyze Rauhut-Currier type reaction when couple with allenoates and a α,β-unsaturated carbonyl compounds. Screening of amine catalyst resulted in no reactivity in any cases. This type of reactivity is most likely hindered by the cyclic structure of the dienone group.

2.2.3 Acid Additives

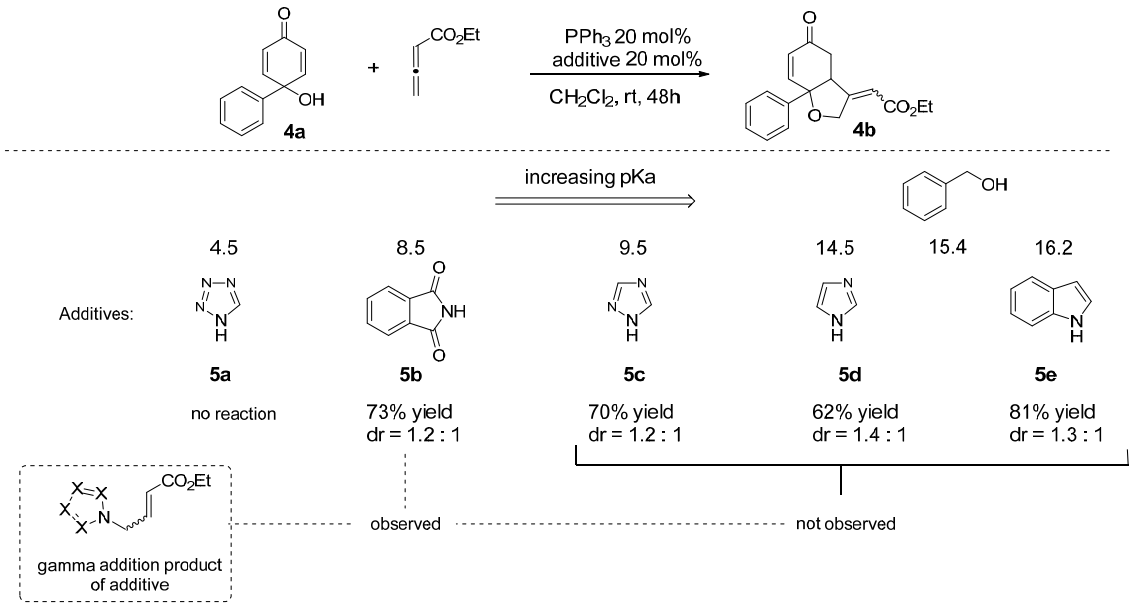
Table 2. Acid additives



entry	additive (x mol%)	yield	d.r.
1	-	72	1:1
2	phenol (50)	60	1.6:1
3	phenol (30)	76	1.4:1
4	phenol (10)	74	1.3:1
5	(*S*)-binol (50)	57	2.1:1
6	thiourea (50)	69	1.2:1

Several articles exist in which an acid additive is added to γ-addition reactions and have resulted in higher yields and enantioselectivity. Earlier work by Trost have shown that an acid additive pushes the formation of intermediate **III** (**Scheme 11**) and prevents farther delocalization of the anion. Furthermore, the resulting conjugate base stabilizes the phosphonium anion. This salt complex occurs before the enantioselective step, specifically the addition of the nucleophile, therefore strong interaction between the phosphonium and conjugate base may improve the chiral environment, leading to higher enantioselectivity. We attempted to increase the diastereomeric ratio of the reaction with an acid additive, beginning with phenol (**Table 2**). There seems to be a slight detrimental effect in reactivity in the presence

of the acid. Increasing the concentration of phenol leads to lower yields of product. Its role in this case is most likely as a competing proton donor. The deprotonation of weak acid substrate **9a** is essential for its activation as a nucleophile. A slight increase in diastereomeric ratio is observed with increase acid concentration possibly confirming the formation of a conjugate base phosphonium conjugate base salt.

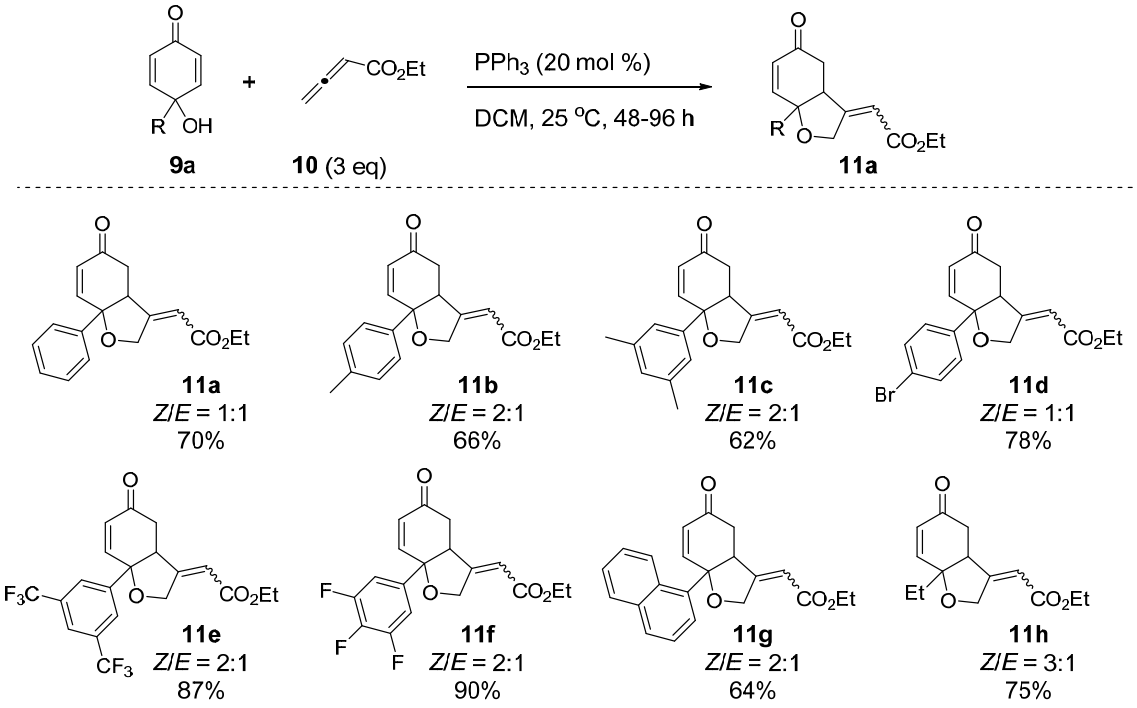


Scheme 12. Acid additive pKa range testing

Following the papers of Cristau,[6] additional acid additive studies were conducted to determine the relative pKa range that may be appropriate as an additive (**Scheme 12**). Several azoles, also known for their umpolung addition to allenes, were added to the reaction along with our model substrate, allenoate, and tirphenylphosphine catalyst. This was in attempt to see at which pKa would stop the reaction completely, assist the intermediates or compete with the substrate, and which would have no effect. At low pKa, tetra-azole (**5a**) halt the reaction entirely due to their over stabilization of the phosphonium intermediate. With phthalimide (**5b**), pKa of 8.5, reactivity was observed affording the product in 73% yield and slight increase in diastereomic ratio, 1.2:1. It does appear as if the phthalimide competed with the substrate for reactivity as its γ-addition product to the allenoate was observed in the crude ^{1}H NMR. **5c**, **5d**, and **5e**, with pKa of 9.5, 14.5, and 16.2 respectively, also saw reactivity with similar results.

Interestingly, like that of phthalimide, these compounds should have competed with the substrate and form addition product, but none were detected in the reaction mixture. From Cristaus studies, these azoles will certainly protonate the phosphonium intermediate before the substrate due to their lower pKa. We suspect the possibility of the formation of the azole phosphonium salt intermediate, in which the Lewis base property of the azole anion is suppressed. Rather, as a Brønsted-base, it extracts the acidic proton from the substrate, activating it for nucleophilic attack of the γ–carbon. The reaction rate is solely determined by the Lewis basicity of the conjugate base of the substrate, therefore the addition of the azole does not increase reactivity.

2.2.4 Substrate Scope

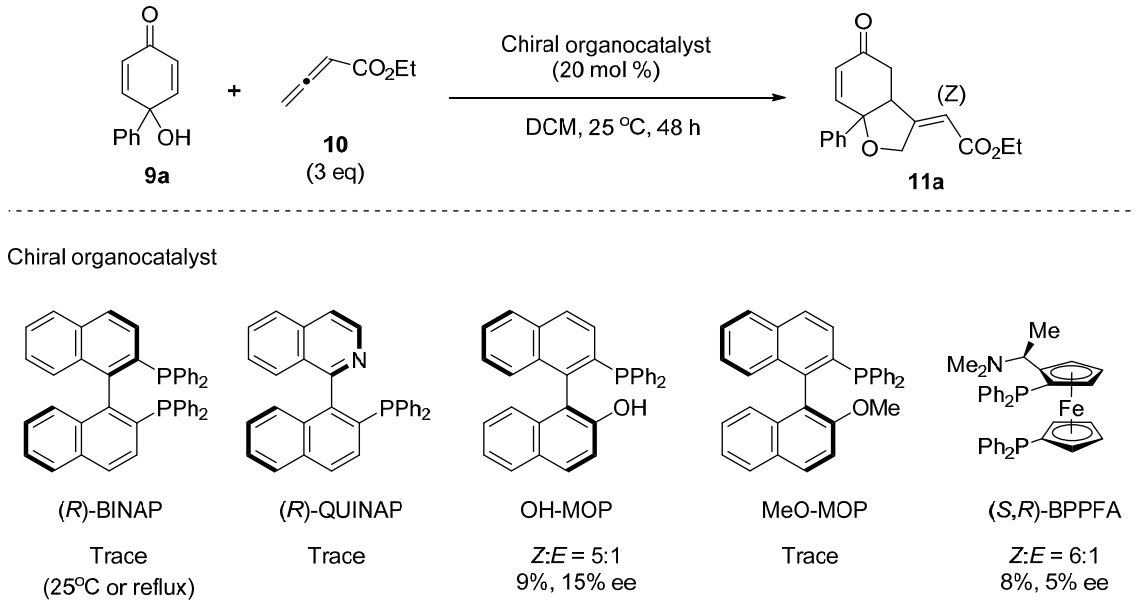


Scheme 13. Substrate scope

The substrate scope of the reaction was conducted in order to search for a more appropriate starting material for further condition screening (**Scheme 13**). Not surprisingly, the result are very similar to the reactivities in our previous Rauhut-Currier research due to similar dienone functional group, however, more sensitive to functional groups at the 4 position of the

cyclic dienone as well as their electronic effect. Aryl groups were much more stable than their akyl counter-part. Aromatic rings with electron donating group displayed lower reactivity rates and require longer reaction times than those with electron withdrawing groups. Similar to our previous Rauhut-Currier research, the intermediate contains competing reactivity between the diene and enolate group. The electron donating effect seems to enhance the diene reactivity while suppressing the enolate reactivity. Electron donating groups have the opposite effect therefore increasing the enolate reactivity. Akyl groups suffered from long reaction times and over reaction, much more than the substrates of the Rauhut-Currier research due to the much higher reactivity of allenoates to dienes. Bulky functional groups, such as naphthol, were not able to significantly increase the diastereomic ratio.

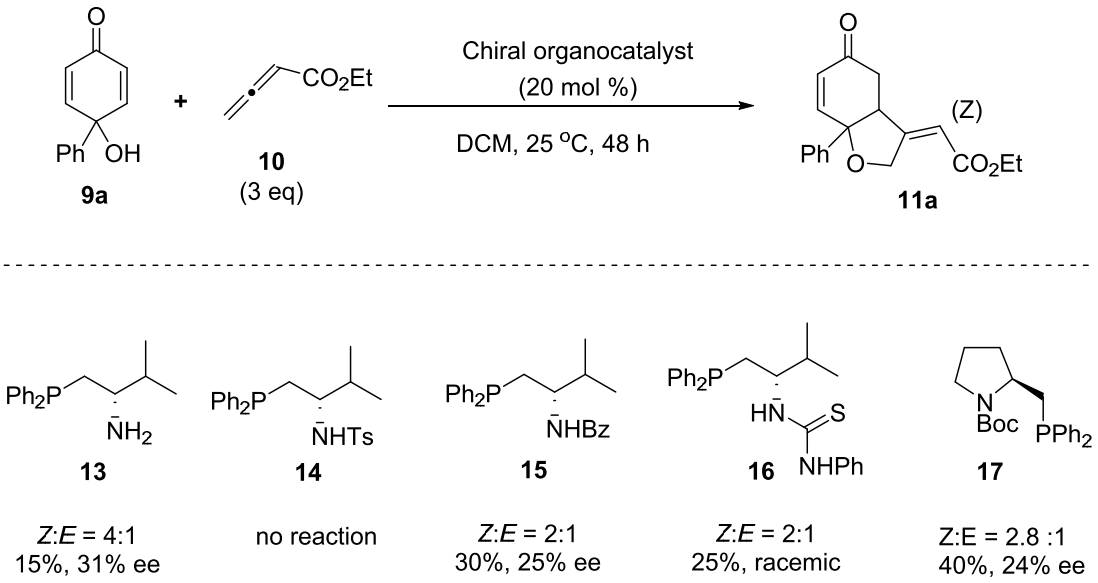
2.2.5 Chiral Catalyst



Scheme 14. Chiral catalyst

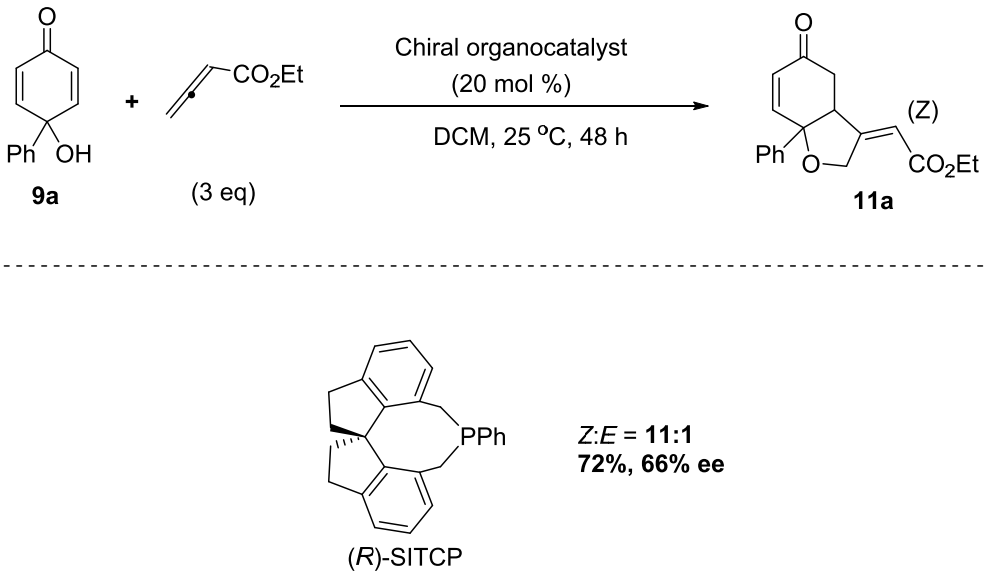
Next we conducted chiral catalyst screening beginning with those that are available in our library. Chiral catalyst in **Scheme 14** were screened first to be tested due to our previous focus on Morita-Baylis-Hillman reaction and aza-MBH reaction. Not surprisingly, reactivity for these catalyst were low as they do not appear in recent literature involving the annulation

of allenoates or α/γ-addition to allenoates. What little reactivity that occur only resulted in low enantioselectivity.



Scheme 15. Chiral catalyst

Amino acid derived phosphine catalyst were also explored (**Scheme 15**). Several examples exist in which enantioselective annulation of allenes afforded good yields and high enantioselectivity due to the cooperation of the Lewis-base and Brønsted-acid groups. The proton donor groups were able to stabilize the intermediates without effecting the proton transfer steps in the reaction mechanism. In attempts to use such bifunctional catalyst with our substrates however, reactivities were sluggish and afforded low yields of products albeit enantioselectivities up to 31%. Much like the acid additive studies, the proton donating groups of the catalyst affect the initial proton transfer step. Without the initial deprotonation of the starting material, it can not act as a strong nucleophile. The tosyl protecting group for example, increases the proton donating strength significantly and halts the reaction completely. Other protecting groups such as benzyl or thiourea are able to conduct the reaction but enantioselectivities did not improve. When proline derived catalyst **17** was used, reactivity rates increased only slightly despite the absence of a proton donating group. We can conclude that Brønsted acid containing bifunctional catalyst are not appropriate for this reaction due the initial deprotonation step of the substrate.



Scheme 16. Chiral catalyst

Results from spinol and binol derived catalyst fared much better. In previous literatures, these types of catalyst have successfully afforded simple γ-addition products as well as annulation with imines in high yields and enantioselectivities. In our reaction, assuming to involve a γ-addition step, improved greatly from the increasing reactivity of the diakyl phosphine and absence of proton donor group. Specifically, spinol derived phosphine **SITCP**[25] afforded products in 11:1 daistereomeric ratio, 72% yield and 66% ee (**Scheme 16**). This represents the best results for the time being.

Conclusion:

We have discovered a unique type of phosphine catalyze [3+2] annulation of allenoate in which the nucleophilic attack occurs at the β-position, unseen in previous literatures regarding allenoate reactivity. This is still an ongoing research as we search for more evidence for the reaction mechanism as well as a more adequate chiral catalyst.

References:

1. B. J. Cowen, S. J. Miller*, Chem. Soc. Rev*., **2009**, *38*, 3102
2. (a) R. W. Lang and H.-J. Hansen, *Org. Synth*., **1984**, *62*, 202; (b) H. Lu, D. Leow, K.-W. Huang and C.-H. Tan*, J. Am. Chem. Soc*., **2009**, *131*, 7212.
3. H.-J. Cristau, J. Viala, H. Christol, *Bull. Soc. Chem. France,* **1985**, 980
4. (a) B. M. Trost, C.-J Li. *J. Am. Chem. Soc*., **1994***, 116*, 3167; (b) B. M. Trost, C.-J Li. *J. Am. Chem. Soc*., **1994***, 116*, 10819
5. C. Zhang, Z. Lu *Synlett*, **1995**, 645
6. D. Virieux, A.-F. Guillouzic, H.-J. Cristau, *Tetrahedron,* **2006***, 62*, 3710
7. C. Zhang, X. Lu, *J. Org. Chem*., **1995**, *60*, 2906
8. C. E. Henry, O. Kwon*, Org. Lett*., **2007**, *9*, 3069
9. M. Sampath, T. Loh, *Chem. Commun*., **2009**, 1568
10. (a) Z. Xu, X. Lu, *Tetrahedron Lett.,* **1997**, *38*, 3461; (b) Z. Wang, S. Castellano, S. S. Kinderman, C. E. Argueta, A. B. Beshir, G. Fenteany, O. Kwon, *Chem. Eur. J*., **2011**, *17*, 649; (c) Y. Wang, Y. Zhang, H. Dong, J. Zhang, J. Zhao, *Eur. J. Org. Chem*., **2013**, 3764
11. (a) T. Wang, S. Ye, *Org. Biomol. Chem.*, **2011***, 9*, 5260; (b) T. Wang, S. Ye, *Org. Lett*., **2010**, *12*, 4168
12. (a) X. Zhu, J. Lan, O. Kwon, *J. Am. Chem. Soc*., **2003***, 125*, 4716; (b) X. Chen, S. Ye, *Eur. J. Org. Chem*., **2012**, 5723
13. (a) T. Wang, S. Ye, *Org. Biomol. Chem.,* **2011**, *9*, 5260; (b)T. Wang , S. Ye, *Org. Lett*., **2010**, *12*, 4168
14. G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc*., **1997**, *119*, 3836
15. R. P. Wurz , G. C. Fu, *J. Am. Chem. Soc*., **2005**, *127*, 12234
16. (a) S. W. Smith, G. C. Fu*, J. Am. Chem. Soc*., **2009**, *131*, 14231; (b) R. Sinsi, J. Sun, G. C. Fu, *PNAS*, **2010**, *48*, 20652
17. B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc*., **2007**, *129*, 10988
18. H. Xiao, Z. Chai, D. Cao, H. Wang, J. Chen, G. Zhao, *Org. Biomol. Chem*., **2012**, *10*, 3195
19. X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem., Int. Ed*., **2012***, 51,* 767
20. Y. Fang, E. N. Jacobsen**,** *J. Am. Chem. Soc.,* **2008**, *130*, 5660

21. (a) S. Tsuboi, H. Kuroda, S. Takatsuka, T. Fukawa, T. Sakai, M. Utaka, *J. Org. Chem*., **1993**, *58*, 5952; (b) S. Tsuboi, S. Takatsuka, M. Utaka, *Chem. Lett*., **1988**, *17*, 2003
22. C. A. Evans, S. J. Miller, *J. Am. Chem. Soc*., **2003**, *125*, 12394
23. S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, H. Sasai, *Org. Lett.*, **2013***, 15,* 4142
24. S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki, H. Sasai, *Asian J. Org. Chem. ,* **2014,** *3*, 412
25. Zhou et al, *J. Am. Chem. Soc*., **2003**, *125*, 4404.