BRØNSTED ACID PROMOTED ADDITIONS OF DIAZOALKANES TO IMINES: THE INTERPLAY OF MECHANISM AND STEREOCHEMICAL OUTCOME AS A TOOL TO DISCOVER AND DEVELOP A NEW SYN-GLYCOLATE MANNICH REACTION

By

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To my BFFs, who I cannot succeed without, David, Claire, and Angie.

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CHAPTER I

BRØNSTED ACID CATALYSIS OF REACTIONS INVOLVING CARBON-OXYGEN AND CARBON-NITROGEN PI BONDS

1. 1. Brønsted Acid Catalysis

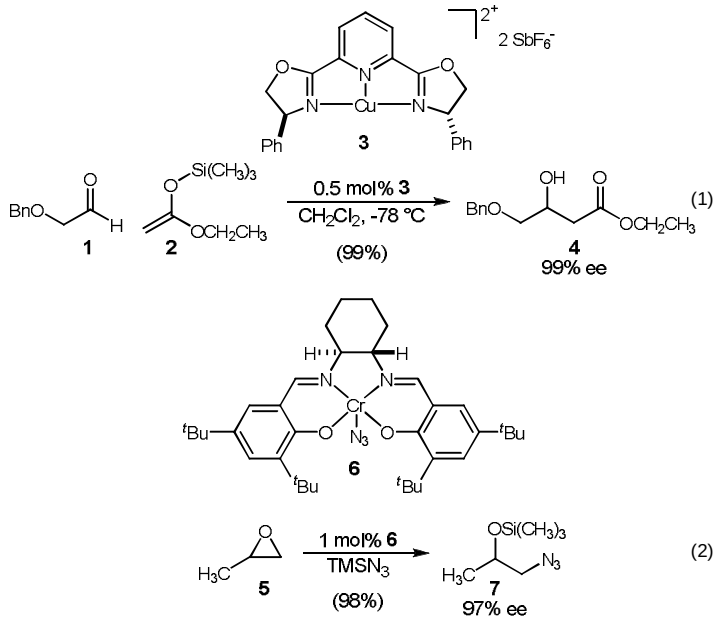
The proton is the smallest Lewis acid as well as arguably the cheapest and most abundant. Mineral Brønsted acids have been utilized in organic and inorganic transformations for as long as chemistry has been studied. Yet protons have been utilized by enzymes both for the catalysis and stereoinduction of a variety of reactions long before chemistry was pursued as a scientific discipline. Strategically placed protons in the conformationally restricted binding site of serine proteases is responsible for the resulting selectivity and reactivity of these enzymes.

Nature has certainly realized that the strong Lewis acidity of the proton allows it to be a rather effective reagent. However, other Lewis acids have received greater attention over the four decades since Yates and Eaton demonstrated the aluminum chloride catalyzed Diels-Alder reaction.[1] It is difficult to speculate as to the motivation of scientists to focus on Lewis acid reagents. Brønsted acids and Lewis acids are typically able to effect the same transformations. Lewis acids have larger nuclei and are capable of higher coordination numbers and highly ordered coordination geometries. In contrast a proton would seem to lack these same design features. Whereas the well studied phenomena of hydrogen bonding could be an example of bidentate coordination to a proton, examples of higher coordination numbers are rarely observed. The spherical

[1] Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436.

nature of the 1s orbital would not likely allow for ordered coordination geometries. Lewis acids are able to bind chiral nonracemic ligands in addition to a carbonyl or imine allowing for high levels of stereoselectivity in the reactions in which they are employed. These Lewis acid complexes are mild enough to accommodate reactive nucleophiles such as silyl enol ethers while maintaining sufficient Lewis acidity to catalyze a reaction and do so at very low catalyst loadings. Some highly successful examples of these elements are demonstrated with Evans' copper (II) complexes with box and pybox ligands[2] and Jacobsen's chromium (III) complexes with Salen ligands (Figure 1).[3]

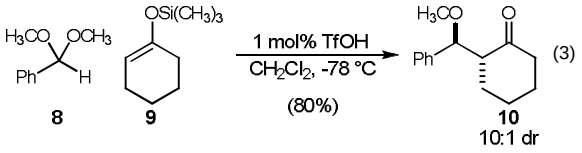
Figure 1. Examples of Lewis Acid Catalyzed Asymmetric Reactions



Strong Brønsted acids would be expected to protonate silyl enol ethers, reverting them to the corresponding ketone. Furthermore, Brønsted acids typically facilitate the

[2] a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814. b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.
[3] a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315. c) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

elimination of β–hydroxy ketones to afford α,β–unsaturated ketones. Onaka and coworkers did report a Mukaiyama aldol reaction in presence of a catalytic amount of



triflic acid in which the β–methoxy ketone **10** was isolated (eq 3).[4] However, since it showed similar results to trimethylsilyl triflate it is possible that triflic acid is simply silylated in the reaction leading to TMSOTf Lewis acid catalysis. Furthermore, the enol silane was derived from a symmetrical ketone, which would not provide any information about the regioselectivity of enol formation.

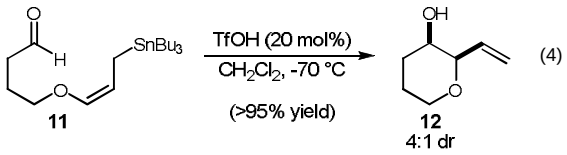
Brønsted acids have been used in substoichiometric amounts for reactions such as esterification, acetal formation, and rearrangement. There exist numerous examples of the use of an equivalent or more of Brønsted acid to facilitate a range of tranformations.[5] The focus here will be on Brønsted acid catalyzed reactions involving activation of ketones, aldehydes, or imines.

There has been a renewed interest in recent years in Brønsted acid catalyzed reactions as a means to reduce the amounts of organic waste and eliminate the use of toxic metals.[6] Catalysts that are stable to air and stored at ambient temperature are also desirable. Triflic acid, for example, is not easily oxidized and is readily dried and distilled as a liquid,

[4] Kawai, M.; Onaka, M.; Izumi, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1237.
[5] Howells, R. D.; Mc Cown, J. D. *Chem. Rev.* **1977**, *77*, 69.
[6] Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

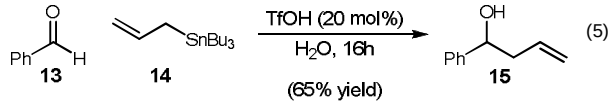
which in turn can be easily measured and dispensed by standard syringe techniques. Triflicacid has also been shown to be an effective catalyst in a range of solvents.

1. 2. Achiral Brønsted Acid Catalyzed Additions to Carbonyls



(4)

Denmark and co-workers utilized stoichiometric amounts of triflic acid to promote the addition of allyl silanes and allyl stannanes to aldehydes.[7] The first report of a triflic acid catalyzed reaction of an allylstannane with an aldehyde was by Yamamoto in 1993 (eq 4).[8] In 1999, Loh and co-workers showed a similar transformation was also effected



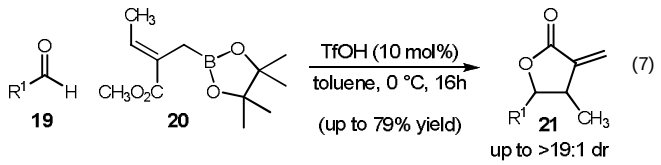
(5)

in water (eq 5).[9] List and co-workers recently reported that the addition of allyl silane

(6)

[7] a) Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475. b) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053.
[8] a) Gevorgyan, V.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 1313. b) Kadota, I.; Kawada, M.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 7439.
[9] Loh, T. P.; Xu, J. *Tetrahedron Lett.* **1999**, *40*, 2431.

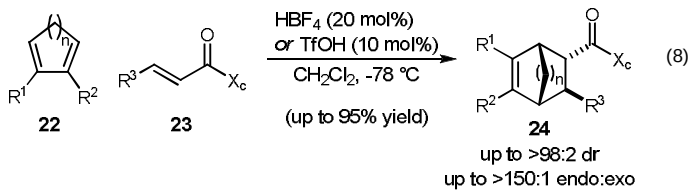
17 to acetals **16** can be performed with several different Brønsted acids with very low catalyst loadings (eq 6).[10] Hall and co workers reported that the addition of chiral allyl boronate **20** to aldehydes **19** could be catalyzed by either triflic acid or triflimide



(7)

(eq 7).[11] Triflimide has also been reported to catalyze the Mukaiyama aldol reaction, but it was not determined that a proton was the actual catalyst.[12] Triflic acid can also catalyze the condensation of aldehydes with phenol at elevated pressures.[13]

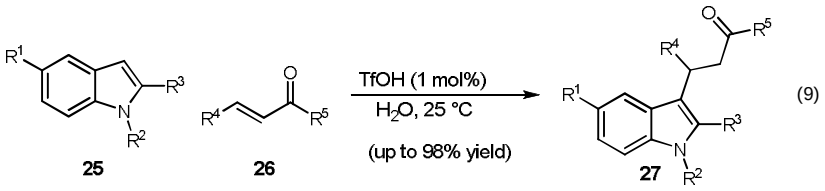
In 1942, Wassermann reported that trichloroacetic acid accelerated the rate of the Diels-Alder reaction between cyclopentadiene and benzoquinone.[14] More recently



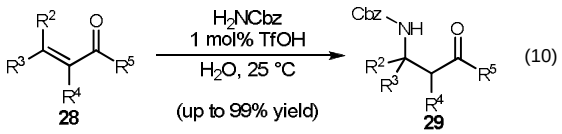
(8)

Diels-Alder reactions utilizing chiral nonracemic α,β–unsaturated ketones **22** were found to proceed with high levels of diastereoselectivity with either triflic acid or

[10] Kampen, D.; List, B. *Synlett* **2006**, 2589.
[11] a) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. b) Elford, T. G.; Arimura, Y.; Yu, S. H.; Hall, D. G. *J. Org. Chem.* **2007**, *72*, 1276.
[12] a) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45. b) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48.
[13] Ohishi, T.; Kojima, T.; Matsuoka, T.; Shiro, M.; Kotsuki, H. *Tetrahedron Lett.* **2001**, *42*, 2493.
[14] a) Wassermann, A. *J. Chem. Soc.* **1942**, 618. b) Wassermann, A. *J. Chem. Soc.* **1942**, 623.



tetrafluoroboric acid as a catalyst (eq 8).[15] Wang and co-workers recently demonstrated the triflic acid catalyzed Michael additions of indoles **25** to α,β–unsaturated ketones **26** (eq 9).[16] Brønsted acids have been shown to be capable catalysts for the hetero-Michael



addition as well (eq 10).[17] Spencer and coworkers demonstrated that Lewis acids were only effective in this reaction upon release of a Brønsted acid. They have suggested that Brønsted acids may be the active catalyst in more reactions that utilize Lewis acids than is typically assumed.[18] Another example of the use of triflic acid to activate α,β-unsaturated ketones and imides for the addition of azide will be discussed in a later chapter.

Maruoka and coworkers recently reported two different Brønsted acid catalyzed additions of aryl diazoacetates to either α,β–unsaturated aldehydes **29** (eq 11)[19] or aryl aldehydes **32** (eq 12).[20]

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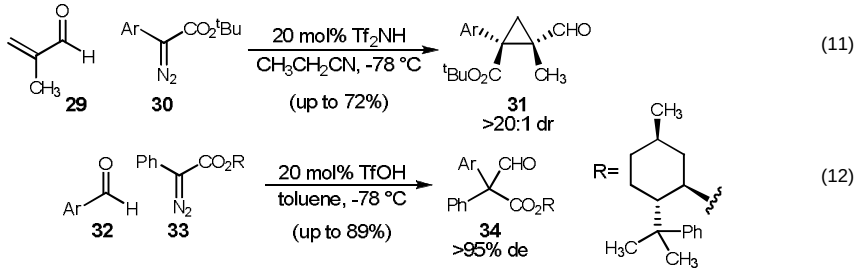
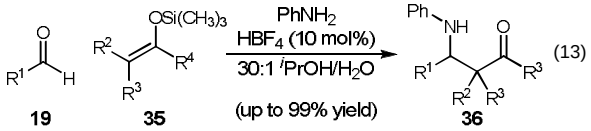
[15] a) Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1995**, *60*, 6652. b) Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Lecumberri, A.; Linden, A. *J. Am. Chem. Soc.* **2002**, *124*, 10288.
[16] Zhang, H. B.; Liu, L.; Liu, Y. L.; Chen, Y. J.; Wang, J.; Wang, D. *Synth. Comm.* **2007**, *37*, 173.
[17] Wabnitz, T. C.; Spencer, J. B. *Org. Lett.* **2003**, *5*, 2141.
[18] Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.-Eur. J.* **2004**, *10*, 484.
[19] Hashimoto, T.; Naganawa, Y.; Kano, T.; Maruoka, K. *Chem. Commun.* **2007**, 5143.

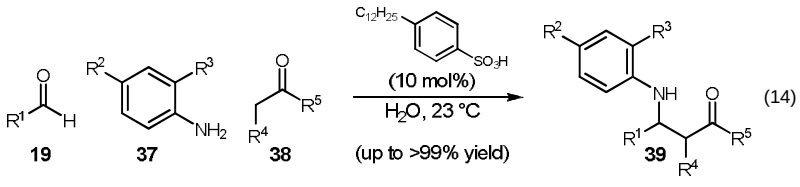
Figure 2. Maruoka's Brønsted Acid Catalyzed Aryl Diazoacetate Additions



1. 3. Achiral Bronsted Acid Catalyzed Additions to Imines



Brønsted acids have been utilized in the Mannich reaction since its inception,[21] but typically in stoichiometric amounts.[22] In 1999, Akiyama and co-workers showed that the Mannich reaction could be catalyzed by tetrafluoroboric acid in the presence of water (eq 13).[23] However, the reaction could be performed with water as the solvent only with



the addition of a surfactant.[24] At the same time, Kobayashi and coworkers demonstrated

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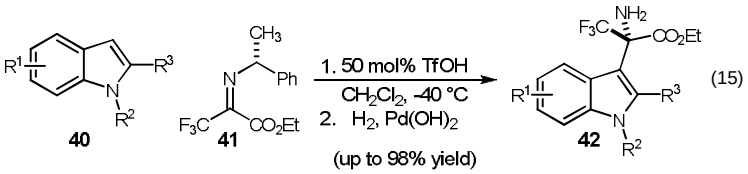
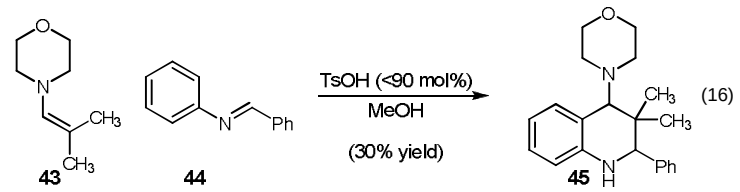
[20] Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 2434.
[21] Mannich, C. *Arch. Pharm. (Weinheim, Ger.)* **1917**, *255*, 261.
[22] In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I., Eds. Pergamon Press: Oxford, 1991; Vol. 2, pp 893.
[23] Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1045.
[24] a) Akiyama, T.; Takaya, J.; Kagoshima, H. *Synlett* **1999**, 1426. b) Akiyama, T.; Takaya, J.; Kagoshima, H. *Adv. Synth. Catal.* **2002**, *344*, 338.



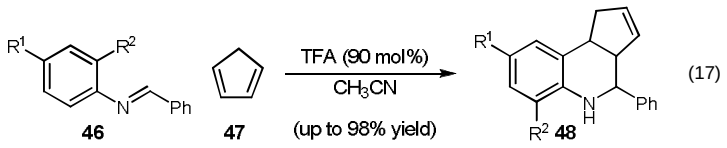
(15)

that the addition of a long alkyl chain to benzene sulfonic acid allowed it to act as surfactant and Brønsted acid to catalyze the Mannich reaction with water as the solvent (eq 14).[25] Triflic acid has been used as a catalyst for the aza-Darzens reaction as well, but will be discussed in a later chapter. The triflic acid catalyzed Friedel-Crafts reaction of imine **41** with indoles **40** has also been reported (eq 15).[26]



(16)

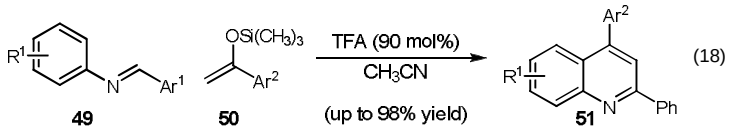
Similar activation of imines is utilized in the aza-Diels-Alder reaction. Tomoda and co-workers were the first to demonstrate that a catalytic amount of tosic acid promoted the cycloaddition of enamine **43** with imine **44** (eq 16).[27] Grieco and co-workers reported the aza-Diels-Alder reaction of aryl imines **46** with cyclopentadiene (**47**) in the



(17)

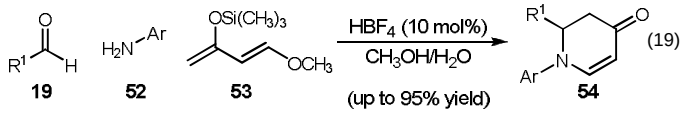
[25] a) Manabe, K.; Mori, Y.; Kobayashi, S. *Synlett* **1999**, 1401. b) Manabe, K.; Kobayashi, S. *Org. Lett.* **1999**, *1*, 1965. c) Manabe, K.; Mori, Y.; Kobayashi, S. *Tetrahedron* **2001**, *57*, 2537.
[26] Abid, M.; Teixeira, L.; Torok, B. *Org. Lett.* **2008**, *10*, 933.
[27] Nomura, Y.; Kimura, M.; Takeuchi, Y.; Tomoda, S. *Chem. Lett.* **1978**, 267.

presence of a substoichiometric amount of trifluoroacetic acid (eq 17).[28] The same transformation was shown to be catalyzed by triphenylphosphonium perchlorate.[29] Triflic



(18)

acid was found to be the most proficient catalyst for the aza-Diels-Alder reaction of aryl imines **49** with silyl enol ethers **50** (eq 18).[30] Akiyama and co-workers demonstrated that tetrafluoroboric acid was an effective catalyst for the aza-Diels-Alder reaction when aryl imines are the dienophile (eq 19).[31]



(19)

1. 4. Hydrogen Bond Induced Asymmetric Organocatalysis

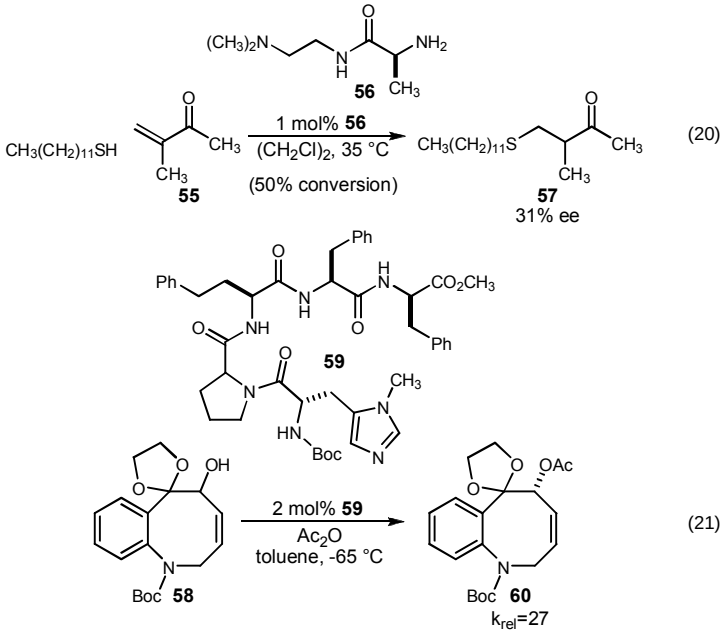
It is a seemingly natural progression then to investigate whether the proton can be used for asymmetric catalysis. Asymmetric catalysts that utilize protons or hydrogen bonds for activation could avoid some of the toxicity that exists in reactions involving metals. These catalysts would be metal free and thus represent an organocatalyst, an area which has seen rapid growth in recent years such that there is now reported a diversity of transformations that can be performed catalytically without the presence of metals and

[28] Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855.
[29] Nagarajan, R.; Chitra, S.; Perumal, P. T. *Tetrahedron* **2001**, *57*, 3419.
[30] Akiyama, T.; Nakashima, S.; Yokota, K.; Fuchibe, K. *Chem. Lett.* **2004**, *33*, 922.
[31] Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831.

with a high level of enantioselectivity.[32] These reactions might also be adapted to water, in a manner similar to enzymes, and thereby reduce the amount of organic waste produced. Ideally the catalysts would be cost effective to produce and achieve high turnover numbers.

Asymmetric catalysis using chiral organocatalysis will ultimately be compared to enzymatic catalysis. Enzymes are known to bind substrates in a highly selective manner utilizing a variety of intermolecular forces. They can lower the activation barrier to various transformations using hydrogen bonding, strategically located acids and bases, and even covalent bonds. Nature is therefore one of the inspirations for the idea of utilizing hydrogen bonds for asymmetric catalysis as well as asking whether the proton

Figure 3. Inoue's and Miller's Peptides for Asymmetric Catalysis



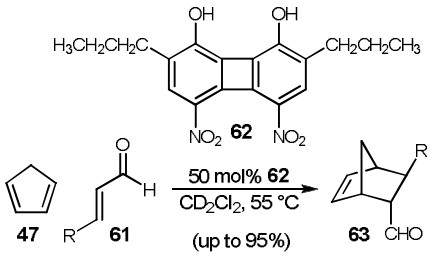
can achieve similar levels of activation and organizational control as metals. Inoue's

[32] a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726. b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

pioneering efforts in this area demonstrated that short peptide fragments were able to provide some asymmetric induction (eq 20).[33] Miller has developed, in recent years, several short peptides as effective asymmetric catalysts (eq 21).[34] Organocatalysts which use a proton for activation utilize two different types of hydrogen bonds. Hydrogen bonding catalysts which are neutral (L-H) utilize a polar covalent hydrogen. Hydrogen bonding catalysts that are positively charged ($[L\text{-}H]^+$) utilize a polar ionic covalent bond. An important consequence is that abstraction of a proton from a polar covalent hydrogen bonds results in an anion, whereas the same transformation with a polar ionic hydrogen bond results in a neutral "ligand".

1. 5. Asymmetric Catalysis Involving Polar Covalent Hydrogen Bonds

1. 5. 1. Hydroxyl Containing Catalysts



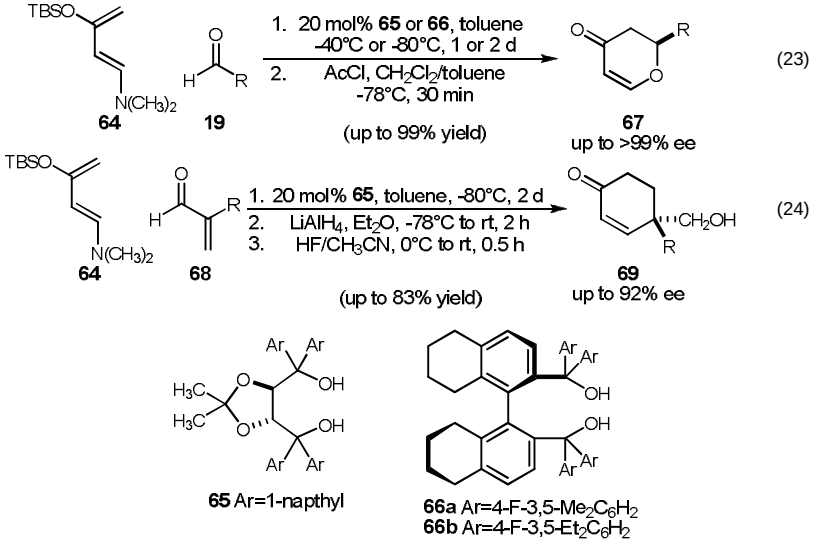
(22)

Asymmetric catalysis involving activation through hydrogen bonding has been accomplished by several different hydrogen bonding sources. Many of these catalysts involve activation using polar covalent hydrogen bonds. Chiral diols, such as TADDOL (α,α,α',α'-tetraaryl-1,3-dioxolan-4,5-dimethanol) and BINOL (1,1'-bi-2-napthol), are one representative of this class. As early as 1990, Kelly and coworkers were able to show that

[33] Inoue, S.; Kawano, Y. *Die Makromolekulare Chemie* **1979**, *180*, 1405.
[34] Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601.

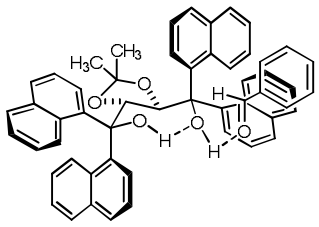
biphenylene diol **62** could catalyze the Diels-Alder reaction by activating aldehydes **61** through hydrogen bonding (eq 22).[35] In 2003, Rawal and co-workers were the first to use

Figure 4. Chiral Diol Catalyzed Asymmetric Diels-Alder Reaction



TADDOL **65** to catalyze the asymmetric hetero-Diels-Alder reaction by activating a carbonyl through hydrogen bonding (eq 23).[36]

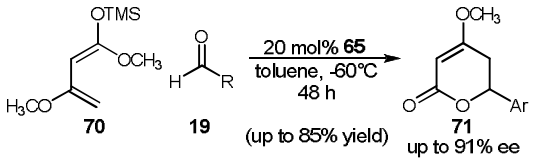
Figure 5. Computational Transition State Model for Rawal's Asymmetric Hetero Diels-Alder Reaction



Computational studies reveal the presence of hydrogen bonding in the enantiodetermining transition states (Figure 5).[37] Further studies found that the related

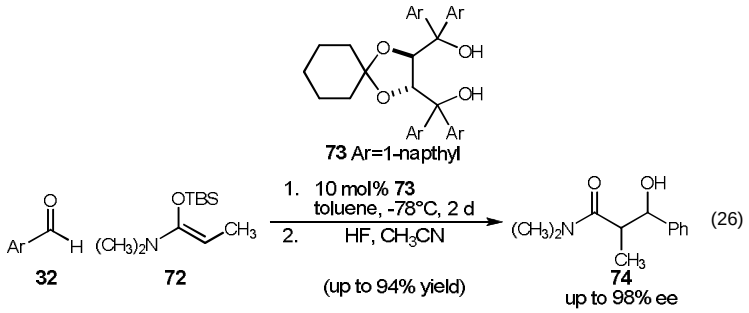
[35] Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381.
[36] Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146.

diol, BAMOL **66**, is a more efficient catalyst for the asymmetric hetero-Diels-Alder reaction.[38] The TADDOL **65** was also shown to activate α,β–unsaturated aldehydes **68** for the asymmetric Diels-Alder reaction (eq 24).[39] An asymmetric hetero-Diels-Alder



(25)

reaction catalyzed by TADDOL **65** using Brassard's Diene **70** was reported by Ding and co-workers (eq 25).[40] TADDOL **65** was also successful in catalyzing the asymmetric *N*-nitroso aldol reaction.[41] An asymmetric Mukaiyama aldol has been disclosed using TADDOL **73** as catalyst (eq 26).[42]



(26)

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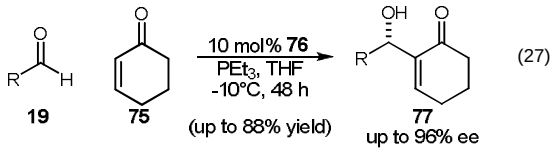
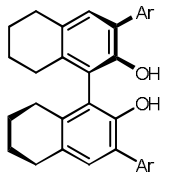
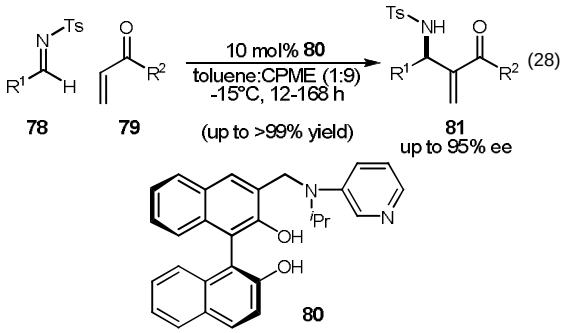
[37] Anderson, C. D.; Dudding, T.; Gordillo, R.; Houk, K. N. *Org. Lett.* **2008**, *10*, 2749.
[38] Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336.
[39] Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5846.
[40] Du, H. F.; Zhao, D. B.; Ding, K. L. *Chem.-Eur. J.* **2004**, *10*, 5964.
[41] Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080.
[42] McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 6130.

Schaus and co-workers have utilized the saturated BINOL **76** to activate cyclic α,β– unsaturated ketones **75** for asymmetric Mortia-Baylis-Hillman reactions (eq 27).[43]





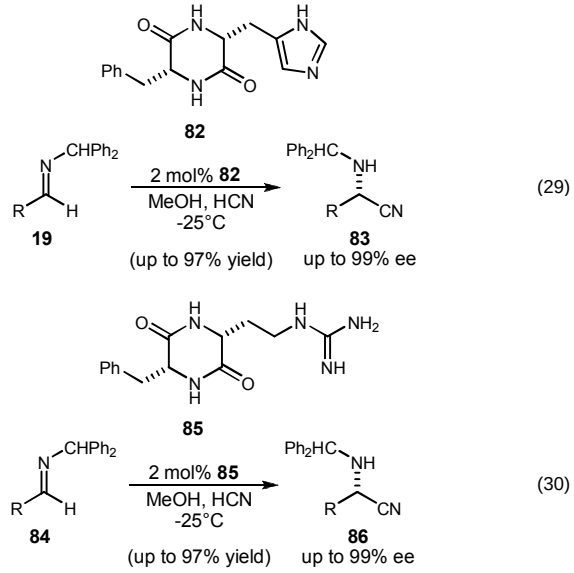
These results have led to the development of a bifunctional BINOL **80** which can catalyze the asymmetric Morita-Baylis-Hillman reaction free of a separate nucleophile (eq 28).[44]



[43] a) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231. b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094.
[44] Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680.

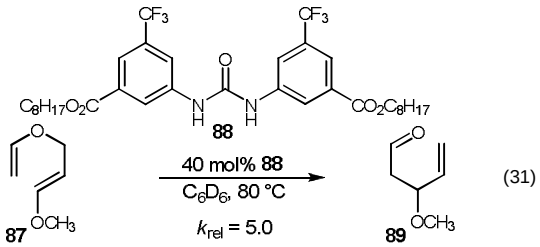
1. 5. 2. Urea and Thiourea Based Catalysts

Figure 6. Cyclic Peptide Catalysts



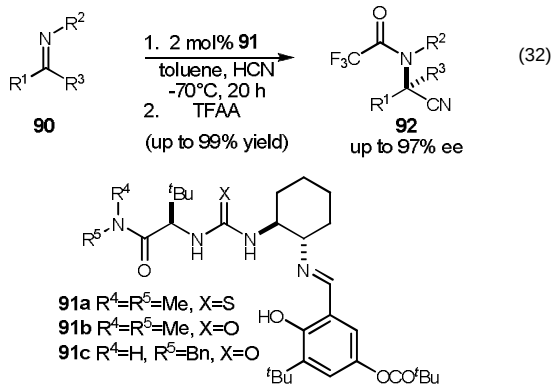
Inoue and co-workers reported that cyclic dipeptide **82** was an effective catalyst for the asymmetric hydrocyanation of imines **19** (eq 29).[45] Lipton and co-workers used a similar cyclic dipeptide **85** for the catalytic asymmetric Strecker reaction (eq 30).[46]

Thioureas and ureas represent two of the most heavily studied sources of polar covalant bonds for use in asymmetric catalysis. As early as 1990, Etter and coworkers



[45] b) Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181. a) Oku, J. I.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229.
[46] Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910.

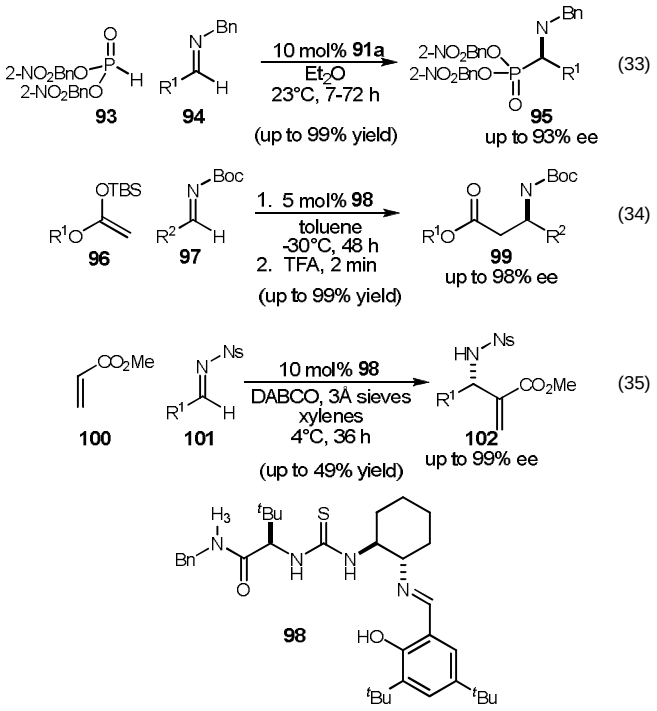
were able to demonstrate that diarylureas form hydrogen bonded complexes with the oxygen of ketones.[47] In 1995, Curran and coworkers reported the use of diarylurea **88** as a catalyst for the Claisen rearrangement (eq 31).[48] Then in 1998, Jacobsen and



co-workers developed a highly enantioselective thiourea catalyst **91** for the Strecker reaction of aldimines and ketimines **90** (eq 32). Further studies have indicated that imines are activated by hydrogen bonding with the hydrogens of the thiourea **91**. The activation of imines allows for the stereoselective attack of a variety of electrophiles such as phosphite **93**[49] (eq 33) and silyl ketene acetals **96** (eq 34).[50] Thiourea **98** was also shown to catalyze the asymmetric aza-Baylis-Hillman reaction (eq 35).[51]

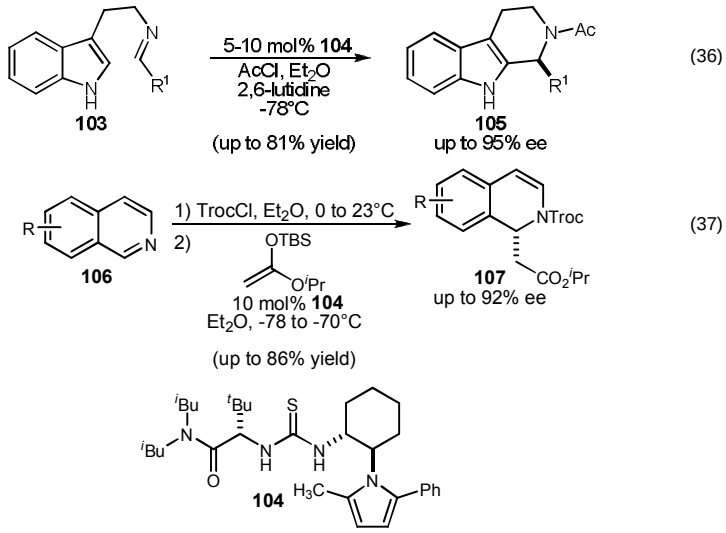
[47] Etter, M. C.; Urbanczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415.
[48] Curran, D. P.; Lung, H. K. *Tetrahedron Lett.* **1995**, *36*, 6647.
[49] Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.
[50] Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
[51] Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701.

Figure 7. Asymmetric Reactions Catalyzed by Thioureas



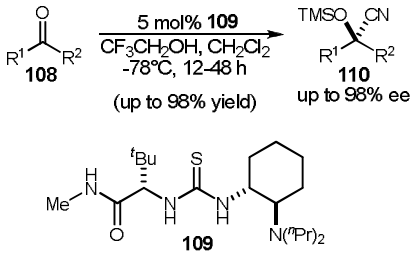
Alteration of the imine affords thiourea catalyst **104** which can catalyze the asymmetric acyl-Pictet-Spengler reaction (eq 36)[52] as well as the asymmetric

Figure 8. Thiourea catlalyzed Pictet-Spengler and acyl-Mannich reactions



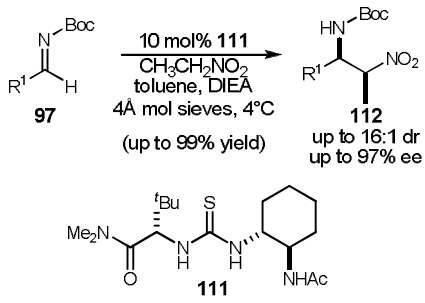
[52] Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.

acyl-Mannich reaction of isoquinolines **106** (eq 37).[53]



(38)

The thiourea **109** has been shown to activate ketones **108** in the asymmetric cyanosilylation reaction (eq 38).[54] Jacobsen and co-workers developed the thiourea **111**



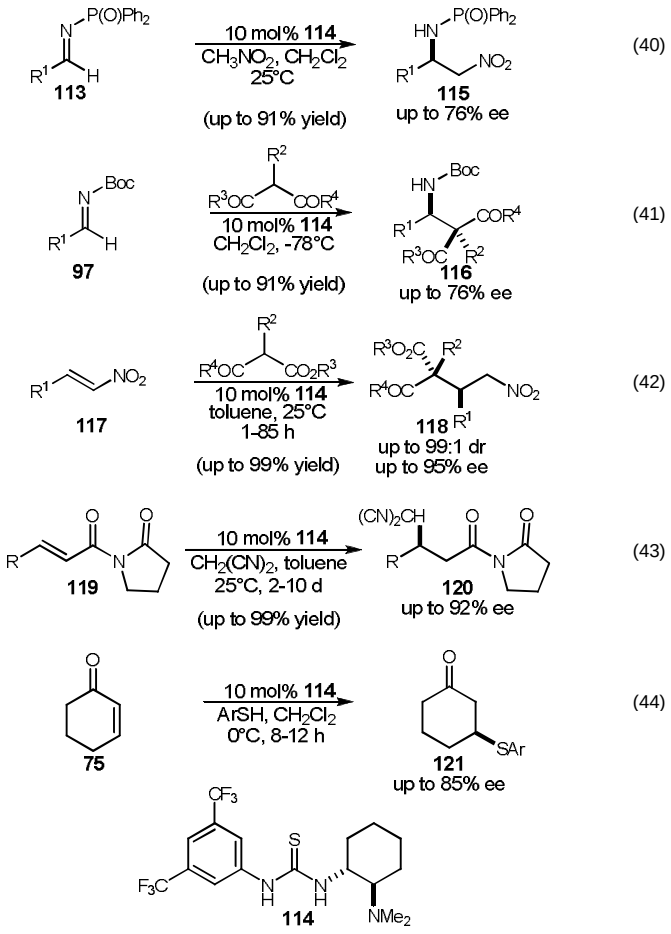
(39)

for catalysis of the asymmetric aza-Henry reaction (eq 39).[55] However, Takemoto and co-workers utilized a similar bifunctional catalyst **114** earlier for the catalysis of the asymmetric aza-Henry reaction (eq 40).[56] It is proposed that catalysis is achieved in both cases by activation of the imine through hydrogen bonds. Takemoto and co-workers have

[53] Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700.
[54] Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.
[55] Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466.
[56] Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625.

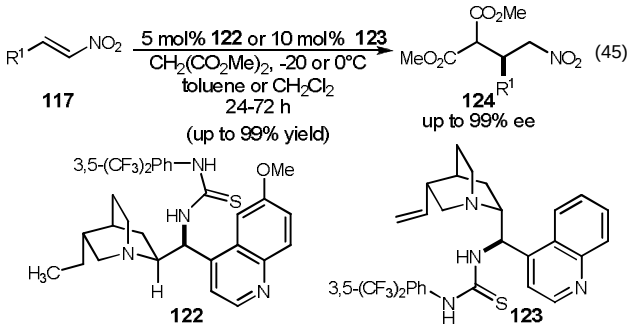
subsequently reported the asymmetric direct Mannich reaction using **114** as a catalyst (eq 41).[57]

Figure 9. Asymmetric Reactions Catalyzed by Takemoto's Thiourea

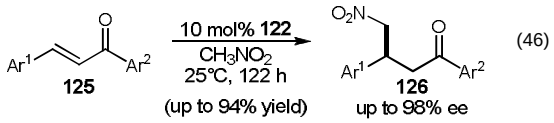


The Takemoto thiourea catalyst **114** was initially developed for the activation of nitroolefins **117** for asymmetric conjugate addition reactions with malonates (eq 42).[58] The Takemoto catalyst **114** was also successful in the catalysis of the asymmetric

[57] Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, 2571.
[58] a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.



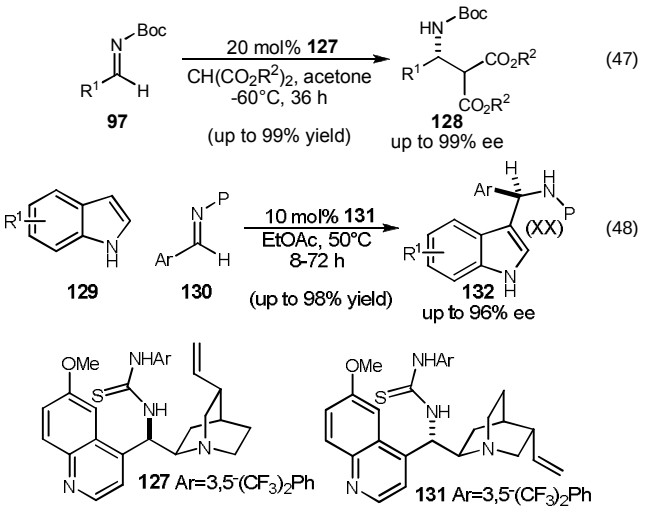
conjugate addition of malononitriles to α,β–unsaturated imides **119** (eq 43).[59] Similar bifunctional thiourea catalysts **122** and **123** utilizing a cinchonidine moiety were reported concurrently by Connon and Dixon for the asymmetric conjugate addition of malonates to nitroolefins **117** (eq 45).[60] Soós and co-workers used cinchonidine **122** to catalyze the asymmetric conjugate addition of nitromethane to α,β–unsaturated ketones **125**



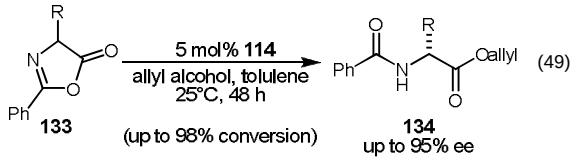
(eq 46).[61] Catalysts **127** and **131** have been used by Deng for the catalytic asymmetric Mannich (eq 47)[62] and Friedel-Crafts reactions (eq 48) respectively.[63]

[59] Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032.
[60] a) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367. b) Ye, J. X.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.
[61] Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967.
[62] Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048.
[63] Wang, Y. Q.; Song, J.; Hong, R.; Li, H. M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156.

Figure 10. Cinchonidine Thiourea Asymmetric Catalysts



Berkessel and co-workers have utilized the bifunctional thiourea **114** to catalyze the dynamic kinetic resolution of azlactones **133** (eq 49).[64]



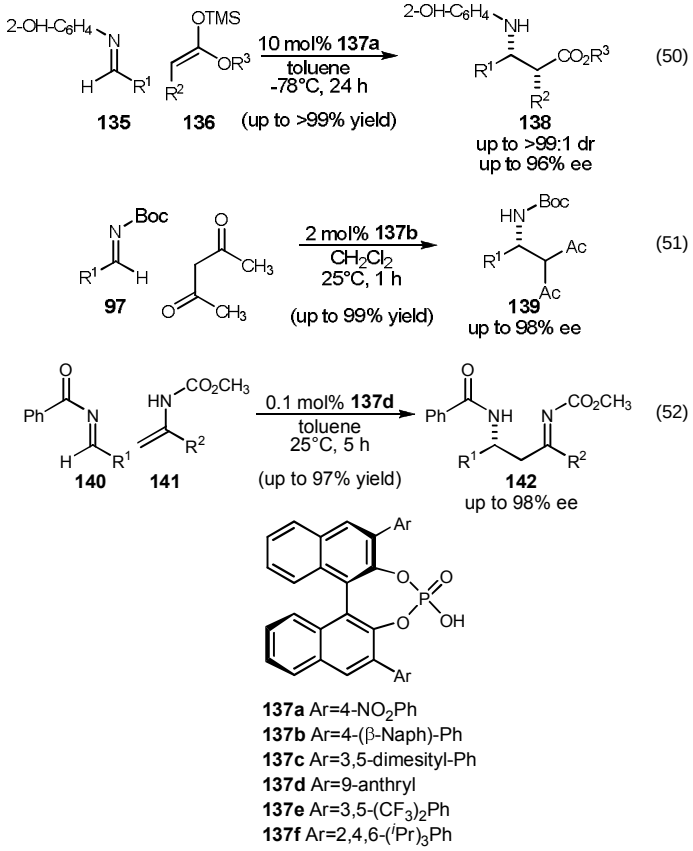
1. 5. 3. Chiral Phophoric Acid Catalysts

The research groups of Terada and Akiyama reported independently nearly identical BINOL derived chiral phosphoric acids **137**. A wide variety of asymmetric transformations have now been reported using catalysts of this type as a result of the considerable attention they have garnered. Akiyama and co-workers reported catalyst **137a** was effective for the indirect Mannich reaction of imines **135** with ketene silyl

[64] a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Muller, T. N.; Lex, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 807. b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Muller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898.

acetals **136** (eq 50).[65] Terada and co-workers have used catalyst **137b** in the asymmetric direct Mannich reaction between *N*-Boc-protected imines **97** and acetyl acetone (eq 51).[66] They have also reported the catalytic asymmetric Mannich reaction of acyl imines **140** with acyl enamines **141** using catalyst **137d** (eq 52).[67] There are several other more

Figure 11. Chiral Phosphoric Catalyzed Asymmetric Reactions



recent reports of direct and indirect Mannich type reactions utilizing similar catalysts with comparable yields and enantioselectivities.[68]

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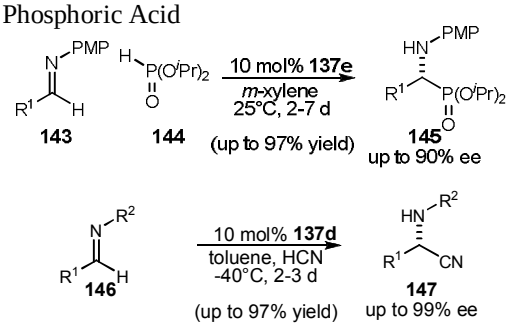
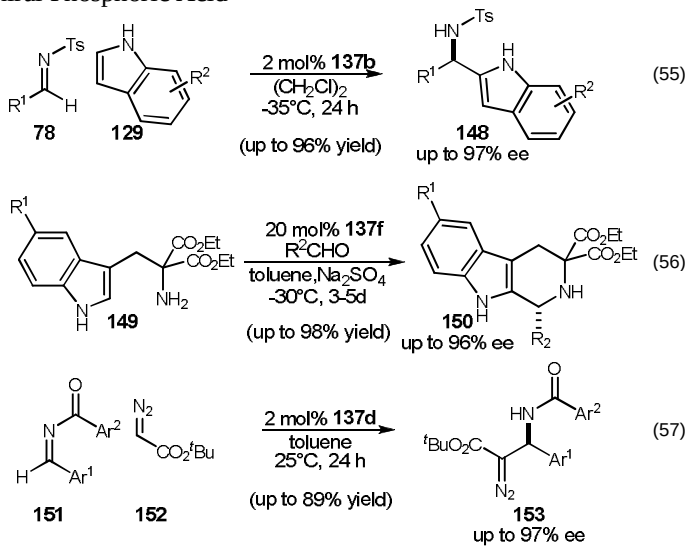
[65] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.
[66] Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
[67] a) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 2254. b) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336.
[68] a) Chen, X. H.; Xu, X. Y.; Liu, H.; Cun, L. F.; Gong, L. Z. *J. Am. Chem. Soc.* **2006**, *128*, 14802. b) Guo, Q. X.; Liu, H.; Guo, C.; Luo, S. W.; Gu, Y.; Gong, L. Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790. c) Jiang, J.;

Figure 12. Asymmetric Nucleophilic Additions Catalyzed by Chiral Phosphoric Acid



Other nucleophiles such as phosphite **144** and cyanide can also be added to imines with high enantioselectivity in the presence of catalyst **137** (Figure 12).[69] Chiral

Figure 13. Asymmetric Friedel-Crafts Reactions Catalyzed by Chiral Phosphoric Acid



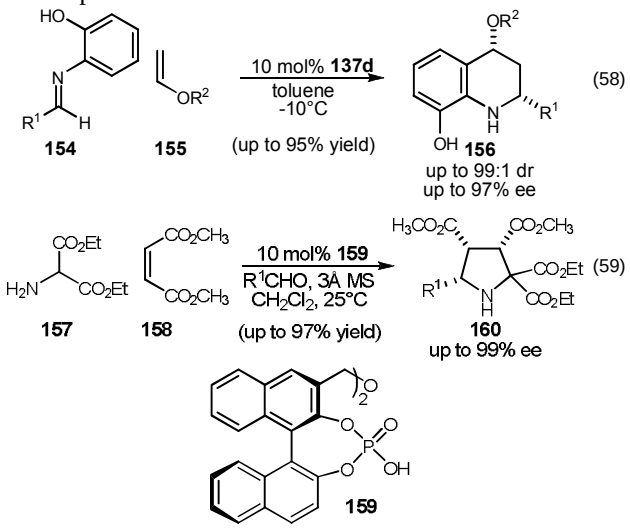
Yu, J.; Sun, X. X.; Rao, Q. Q.; Gong, L. Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 2458. d) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399. e) Sickert, M.; Schneider, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3631. f) Rueping, M.; Antonchick, A. P. *Org. Lett.* **2008**, *10*, 1731.

[69] a) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583. b) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 2617.

non-racemic phosphoric acids have also been shown to be effective catalysts for several asymmetric Friedel-Crafts type reactions (Figure 13).[70]

Akiyama and co-workers have reported the asymmetric inverse electron demand aza-Diels-Alder reaction using **137d** as a catalyst (eq 58).[71] The asymmetric aza-Diels-Alder reaction in which the imine is the dienophile has also been reported with similar

Figure 14. Asymmetric Cycloaddition Reactions Catalyzed by Chiral Phosporic Acid



catalysts.[72] Gong and co-workers recently reported an asymmetric 1,3-dipolar

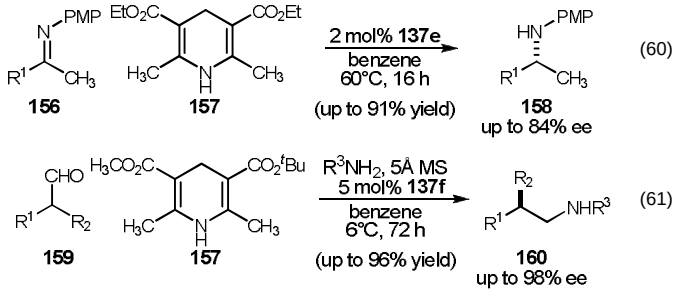
[70] a) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. b) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360. c) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc*. **2007**, *129*, 292. d) Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synth. Catal*. **2007**, *349*, 1863. e) Kang, Q.; Zhao, Z. A.; You, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. f) Kang, Q.; Zheng, X. H.; You, S. L. *Chem.-Eur. J.* **2008**, *14*, 3539. g) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc*. **2006**, *128*, 1086. h) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 4016. i) Rueping, M.; Sugiono, E.; Theissmann, T.; Kuenkel, A.; Kockritz, A.; Pews-Davtyan, A.; Nemati, N.; Beller, M. *Org. Lett.* **2007**, *9*, 1065.

[71] Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc*. **2006**, *128*, 13070.

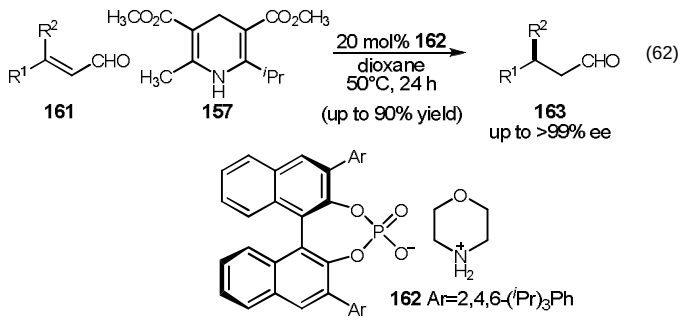
[72] a) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141. b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796. c) Rueping, M.; Azap, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 7832. d) Liu, H.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Org. Lett.* **2006**, *8*, 6023.

cycloaddition reaction with in situ formation of an azomethine ylide in the presence of catalyst **159** (eq 59).[73]

Figure 15. Asymmetric Transfer Hydrogenations Catalyzed by Chiral Phosporic Acid



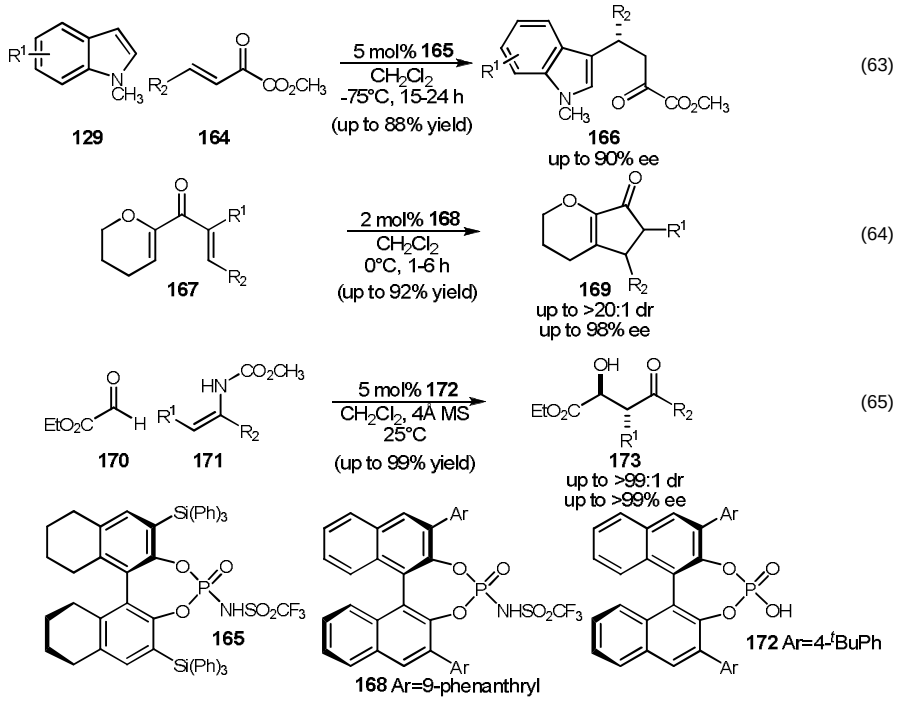
Rueping and co-workers were the first to report the use of chiral phosphoric acid **137e** to catalyze the asymmetric transfer hydrogenation of imines **156** (eq 60).[74] There are now several reports of similar approaches to the reduction of imines as well as activated olefins.[75] List and co-workers have demonstrated an elegant application of this system for



[73] Chen, X. H.; Zhang, W. Q.; Gong, L. Z. *J. Am. Chem. Soc*. **2008**, *130*, 5652.
[74] Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781.
[75] a) Kang, Q.; Zhao, Z. A.; You, S. L. *Org. Lett.* **2008**, *10*, 2031. b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 7424. c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2006**, *128*, 84. d) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6751. e) Rueping, M.; Antonchick, A. R.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3683. f) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001.

dynamic kinetic resolution (eq 61).[76] A rather significant discovery in this field is the retention of asymmetric induction with the addition of an achiral amine for the reduction of α,β-unsaturated aldehydes (eq 62).[77]

Figure 16. Asymmetric Conjugate Addition, Nazarov, and Aldol Reaction Catalyzed by Chiral Phosphoric and Phosphorimide Acids



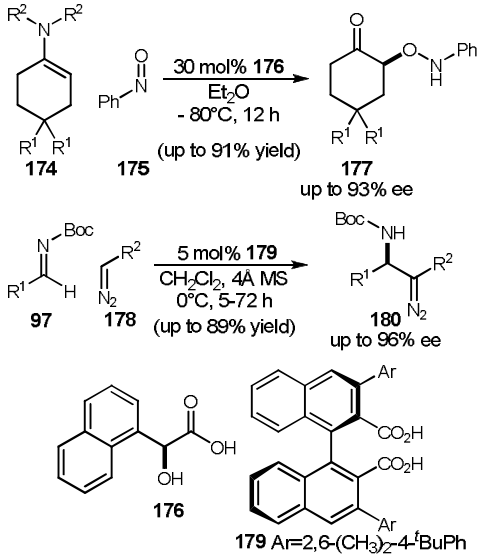
Chiral non-racemic phosphoric acid has also been found to provide asymmetric induction in reactions involving carbonyl substrates. Rueping and co-workers have reported the asymmetric Nazarov reaction catalyzed by **168** (eq 64)[78] and the conjugate addition of indoles **129** to α,β-unsaturated α-keto esters **164** catalyzed by **165** (eq 63).[79]

[76] Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.
[77] a) Mayer, S.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193. b) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.
[78] Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593.
[79] Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2097.

Terada and co-workers reported the asymmetric addition of enamines **171** to ethyl glyoxylate (**170**) with **172** as catalyst (eq 65).[80]

1. 5. 4. Chiral Carboxylic Acid Catalysts

Figure 17. Asymmetric Reactions Catalyzed by Chiral Carboxylic Acids



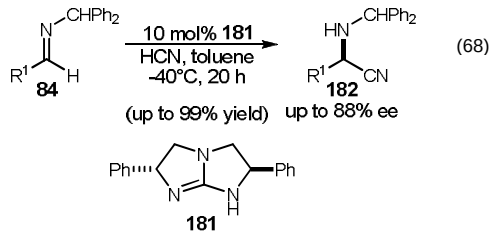
Yamamoto and co-workers utilized the structurally simplified glycolic acid **176** for catalysis of the asymmetric *O*-nitroso aldol reaction (eq 66).[41] In 2007, Maruoka and coworkers reported the asymmetric Mannich reaction using the BINOL inspired dicarboxylic acid catalyst **179** (eq 67).[81]

1. 5. 5. Chiral Guanidine Catalysts

Corey and co-workers reported that guanidine **181** was an efficient catalyst for the asymmetric Strecker reaction (eq 68).[82] The guanidinium salt was never isolated, chararacterized, and used in the reaction and is unlikely to be the active catalyst. It is

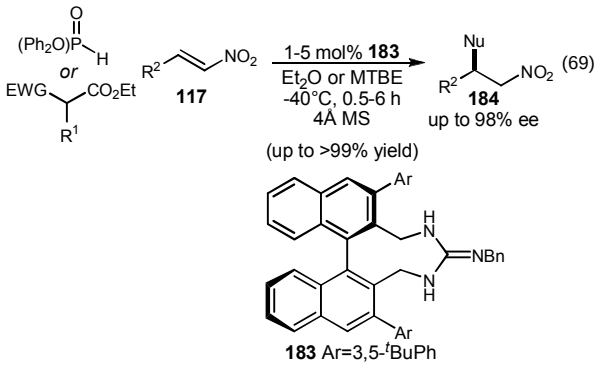
[80] Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4122.
[81] a) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. b) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556.
[82] Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157.

significant that similar catalysts have been utilized recently for an asymmetric Diels-Alder reaction[83] and an asymmetric conjugate addition to nitroalkenes in their neutral form.[84]



(68)

More recently the binaphthyl guanidine **183** was shown to be an efficient catalyst for activation of nitroalkenes **117** for enantioselective addition of nucleophiles (eq 69).[85]

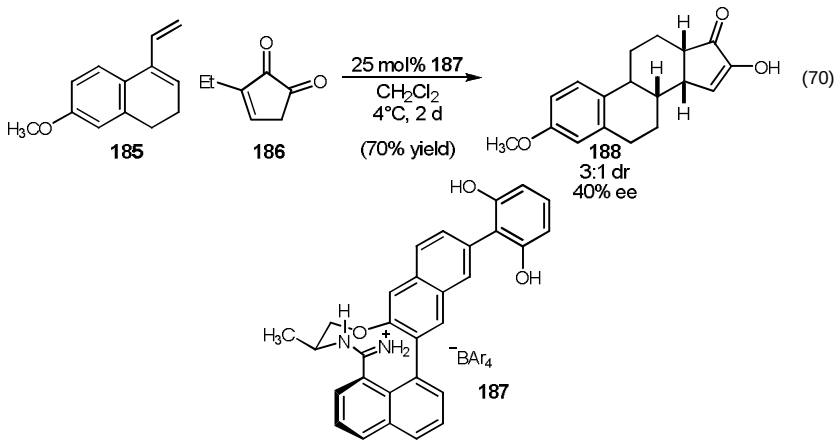


(69)

1. 6. Asymmetric Catalysis Involving Polar Ionic Hydrogen Bonds

There are only a couple of examples of asymmetric catalysis in which a polar ionic hydrogen bond is involved. Göbel and co-workers were the first to demonstrate that an

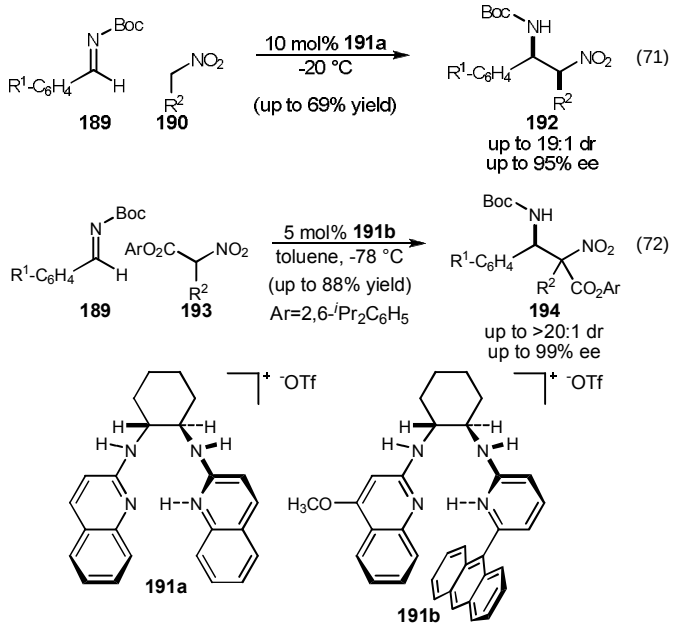
[83] Shen, J.; Nguyen, T. T.; Goh, Y. P.; Ye, W. P.; Fu, X.; Xu, J. Y.; Tan, C. H. *J. Am. Chem. Soc.* **2006**, *128*, 13692.
[84] Fu, X.; Jiang, Z.; Tan, C. H. *Chem. Commun.* **2007**, 5058.
[85] a) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. b) Terada, M.; Ikehara, T.; Ube, H. *J. Am. Chem. Soc.* **2007**, *129*, 14112.



amidinium ion **187** could catalyze an asymmetric Diels-Alder reaction (eq 70).[86]

More recently, Johnston and co-workers reported a chiral bisamidine (BAM) that, when protonated with triflic acid (**191a**) serves as an efficient catalyst for the aza-Henry reaction (eq 71).[87] They have subsequently reported the related BAM **191b** was an

Figure 18. Chiral Bisamidine Catalyzed aza-Henry Reactions



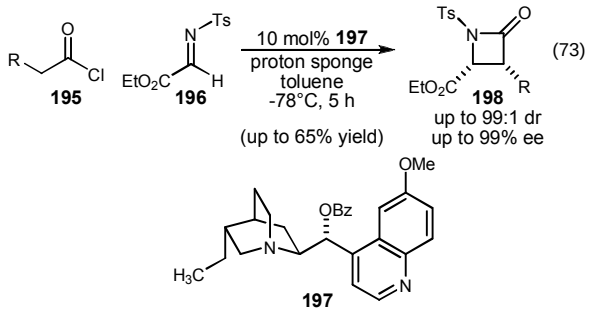
[86] a) Schuster, T.; Bauch, M.; Durner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179. b) Schuster, T.; Kurz, M.; Gobel, M. W. *J. Org. Chem.* **2000**, *65*, 1697.
[87] Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.

efficient catalyst for the addition of nitroacetates **193** to imines **189** (eq 72).[88]

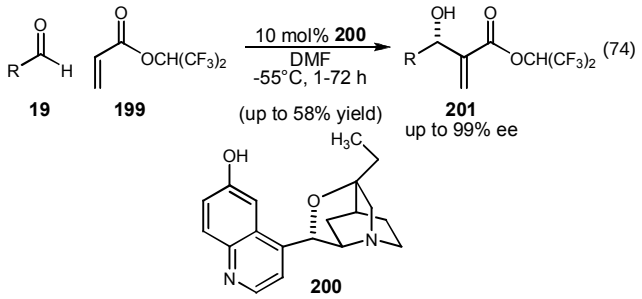
1. 7. Asymmetric Organocatalysts Involving a Hydrogen Bond in the Transition State

1. 7. 1. Cinchona Alkaloid based Catalysis

Cinchona alkaloids have proven themselves as useful ligands for metal mediated asymmetric catalysis[89] and asymmetric phase transfer catalysis.[90] Lectka and coworkers have used cinchona alkaloid **197** as a nucleophilic catalyst for the asymmetric synthesis of β–lactams **198** (eq 73) as well as in asymmetric α–halogenation reactions.[91] Molecular modeling of the the proposed transition state in this reaction indicates that a polar covalent hydrogen bond could be involved in the transition state that produces the observed reactivity and stereoselectivity.[92] Whereas the addition of Lewis acid salt has been shown to enhance the yield of β–lactam formed, the analogous use of a Brønsted acid or a polar ionic hydrogen bond has not been reported.

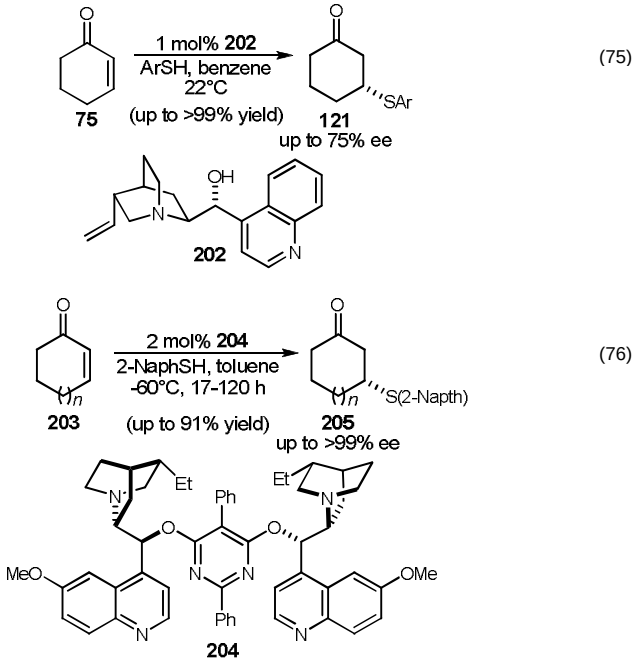


[88] a) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866. b) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466. c) Wilt, J. C.; Pink, M.; Johnston, J. N. *Chem. Commun.* **2008**, 4177.
[89] a) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483. b) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317.
[90] a) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961. b) Hoffmann, H. M. R.; Frackenpohl, J. *Eur. J. Org. Chem.* **2004**, 4293. c) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.
[91] France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592.
[92] Taggi, A. E.; Hafez, A. M.; Dudding, T.; Lectka, T. *Tetrahedron* **2002,** 58, 8351.



The use of cinchona alkaloid **200** as a nucleophilic catalyst has been developed by Hatakeyama for the asymmetric Morita-Baylis-Hillman reaction (eq 74).[93] A strategically located hydroxyl group is proposed to stabilize the intermediate enolate through a polar covalent hydrogen bond, which accounts for the observed stereoselectivity.

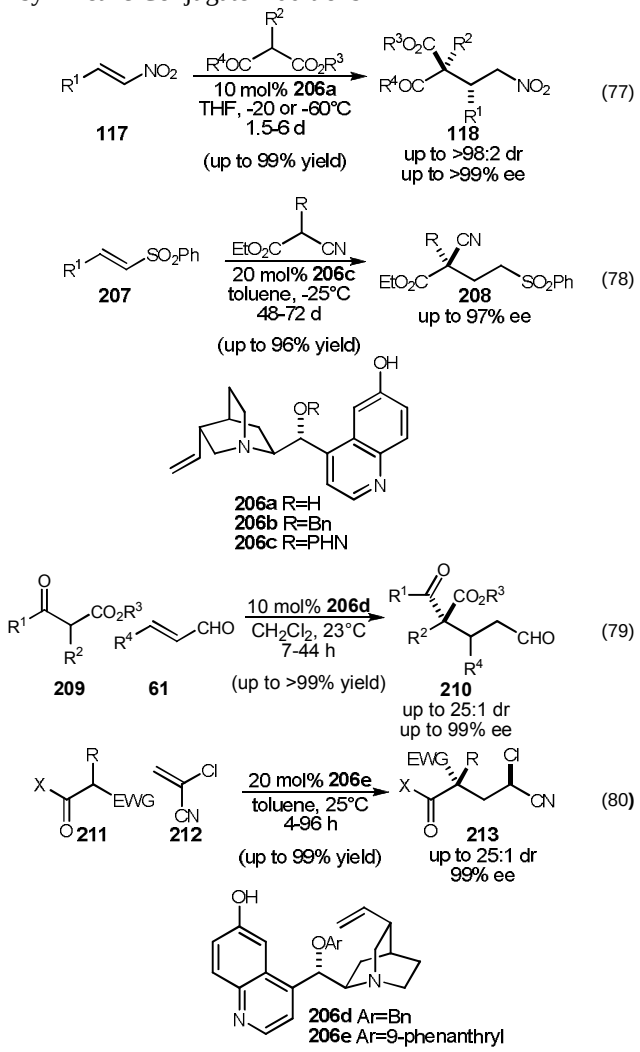
Figure 19. Cinchona Alkaloid Catalyzed Asymmetric Conjugate Addition



[93] Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103.

The asymmetric addition of thiols to cyclic enones **75** using cinchona alkaloid **202** as catalyst was proposed by Wynberg and Hiemstra to also involve bifunctional catalysis (eq 75). Using kinetic and spectroscopic data they proposed that the C-9 hydroxyl group activated the enone by a polar covalent hydrogen bond and the tertiary amine activated the thiol by deprotonation.[94] Deng and coworkers have shown more recently that high

Figure 20. Deng's Cinchona Alkaloid Catalyzed Asymmetric Conjugate Additions

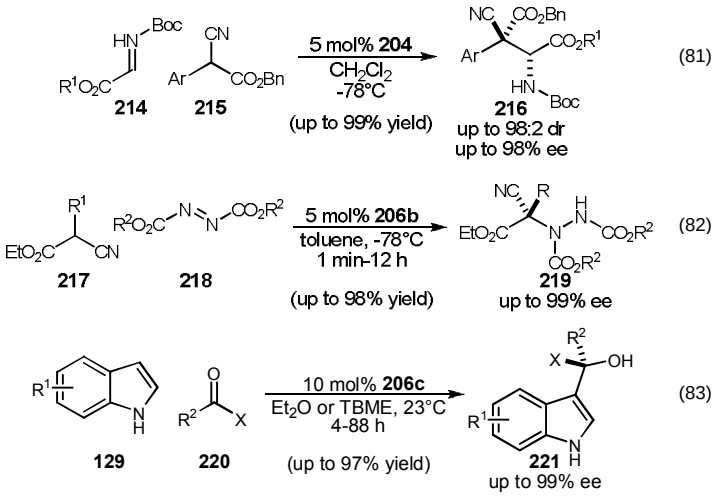


[94] Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

enantioselectivities can be obtained by tethered cinchona alkaloid **204** which lacks a hydroxyl group (eq 76).[95] No explanation has been offered for the difference in outcomes, but it is conceivable that the polar ionic hydrogen bond that exists as a result of deprotonation of the thiol subsequently provides stereocontrol to the transition state.

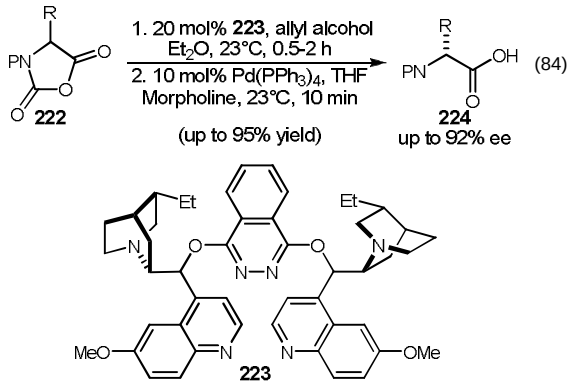
Deng and coworkers have used related cinchona alkaloids **206** for the catalysis of a variety of asymmetric 1,4-conjugate additions (*Figure 20*)[96] and more recently an asymmetric Diels-Alder reaction.[97] They have proposed that the observed stereoselectivity is a result of the ability of the catalyst to form two hydrogen bonds. A polar covalent hydrogen bond can form between the phenolic hydroxyl and the electrophile and a polar ionic hydrogen bond can form between the nucleophile and the

Figure 21. Cinchona Alkaloid Catalyzed Assymetric Mannich, Amination, and Friedel-Crafts Reactions

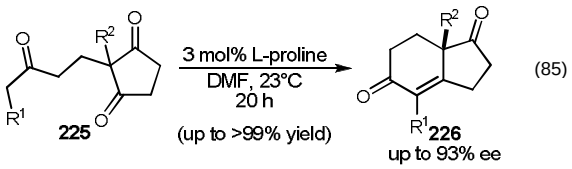


[95] McDaid, P.; Chen, Y. G.; Deng, L. *Angew. Chem. Int. Ed.* **2001**, *41*, 338.
[96] a) Wang, Y.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. b) Li, H. M.; Song, J.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948. c) Li, H. M.; Wang, Y.; Tang, L.; Wu, F. H.; Liu, X. F.; Guo, C. Y.; Foxman, B. M.; Deng, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 105. d) Li, H. M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. Wu, e. F.; Hong, R.; Khan, J.; Liu, X.; Deng, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 4301.
[97] Wang, Y.; Li, H. M.; Wang, Y. Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364.

tertiary amine. Jørgensen and coworkers were able use catalyst **204** in a catalytic asymmetric Mannich reaction (eq 81).[98] Catalysts **206b** and **206c** were also shown to be effective for the asymmetric α–amination (eq 82)[99] and Friedel-Crafts reactions (eq 83).[100] Deng and coworkers have used the formation of a polar covalent hydrogen bond between an alcohol and cinchona alkaloid **223** to effect catalytic asymmetric alcoholysis as well as dynamic kinetic resolution of *N*- and *O*-carboxy anhydrides **222** (eq 84).[101]



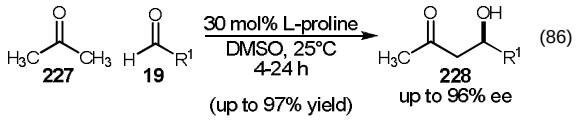
1. 7. 2. Proline Based Catalysts



A brief coment is appropriate to acknowledge a class of organocatalysts that have evolved rapidly in the past decade, but should be considered separately. In the early

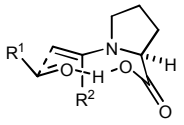
[98] Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896.
[99] a) Liu, X. F.; Li, H. M.; Deng, L. *Org. Lett.* **2005**, *7*, 167. b) Saaby, S.; Bella, M.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120.
[100] Li, H.; Wang, Y. Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063.
[101] Tian, S. K.; Chen, Y. G.; Hang, J. F.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621.

1970's Hajos and Parrish, and independently Eder, Sauer, and Wiechert reported the first asymmetric intramolecular aldol condensation using L-proline (eq 85).[102] In 2000, List, Lerner, and Barbas reported that L-proline was an efficient catalyst for asymmetric



intermolecular aldol condensations as well (eq 86).[103] Other primary amino acids and cyclic secondary amino acids are not as efficient catalysts.

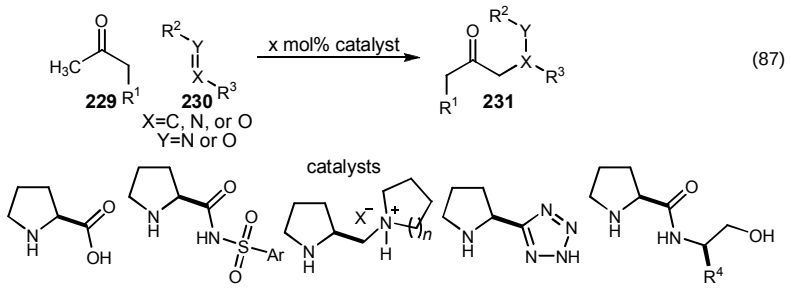
Figure 22. The Potential Transition State for Proline Based Catalysis.



A key feature of these catalysts is their formation of a covalent intermediate with a substrate. In this way, they might be considered chiral auxiliaries, as stereochemical information is translated through an entirely covalent framework. As part of the framework, studies have suggested the carboxylic acid of the enamine formed from proline forms a hydrogen bond with the aldehyde to bring the two reactants together in a highly ordered transition state[104] reminiscent of the Zimmerman-Traxler transition state

[102] a) Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496. b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.
[103] List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
[104] a) Clemente, F. R.; Houk, K. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 5766. b) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H. Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558. c) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. d) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. e) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911. f) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

(Figure 22).[105] Interestingly, the stereochemical outcome of proline catalyzed reactions can be explained in much the same way as is done with reactions in which a Zimmerman-Traxler transition state is invoked. Thus, the metal that makes up one member of the six-membered chair-like transition state can be generalized to be any metal including hydrogen. The strength of the hydrogen bonding likely determines the level of reactivity and asymmetric induction of the catalyst. Other proline based catalysts have been made in which the carboxylic acid is replaced with hydrogen bond donors such as ammonium,[106] amide,[107] sulfonamide,[108] and tetrazole[109] (eq 87). The reaction has been extended to a wide variety of electrophiles.[110]



(87)

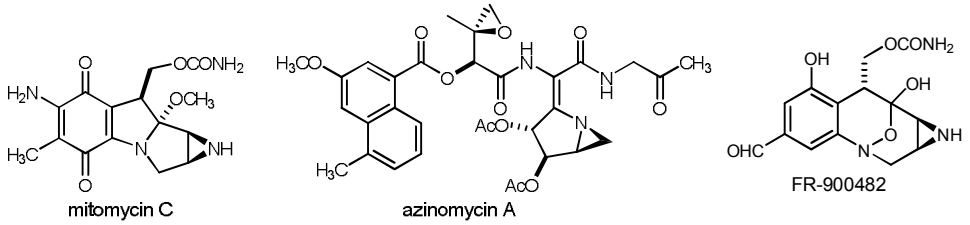
[105] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.
[106] a) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167. b) Saito, S.; Nakadai, M.; Yamamoto, H. *Synlett* **2001**, 1245.
[107] a) Kofoed, J.; Nielsen, J.; Reymond, J. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445. b) Martin, H. J.; List, B. *Synlett* **2003**, 1901. c) Tang, Z.; Jiang, F.; Yu, L. T.; Cui, X.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z.; Wu, Y. D. *J. Am. Chem. Soc.* **2003**, *125*, 5262.
[108] Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141.
[109] a) Hartikka, A.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2004**, *15*, 1831. b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 1983.
[110] a) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. b) Dahlin, N.; Bogevig, A.; Adolfsson, H. *Adv. Synth. Catal.* **2004**, *346*, 1101. c) Groger, H.; Wilken, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 529. d) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. e) Merino, P.; Tejero, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 2995. f) Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5374. g) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G. F.; Barbas, C. F. *Tetrahedron Lett.* **2001**, *42*, 199. h) Notz, W.; Tanaka, F.; Barbas, C. F. *Acc. Chem. Res.* **2004**, *37*, 580. i) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260.

CHAPTER II

STUDIES TO ELUCIDATE THE MECHANISM OF THE BRØNSTED ACID CATALYZED AZA-DARZENS REACTION

2. 1. The Biological Importance and Synthetic Utility of Aziridines

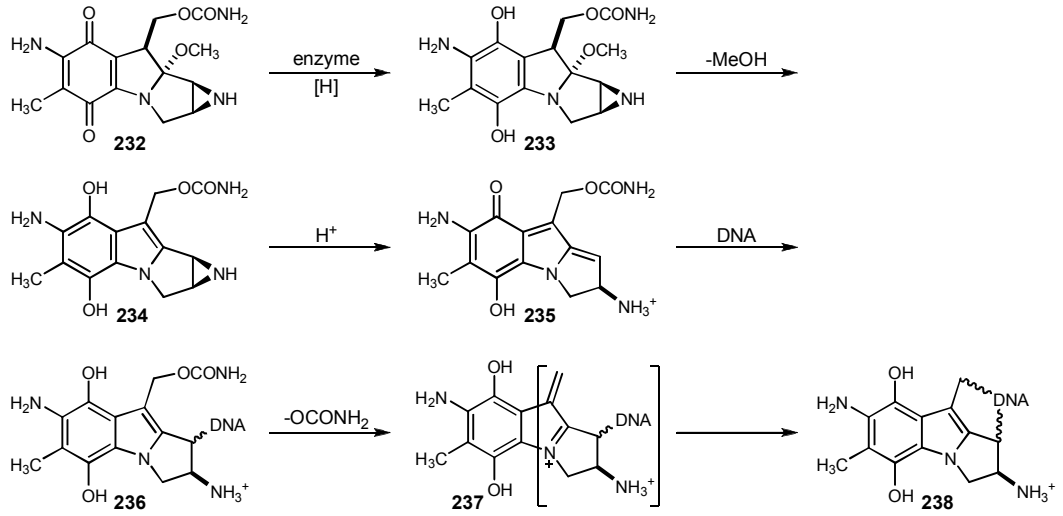
Figure 23. Natural Products Exhibiting an Aziridine Ring



Aziridines, like epoxides, combine a high degree of ring strain (111 kJ/mol) with an electronegative heteroatom, which makes them susceptible to a variety of transformations involving ring opening. These features make aziridines useful intermediates in organic chemistry, and a unique challenge for synthesis. The reactivity of the aziridine ring also translates into the more complex setting of natural products, and there are several examples of natural products with biological acitivity bearing an aziridine ring (Figure 23).[111] Moreover, the aziridine is often responsible for the biological activity. The natural product mitomycin C is representative. When mitomycin C reaches a cell's DNA, it selectively alkylates the quinone nucleoside in the sequence 5'-CpG-3'. Acitvation is achieved by reduction of the quinone ring to the more electronically rich hydroquinone **233**, and ring strain then drives unimolecular aziridine ring opening to form a highly

[111] a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. b) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. c) Hodgkinson, T. J.; Shipman, M. *Tetrahedron* **2001**, *57*, 4467. d) Kiyoto, S.; Shibata, T.; Yamashita, M.; Komori, T.; Okuhara, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 594. e) Iwami, M.; Kiyoto, S.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1987**, *40*, 589. f) Katoh, T.; Itoh, E.; Yoshino, T.; Terashima, S. *Tetrahedron* **1997**, *53*, 10229.

Scheme 1. Mitomycin C Mechanism of Action



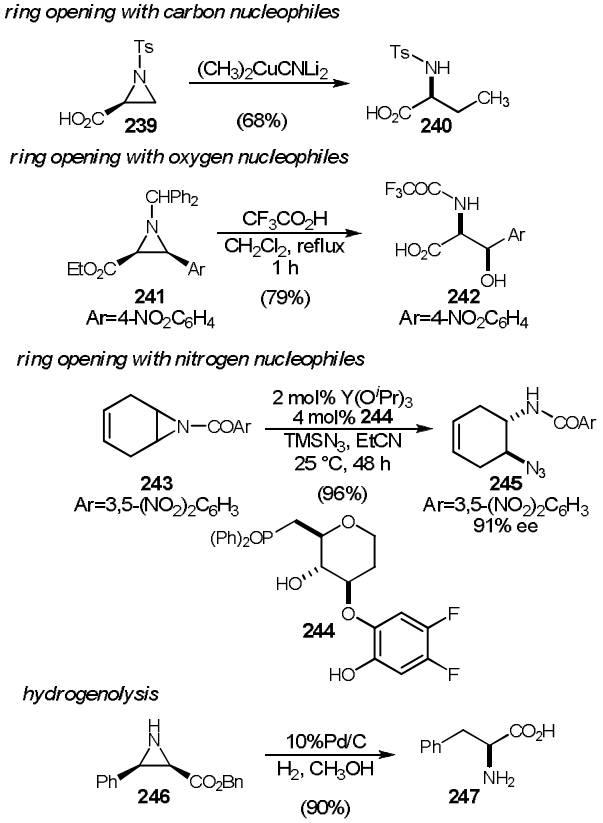
reactive carbon electrophile **235** (Scheme 1). The result is a reactive, yet selective chemotherapeutic agent with great practical value.

Among the countless stable aziridines, those bearing a Lewis basic nitrogen can be activated by Lewis acids toward nucleophilic ring-opening (Figure 24). An elegant demonstration of this strategy in asymmetric synthesis is Shibaski's desymmetrization of meso aziridine **243** with a chiral nonracemic Lewis acid and azide.[112] Functional groups which can stabilize the resulting negative charge from ring opening also enhance the rate of nucleophilic attack. For example, *N*-tosyl aziridines **239** can be efficiently opened with a cuprate.[113] Aziridines can also be reductively opened by hydrogenolysis.[114]

Vinyl aziridines utilize the ring strain to facilitate a variety of rearrangement reactions (Figure 25).[115] Pommelet and Chuche reported the aza-[3,3]-Claisen rearrangement of

[112] Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.
[113] Church, N. J.; Young, D. W. *Tetrahedron Lett.* **1995**, *36*, 151.
[114] Xiong, C. Y.; Wang, W.; Cai, C. Z.; Hruby, V. J. *J. Org. Chem.* **2002**, *67*, 1399.
[115] In *Aziridines and Epoxides in Organic Synthesis*, Yudin, A. K., Ed. Wiley-VCH: Weinheim, Germany, 2006.

Figure 24. Chemistry of Aziridines: Examples of C-N Activation Modes Enabled by Aziridine Ring Strain



divinyl aziridines **248**.[116] Somfai and coworkers have developed the aza-[2,3]-Wittig rearrangement[117] and the [1,5]-hydrogen shift[118] reactions of vinyl Aziridines. Another example of a rearrangement of vinyl aziridines was reported by Rees and coworkers in which pyrrolines **253** are formed.[119] Azomethine ylides are formed from aziridines and can be subsequently utilized in dipolar cycloadditions.[120] The stereospecificity of this reaction type was utilized by Padwa and coworkers in an intramolecular cyclization to fused bicyclic lactones **257**.[121]

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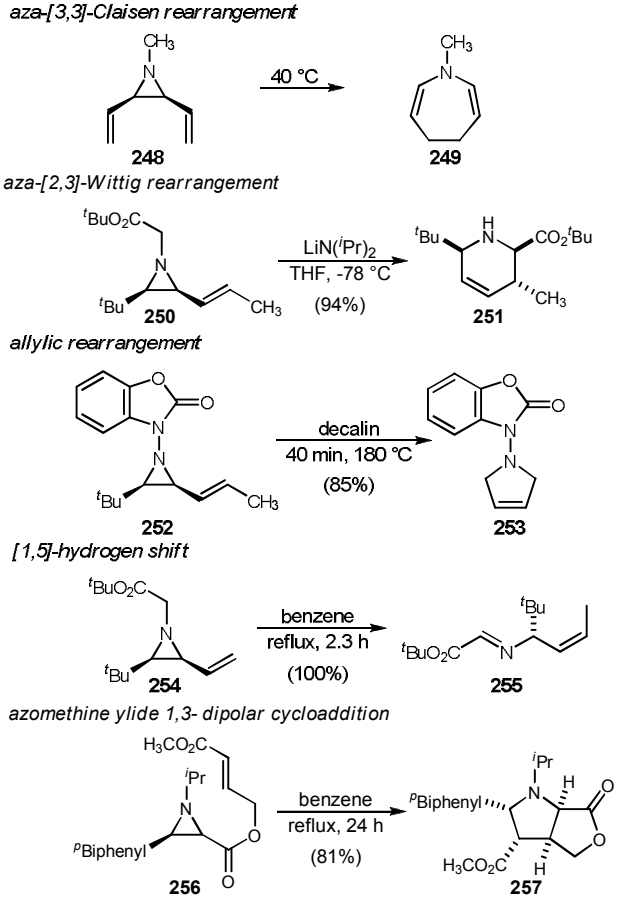
[116] Pommelet, J. C.; Chuche, J. *Tetrahedron Lett.* **1974**, 3897.
[117] Ahman, J.; Jarevang, T.; Somfai, P. *J. Org. Chem.* **1996**, *61*, 8148.
[118] Ahman, J.; Somfai, P. *Tetrahedron* **1999**, *55*, 11595.
[119] Atkinson, R. S.; Rees, C. W. *J. Chem. Soc. C* **1969**, 778.
[120] Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.
[121] Padwa, A.; Ku, H. *J. Org. Chem.* **1979**, *44*, 255.

Figure 25. Chemistry of Aziridines: Rearrangements Enabled by Vinyl Aziridine Ring Strain



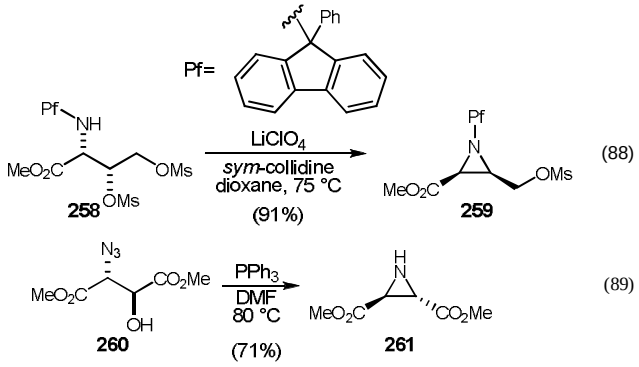
2. 2. The Synthesis of Aziridines

2. 2. 1. Aziridines from 1,2-Amino Alcohols

Among aziridine preparations, a great many fall into three approaches: nucleophilic ring closing, nitrene addition to olefins, and carbene addition to imines. Nucleophilic ring closure of *vic*-amino alcohols was first reported by Gabriel and developed further by

Wenker.[122] Several variants of this reaction now exist, but all utilize a leaving group vicinal to amine in some form (Figure 26).[123] These reactions require non-racemic starting materials in order to obtain non-racemic products.

Figure 26. Aziridine Ring Closure by Intramolecular Nucleophilic Substitution



2. 2. 2. Aziridine Formation via Nitrene Addition to Olefins

Several methods have been developed for nitrene or nitrenoid addition to olefins. Nitrenes can be formed by metals such as copper, rhodium, and manganese that when used with chiral ligands such as bisoxazolines **263** and diamines **266**, provide a route for catalytic asymmetric aziridination (Figure 27).[124] Evans[125] (eq 90) and Jacobsen[126] (eq 91) independently reported the first catalytic asymmetric aziridination involving nitrenes generated by copper(I) complexes. The scope of these reactions is quite limited. The enantioselectivity of these reactions decreases dramatically with other olefins.

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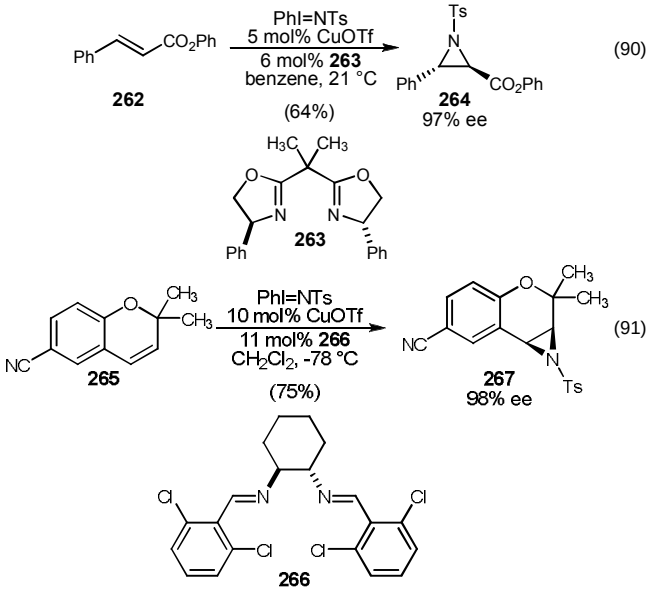
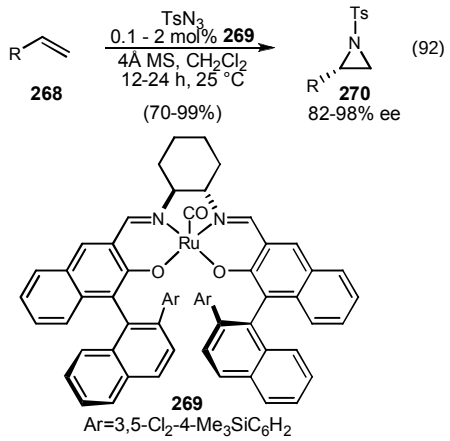
[122] a) Gabriel, S. *Chem. Ber.* **1888**, *21*, 1049. b) Gabriel, S. *Chem. Ber.* **1888**, *21*, 2664. c) Wenker, H. *J. Am. Chem. Soc.* **1935**, *57*, 2328.
[123] a) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 5287. b) Fernandez-Megia, E.; Montaos, M. A.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 6780.
[124] Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.
[125] Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
[126] Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.

Figure 27. Asymmetric Aziridination via Nitrenes



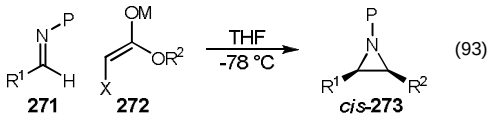
More recently, Katsuki and coworkers have made dramatic improvements in expanding the scope of olefins to which nitrenes can be added with high enantioselectivity by utilizing a ruthenium salen complex **269** (eq 92).[127]



[127] Kawabata, H.; Omura, K.; Uchida, T.; Katsuki, T. *Chemistry-an Asian Journal* **2007**, *2*, 248.

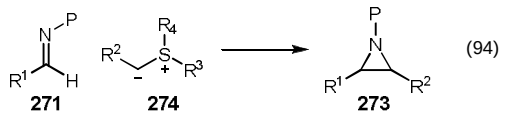
2. 2. 3. Aziridine Formation from Imines

Analogously, carbenes can be added to imines to form aziridines. Attempts to utilize metallocarbenes have met with limited success. Diazos and sulfur ylides can act as both electrophiles and nucleophiles and therefore provide carbene-like behavior. The aza-



(93)

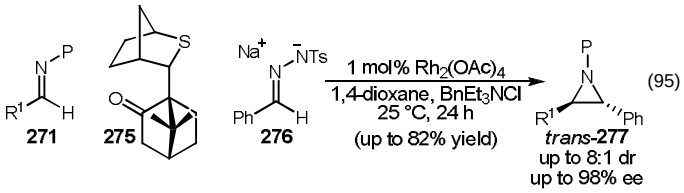
Darzens reaction involves the reaction of an α–haloenolate **272** with imine **271** (eq 93). The enolate is often formed with lithium bases so that when exposed to imine, a Zimmerman-Traxler transition state can form. The use of a chiral auxiliary on the imine



(94)

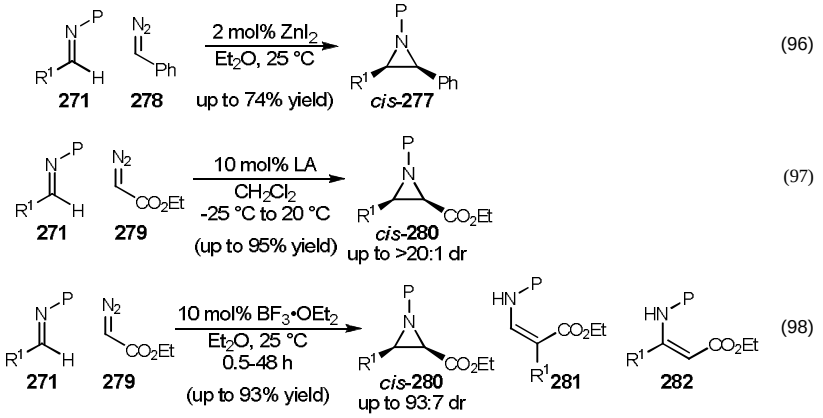
or the enolate allows for the diastereoselective synthesis of aziridines. Analogously, a sulfur ylide **274** can react with an imine to form the aziridine (eq 94). A chiral auxiliary on the imine or ylide allows for the asymmetric synthesis of aziridines. Both of these employ stoichiometric amounts of the chiral influence. More recently Aggarwal and co-workers utilized an *in situ* formation of non-racemic sulfur ylides from metallocarbenes for a catalytic asymmetric ylide-mediated aziridination (eq 95).[128]

[128] a) Aggarwal, V. K.; Alonso, E.; Fang, G. Y.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1433. b) Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159. c) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368.



In 1983, Bartnik and Mlostoń reported the Lewis acid catalyzed aza-Darzens reaction of imines **271** with phenyl diazomethane **278** using zinc iodide as the Lewis acid (eq 96).[129] Jørgensen has shown that a variety of Lewis acids catalyze the aza-Darzens reaction of imines **271** with ethyl diazoacetate **279** (eq 97).[130] The research group of Brookhart and Templeton utilized $BF_3{\cdot}OEt_2$, $AlCl_3$, and $TiCl_4$ for Lewis acid catalyzed aziridination of imines **271** with ethyl diazoacetate **279** (eq 98).[131] They were able to get better yields and more consistent diasteroselectivity and found that the reaction did not

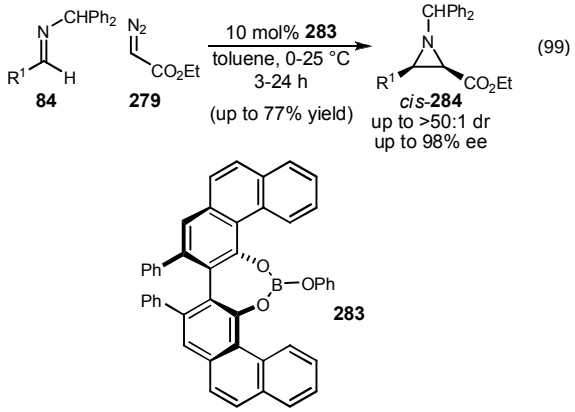
Figure 28. Lewis Acid Catalyzed Aza-Darzens Reactions



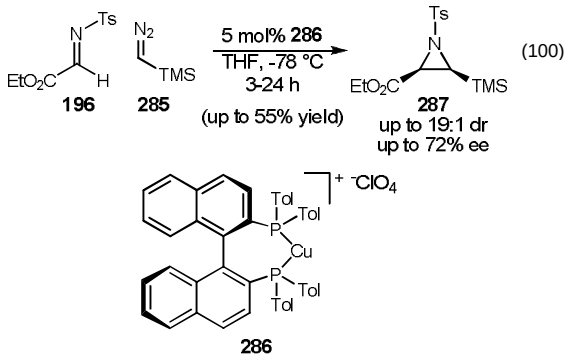
produce any maleate or fumarate byproducts typical of reactions involving carbenes. However they did observe two enamine byproducts **281** and **282** that were proposed to be

[129] Bartnik, R.; Mloston, G. *Synthesis* **1983**, 924.
[130] a) Rasmussen, K. G.; Jorgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1401. b) Rasmussen, K. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1287.
[131] Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358.

the result of 1,2-hydride or aryl shifts. The shifts could occur from an aminodiazonium intermediate formed during a stepwise addition.

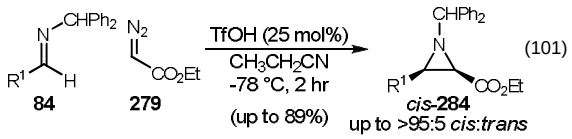


Antilla and Wulff developed the first Lewis acid catalyzed asymmetric aziridination utilizing boron bound to S-VAPOL as the catalyst **283** (eq 99).[132] The reaction is successful in producing aziridines with high enantio- and diastereoselectivity as well as reducing the amounts of the previously mentioned enamine byproducts.



[132] a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc*. **1999**, *121*, 5099. b) Antilla, J. C.; Wulff, W. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 4518.

At about the same time Jorgensen and co-workers reported the Lewis acid catalyzed asymmetric aziridination using trimethylsilyldiazomethane **285** albeit with lower enantio- and diastereoselectivities (eq 100).[133] More recently Johnston and Williams reported the Brønsted acid catalyzed diasteroselective aziridination of imines **84** with ethyl diazoacetate **279** (eq 101).[134] This reaction proceeds with high diastereoselectivity for the *cis*-aziridine for a variety of benzhydryl imines. The mechanism of these reactions has not been studied in detail, but a triazoline was thought to be a possible intermediate.

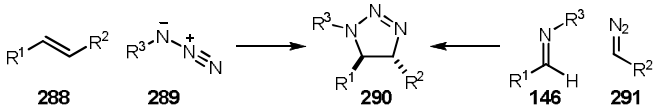


(101)

2. 2. 4. Transformation of Triazolines to Aziridines

Triazolines **290** have long been recognized as useful synthetic intermediates. The preparation of triazolines often involves either a [3+2] cycloaddition of olefins **288** with azides **289** or a [3+2] cyloaddition of diazos **291** with imines **146** (Scheme 2).[135]

Scheme 2. Synthesis of Triazolines

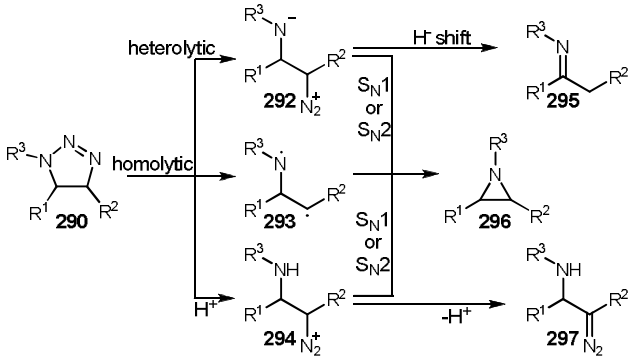


Triazolines **290** have been shown to form aziridines **296** thermally, photolytically, and in the presence of acid (Figure 29). Mechanistic studies of these reactions have

[133] f) Juhl, K.; Hazell, R. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293.
[134] Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612.
[135] Scheiner, P., Triazoline Decomposition. In *Selective Organic Transformations*, Thyagarajan, B. S., Ed. Wiley-Interscience: New York, USA, 1970; Vol. 1.

depended primarily on the distribution of products. The products isolated are dependent on the specific triazoline used and the solvent used. No clear picture of the mechanism has evolved for thermal or acid catalyzed decomposition of triazolines **290**. It seems that the sigma bond between N1 and N2 is cleaved either heterolytically or homolytically.

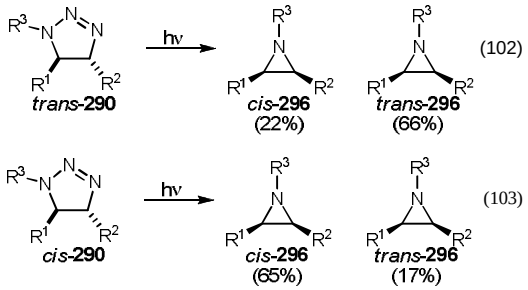
Figure 29. Modes of Triazoline Conversion



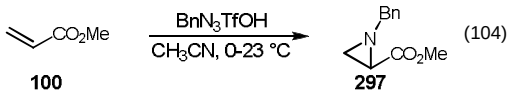
Acids protonate N1 leading to heterolytic cleavage of the N1-N2 bond. It is unclear whether the subsequent key intermediate involves an amino diazonium ion **294**, aziridinium ion, or a carbocation.[136] Photolytic decomposition may occur via homolytic cleavage of the N1-N2 bond and involve a diradical intermediate **293**. Stereochemistry has not been utilized in studying the mechanism of thermal or acid-catalyzed decomposition of triazolines **290**. Scheiner has studied aziridine formation from triazolines **290** by photodecomposition.[137] It was found that triazoline *trans*-**290** afforded predominantly *trans*-**296** (eq 102) and triazoline *cis*-**290** afforded predominantly *cis*-**290** (eq 103).

[136] Smith, R. H.; Wladkowski, B. D.; Taylor, J. E.; Thompson, E. J.; Pruski, B.; Klose, J. R.; Andrews, A. W.; Michejda, C. J. *J. Org. Chem.* **1993**, *58*, 2097.
[137] a) Scheiner, P. *J. Am. Chem. Soc.* **1966**, *88*, 4759. b) Scheiner, P. *J. Am. Chem. Soc.* **1968**, *90*, 988.

Figure 30. Scheiner's Photolytic Conversion of Triaolines to Aziridines

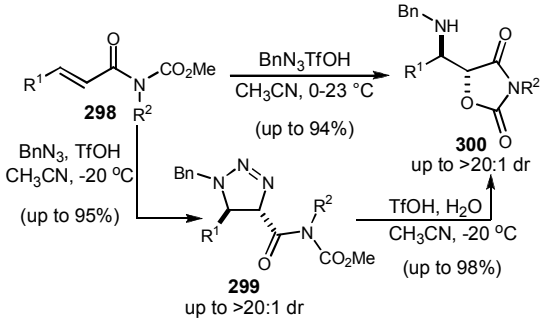


2. 3. The Potential for Mechanistic Convergency Between the Conversion of Triazolines to Aziridines and the Brønsted Acid Catalyzed aza-Darzens Reaction



Johnston and co-workers discovered the Brønsted acid promoted azide/olefin addition reaction. This reaction does form aziridines **297** when acrylates **100** were used as substrates (eq 104), but the products contain only one stereocenter. Inclusion of a pendant nucleophilic carbamate on the olefin affords an oxazolidine dione **300** as the *anti*-diastereomer (Scheme 3).[138] In 2008, they demonstrated that a *trans*-triazoline **299** is

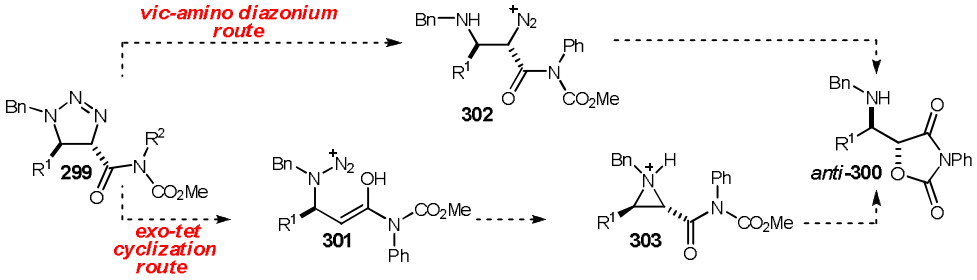
Scheme 3. The Azide-Olefin/Addition Reaction



[138] Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354.

at least a resting state, if not an intermediate in these reactions.[139] The conversion of *trans*-triazoline **299** to *anti*-oxazolidine dione **300** could involve a *trans*-aziridine **303** as an intermediate (Scheme 4). A *trans*-aziridine may form from a *trans*-triazoline via a 3-*exo-tet* cyclization at nitrogen. It is also possible that a *vic*-amino diazonium ion **302** is formed, leading to the *anti*-oxazolidine dione as a result of a direct S_N2 attack. Both of

Scheme 4. Possible Mechanisms for the Brønsted Acid Promoted Azide-Olefin/Addition R

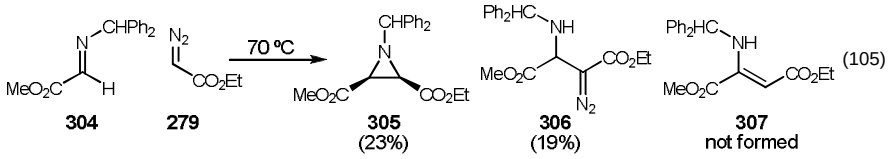


these mechanisms are possibly convergent with the mechanism of the Brønsted acid catalyzed aza-Darzens reaction. Since *cis*-aziridines are produced in this reaction, it was thought that a *syn*-oxazolidine dione could result from the reaction of imines with a diazoimide via a *cis*-aziridine. Our mechanistic studies were designed to determine the probable intermediates in these two reactions, whether they involved similar pathways, and how this affected the stereochemical outcome. Ultimately these studies would allow us to extend the scope of the Brønsted acid catalyzed aza-Darzens reaction and develop – perhaps rationally - new reactions.

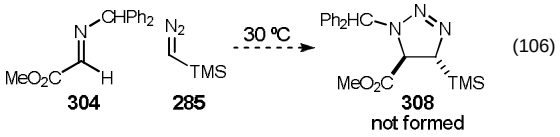
[139] Hong, K. B.; Donahue, M. G.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 2323.

2. 4. Studies of Brønsted Acid Promoted Triazoline Fragmentation

2. 4. 1. Attempted Synthesis of Triazolines from [3+2]-Cyclization of Diazos with Imines



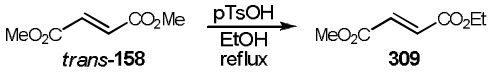
We first investigated whether or not a triazoline could be thermally prepared from the substrates in a typical Brønsted acid catalyzed aza-Darzens reaction. Imine **304** was treated with an excess of ethyl diazoacetate (**279**) as solvent and followed at several temperatures over several days (eq 105) to see if any triazoline could be observed. Reaction progress was monitored by ^{1}H NMR which showed no conversion until the temperature reached 50 °C and complete conversion after 5 days at 50 °C. The reaction was repeated at 70 °C and proceded with 82% conversion after 2 days, to give 23% of the *cis*-aziridine **305** and 19% of the *vic*-diazoamine **306**. The dehydroamino acid **307** has been reported to be a byproduct in certain aza-Darzens reactions.[132] However, there was no evidence of **307** in this reaction.



A 1,2,4-triazoline was reportedly isolated from the reaction of an *N*-tosylimine and trimethylsilyldiazomethane.[140] However, after 10 days at 30 °C, the reaction of trimethylsilyl diazomethane (**285**) with imine **304** showed little conversion and no triazoline (**308)** formation (eq 106).

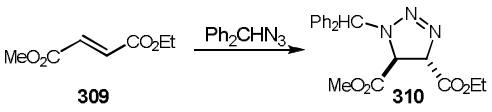
2. 4. 2. Synthesis of Triazolines by Thermal Addition of Azides to Olefins

Triazolines are known to form from the reaction of azides with olefins.[138] The *trans*-triazoline **310** was synthesized by the reaction of the mixed fumarate **309** with diphenylmethyl azide (eq 108). Optimal conditions for the synthesis of the unsymmetrical fumaric diester **309** was found to be a simple transesterification of dimethyl fumarate (*trans*-**158**) with an excess of ethanol and a small amount of TsOH which produced a mixture of starting material (*trans*-**158)**, diethyl ester, and mixed



(107)

ester **309**, which could be separated by chromatography (eq 107). The two methylene protons that are part of the triazoline ring appear in the ^{1}H NMR spectrum at 5.13 ppm and 4.82 ppm as doublets with a coupling constant of 15.0 Hz, which is consistent with a *trans* relationship.

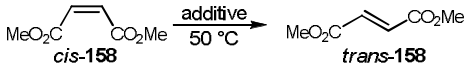


(108)

[140] Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335.

Low yields are due in part to tautomerization of the triazoline **310** to the *vic*-diazoamine **306**, which can occur even at ambient temperature. Tautomerization is indicated by a change in the ^{1}H NMR spectrum from the two doublets characteristic of the triazoline **310** to one singlet at 4.27 ppm (coupling to NHDPM not observed) and an IR absorbance at 2083 cm^{-1}. Surprisingly the reaction of diphenylmethyl azide with dimethyl maleate (*cis*-**158**) also produced the *trans*-triazoline rather than the desired

Table 1. The Isomerization of Dimethyl Maleate

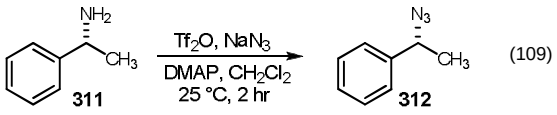


cis-**158** *trans*-**158**

entry	additive	time	result[a]
1	none	1 hr	no isomerization
2	DBU	16 hr	complete isomerization[b]
3	DMAP	16 hr	complete isomerization[b]
4	DABCO	16 hr	partial isomerization[b]
5	pyridine	16 hr	no isomerization
6	DMSO	16 hr	no isomerization
7	MeOH	16 hr	no isomerization

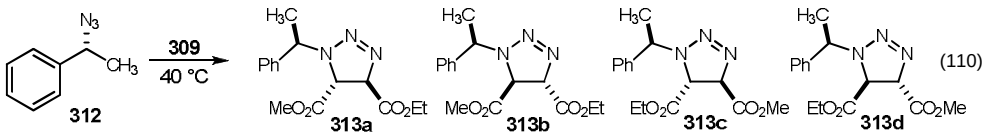
[a]Observed by TLC. [b]Confirmed by ^{1}H NMR

cis-triazoline. A variety of conditions were tried to determine how the maleic diester might be isomerizing under the reaction conditions (Table 1). The data indicates that the isomerization is due to nucleophiles that are presumably performing a Michael addition. The alkyl azide may act like a nucleophile in a reversible addition reaction leading to olefin isomerization. Therefore, either an initial olefin isomerization precedes the cycloaddition, or the cycloaddition is not concerted.



311 **312** (109)

Synthesis of the chiral nonracemic triazoline started from a chiral azide. Chiral azides can be synthesized using the diazo transfer method of Aubé.[141] Thus readily available (*R*)-α-methylbenzyl amine (**311**) was reacted with a freshly prepared solution of trifyl azide in the presence of DMAP to produce the corresponding (*R*)-α-methylbenzyl azide (*R*-**312**) in 77% yield (eq 109). The procedure was scaled up to afford 10 g of (*R*)-α-methylbenzyl azide (*R*-**312**).



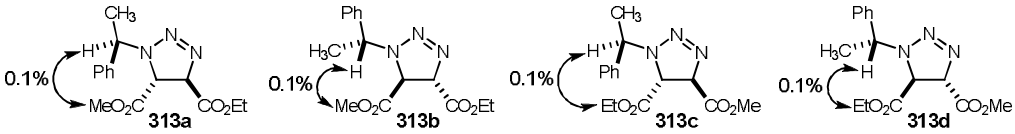
(110)

(*R*)-α-Methylbenzyl azide (*R*-**312**) was reacted with the unsymmetrical fumarate *trans*-**309** to afford the triazoline *R*-**313** as a mixture of four products (eq 110). Isolation of these triazolines was complicated by the formation of the *vic*-diazoamine similar to previous examples. The triazolines **313** were separated from the excess azide **309** by column chromatography with silica gel cooled to 0 °C. Conditions for prepartory HPLC using a normal phase column were found that allowed for the separation of all four products. Triazolines **313a**, **313c**, and **313d** could all be isolated in high enough purity to appear as a single triazoline by ^{1}H NMR. Triazoline **313b** could only be isolated in 10:1 ratio of **313b**:**313a**. The isolated triazolines experienced some conversion to *vic*-diazoamine, so they were stored at -4 °C and used within 24 hours. Structural assignment of the triazolines was accomplished using 2D NMR. Further confirmation of regiochemistry was made by the observance of an NOE between the benzylic proton and

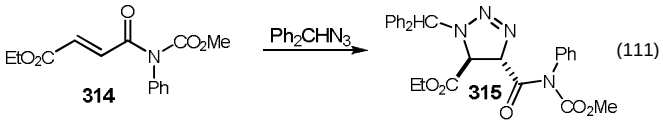
[141] Ramanathan, S. K.; Keeler, J.; Lee, H. L.; Reddy, D. S.; Lushington, G.; Aubé, J. *Org. Lett.* **2005**, *7*, 1059.

the protons of the ester which is closest to the benzylic proton; no NOE is observed between the benzylic proton and the other ester. An anisotropic effect of the phenyl ring on the protons of the ester and triazoline proton exists in the most probable lowest energy conformation for **313a** and **313c** allowing for an assignment of the diastereomers.

Figure 31. Assignment of Triazoline Regiochemistry by NOE



Imide **314** was treated with diphenylmethyl azide in a similar fashion to afford triazoline **315**. The triazoline **315** was isolated by chilled column chromatography in 4% yield (eq 111). The relative stereochemistry was assigned by coupling constants for the triazoline protons. Regiochemistry was determined by 2D NMR and by comparison to the NMR spectra of similar triazolines produced by a different route in which the



structural assignment was accomplished by X-ray crystallography.[142] Several products were formed from this reaction. One of the products is the *vic*-diazoamine which has been observed in the synthesis of similar triazolines. Another possible product was the regioisomer of triazoline **315**, however this was never fully characterized. The other products in this reaction were not isolated as pure compounds for accurate analysis. It

[142] Hong, K. B.; Donahue, M. G.; Johnston, J. N. *unpublished results.*

was also noted that triazoline **315** was extraordinarily unstable. Attempts at the synthesis of triazoline **315** using other conditions were unsuccessful. The reaction as shown was extremely sensitive to the temperature of the reaction as well as the time of reaction. Furthermore, the triazoline had to be used within a few hours of isolation in order to avoid decomposition. Isolated **315** could not even be stored under N_2 at -4 °C for more than 12 hours.

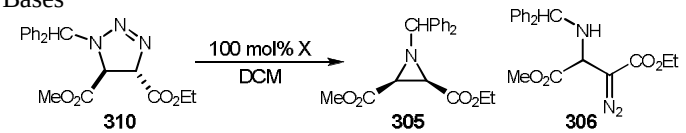
2. 4. 3. Conversion of Racemic Triazolines to Aziridine

In an attempt to convert a *trans*-triazoline to the *cis*-isomer, the *trans*-triazoline was treated with 1 equivalent of LDA and then quenched with 1 equivalent of AcOH. Unfortunately, the product that formed was a *vic*-diazoamine, as indicated by the absence of the doublets for the starting material and the appearance of a singlet at 4.23 ppm in the ^{1}H NMR spectrum of the crude reaction mixture. Furthermore, the synthesis of *trans*-triazoline **310** on a larger scale was complicated by the complete conversion to the *vic*-diazoamine **306** during chromatography. It should be noted that when *trans*-triazolines **310** are pure by NMR, they still show both *trans*-triazoline **310** and *vic*-diazoamine **306** by TLC. These results indicate that triazolines can covert to *vic*-diazoamine in the presence of base or weak acid.[143] A screen of various solvents was performed using the unsymmetrical *trans*-triazoline **310** with TfOH and TFA (Table 3). This data shows that with TfOH the aziridine **305** is formed rapidly at low temperatures. TLC of the reactions show that with either TFA or TfOH the reactions are most rapid in DCM. It isn't known for certain, but it is possible that the *vic*-diazoamine **306** observed with TfOH may be from the triazolines **310** breaking down to the *vic*-diazoamine **306** spontaneously during

[143] a) Rejzek, M.; Stockman, R. A.; van Maarseveen, J. H.; Hughes, D. L. *Chem. Commun.* **2005**, 4661. b) Herdeis, C.; Schiffer, T. *Tetrahedron* **1996**, *52*, 14745. c) Herdeis, C.; Schiffer, T. *Synthesis* **1997**, 1405.

the time it took to weigh it out. However, in DCM the amount of *vic*-diazoamine **306** is less. It has been observed that these triazolines are unstable at ambient temperature and can significantly convert to *vic*-diazoamine **306**.

Table 2. Transformation of Triazoline Using Various Acids and Bases[a]



310 **305** **306**

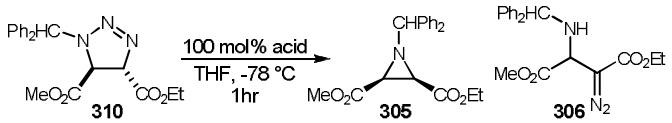
				yield (%)			
entry	X	temp	time (h)	**310**[b]	**306**[b]	**305x**[b]	**306:305**
1	LDA	-78 °C	1 h	0	73	0	>99:1
2	DBU	-78 °C	1 h	0	57	0	>99:1
3	DIEA	-20 °C	36 h	0	77	0	>99:1
4	Al_2O_3	-20 °C	36 h	0	65	0	>99:1
5	NH_4Cl	25 °C	36 h	22	67	0	>99:1
6	HCl	-78 °C	1 h	0	70	17	4:1
7	TsOH	-20 °C	36 h	0	72	11	6:1
8	BF_3•OEt_2	-20 °C	36 h	0	38	46	1:1
9	SiO_2	25 °C	36 h	35	46	0	>99:1
10	MeOH	-20 °C	36 h	0	75	15	5:1

[a]All reactions were 0.10 M in substrate. [b]Isolated yields after column chromatography.

Finally, a larger screen of acids and bases was performed using the unsymmetrical *trans*-triazoline **310** using DCM as solvent (Table 3). Aziridine **305** formation is always a competitive process with the formation of *vic*-diazoamine **306** when acids are used, but is never observed when bases are used. The reactions are faster with stronger bases and stronger acids. When DBU was used, the *vic*-diazoamine **306** was formed almost immediately with complete conversion and no aziridine formed (analysis by TLC). The aziridine **305** formed in these reactions was analyzed by ^{1}H NMR, which showed the product to be soley *cis*-aziridine.

A possible explanation for the lower amount of *vic*-diazoamine **306** formation in DCM (Table 3, entry 2) was that the *vic*-diazoamine **306** can be converted to aziridine **305**, albeit at a much slower rate. Furthermore, in the presence of 1 equivalent of TFA,

Table 3. Effect of Solvent on the Transformation of Triazolines[a]



					yield (%)			
entry	acid	solvent	temp	time (h)	**310**[b]	**306**[b]	**305**[b]	**306:305**
1	TfOH	THF	-78 °C	1 h	0	57	18	3:1
2	TfOH	DCM	-20 °C	16 h	0	13	77	1:6
3	TfOH	CH_3CH_2CN	-20 °C	16 h	0	30	53	1:2
4	TfOH	EtOAc	-78 °C	1 h	0	27	59	1:2
5	TFA	THF	-20 °C	16 h	34	37	0	>99:1
6[c]	TFA	DCM	-78 °C	1 h	25	55	0	>99:1
7	TFA	DCM	-78 °C	1 h	38	40	0	>99:1
8	TFA	DCM	-20 °C	16 h	0	26	48	1:2
9	TFA	CH_3CH_2CN	-78 °C	1 h	47	34	0	>99:1
10	TFA	EtOAc	-20 °C	16 h	0	75	15	5:1

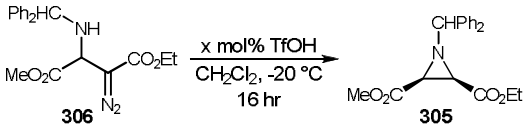
[a]All reactions were 0.10 M in substrate. [b]Isolated yields after column chromatography.
[c]110 mol% acid used.

the triazoline **310** forms 40% *vic*-diazoamine **306** in 1 hour at -78 °C (Table 3, entry 7). Yet if the same conditions are used and then warmed to -20 °C for several hours only 26% *vic*-diazoamine **306** is formed (Table 3, entry 8). Thus it must be concluded that 14% of the *vic*-diazoamine **306** was converted to aziridine **305**. This does not seem to be nearly as efficient a transformation in other solvents such as ethyl acetate (Table 3, entry 10). To test this hypothesis, the *vic*-diazoamine **306** was isolated and then treated with TfOH in DCM at -20 °C (Table 4). When 2 equivalents of TfOH are used, the starting material is completely consumed and 44% of aziridine **305** is formed. It was anticipated that the aziridine **305** formed from the *vic*-diazoamine **306** should be a mixture of diastereomers, yet the product was exclusively the *cis*-aziridine **305**. Thus, the α-diazonium **316** is the likely intermediate in the formation of aziridine and may represent the key intermediate responsible for the observed stereochemistry.

The proposed mechanism, which is consistent with the literature[135,136,144] for the conversion of the *trans*-triazolines **310** to *vic*-diazoamine **306** and aziridines **305** is shown

[144] Broeckx, W.; Overberg.N; Samyn, C.; Smets, G.; L'Abbe, G. *Tetrahedron* **1971**, *27*, 3527.

Table 4. The Conversion of *vic*-Diazoamine to Aziridine[a]

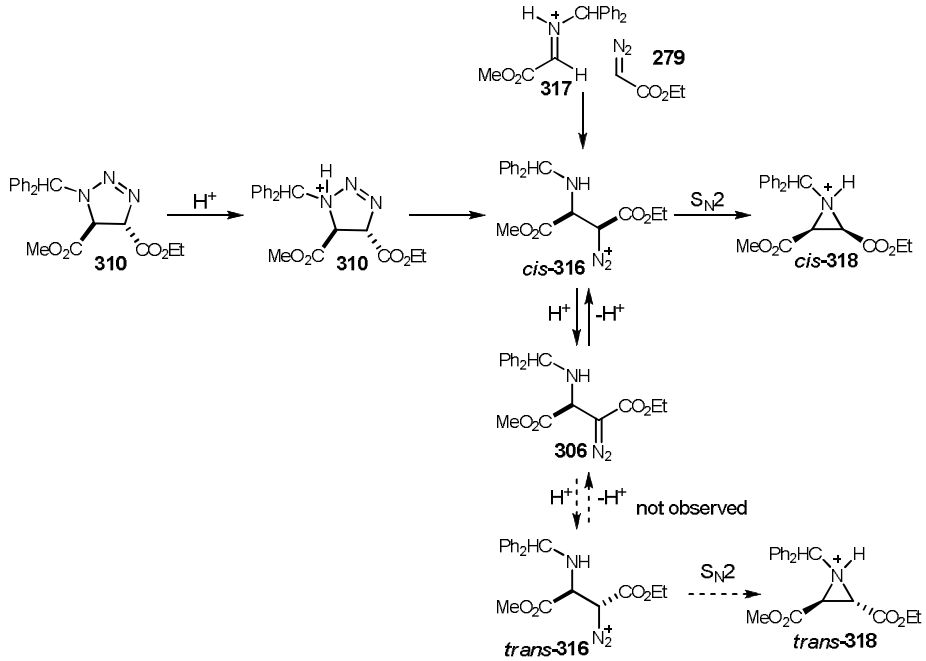


entry	x	%**306**[b]	%**305**[b]
1	25	46	3
2	100	68	13
3	200	0	44
4	300	0	26

[a]All reactions were 0.10 M in substrate.
[b]Isolated yields after column chromatography.

in Scheme 5. Under acidic conditions the more basic nitrogen of the triazoline is protonated, which causes ring opening. This leads to intermediate **316**, which after bond rotation, is susceptible to S_N2 attack by the amine, expelling N_2, and leading to the aziridine product via aziridinium *cis*-**318**. However the methine hydrogen of the diazonium is quite acidic, since it is experiencing an inductive affect from both the ester and the diazonium.

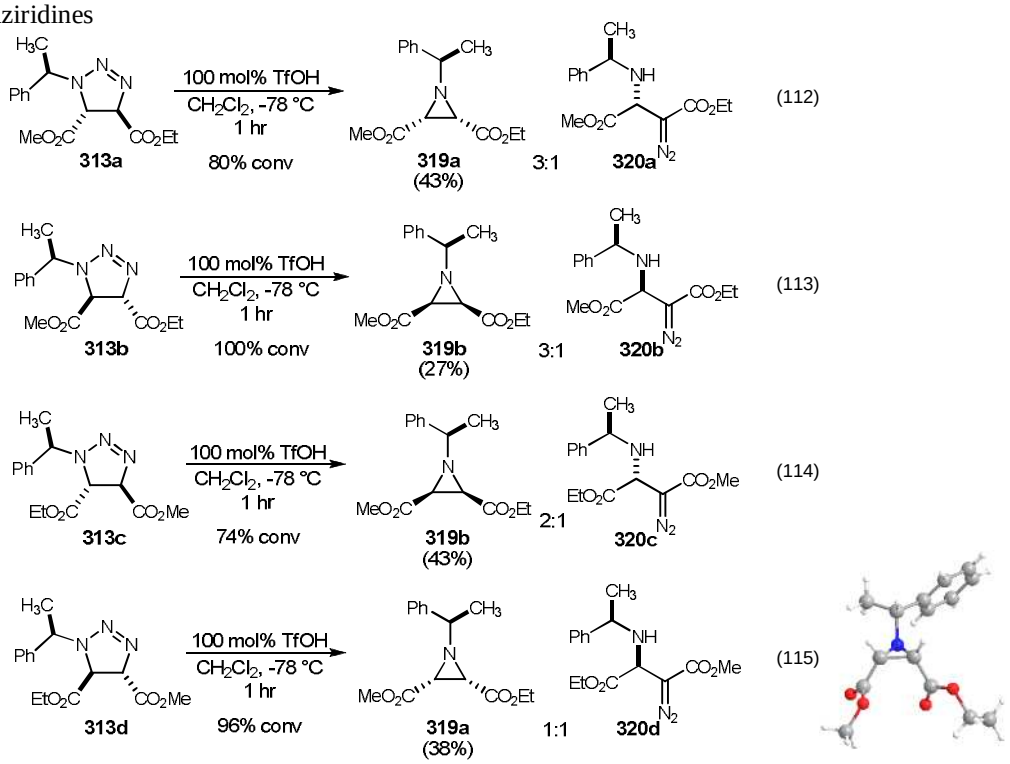
Scheme 5. Convergent Mechanism for the Formation of Aziridine from Triazolines and Imines and Diazos



The data in Table 3 would seem to indicate that this proton is sufficiently acidic in the triazoline to be deprotonated by bases as weak as DIEA. Thus cyclization to aziridine is in competition with proton loss to *vic*-diazoamine. The strength of acid (or base), solvent, and temperature then determine which path is favored. Intermediate **316** is likely circumvented under basic conditions, where the α–methine proton is abstracted concomitant with N-N bond cleavage and thus no aziridine is observed.

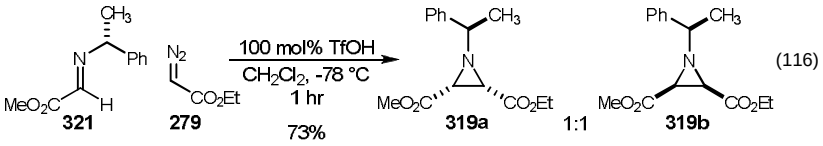
2 .4. 4. Conversion of Chiral Non-Racemic Triazoline to Aziridine

Figure 32. Sterespecific conversion of Chiral Non-Racemic Triazolines to Aziridines



Non-racemic triazolines **313a**, **313b**, **313c**, and **313d** were then treated individually with TfOH and converted smoothly to the corresponding aziridines **319** (Figure 32). The products were purified and characterized. Triazolines **313a** and **313d** were converted to aziridine **319a** as a single diastereomer as indicated by ^{1}H NMR. Likewise, triazoline

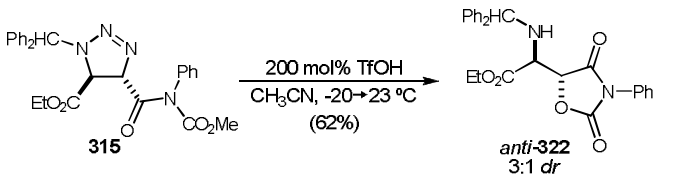
313c converted to aziridine **319b** as a single diastereomer. And finally, a 10:1 mixture of **313b** to **313a** was converted to aziridine **319b** with 10:1 dr. The data suggests that each conversion from triazoline to aziridine was stereospecific. The relative stereochemistry of **319a** was assigned by X-ray crystallography. The reaction of imine **321** with ethyl diazoacetate **279** in the presence of triflic acid affords a 1:1 mixture of aziridines **319a** and **319b** and in 69% yield (eq 116) under reaction conditions identical to those used in Figure 32. This confirms that no retro-Mannich pathway is occurring. It should be noted here that a full equivalent of acid was used for the decomposition of triazolines **313** and **310**. This requirement was elucidated previously in the Johnston group with similar substrates.[138] This would imply that the triazoline actually interferes with turnover in the reactions. Thus, the triazoline, if formed in the Brønsted acid catalyzed aza-Darzens reaction must not reach any appreciable amount since it is only converted to aziridine through the use of a full equivalent of triflic acid.



(116)

2. 4. 5 Conversion of Racemic Triazoline to Oxazolidine Dione

Triazoline **315** was converted in the presence of triflic acid to *anti*-oxazolidine dione

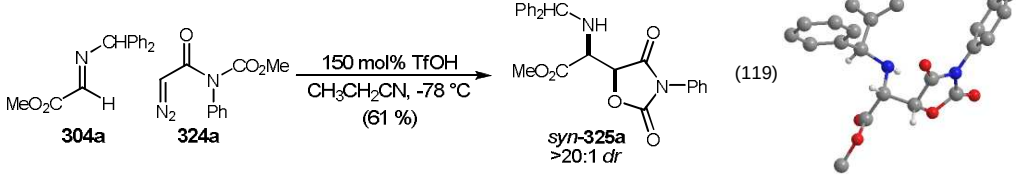


(117)

anti-**322** in 62% yield with 3:1 dr (eq 117). The reaction of imine **323** with diazo **324a** in the presence of triflic acid afforded *syn*-oxazolidine dione *syn*-**322** in 65% yield and 10:1 dr (eq 118). The *syn*-oxazolidine dione *syn*-**322** is distinguishable from *anti*-oxazolidine

(118)

dione *anti*-**322** in the ^{1}H NMR spectrum. Specifically, the resonance for the diphenyl methyl methine proton in *syn*-oxazolidine dione *syn*-**322** is a doublet at 5.00 ppm with a coupling constant of 3.8 Hz. The resonance for the same proton in *anti*-**322** is a doublet at 5.09 ppm with a coupling constant of 4.6 Hz. The rest of the protons overlap and are difficult to analyze. Imine **304** was reacted with diazo **324a** in a similar manner to afford *syn*-oxazolidine dione *syn*-**325a** in 61% yield (eq 119). No *anti*-oxazolidine dione *anti*-**325a** could be indentified in the ^{1}H NMR.

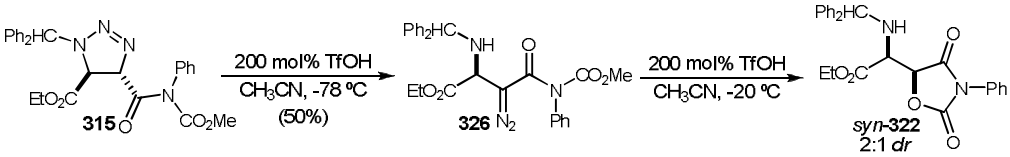


(119)

A crystal of purified *syn*-oxazolidine dione *syn*-**325a** was grown from toluene and petroleum ether, and the relative stereochemistry was determined by X-ray

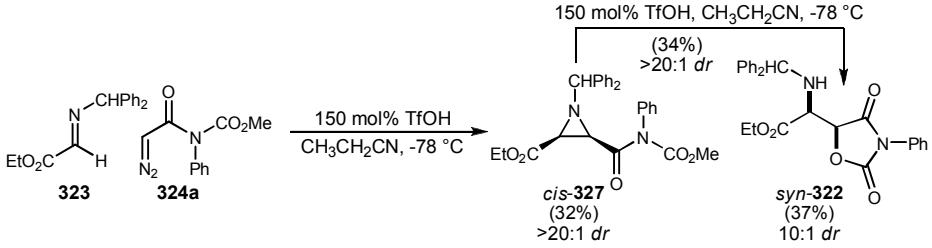
crystallography. The relative stereochemistry of a similar *anti*-oxazolidine dione isolated from the azide/olefin reaction has been previously confirmed by X-ray crystallography.[138]

Scheme 6. Conversion of Triazoline to Oxazolidine Dione via *vic*-Diazoamine Intermediate



The treatment of *tran*s-triazoline **315** with triflic acid at -78 °C afforded the *vic*-diazoamine **326** in 50% yield (Scheme 6). The *vic*-diazoamine **326** was converted with triflic acid at -20 °C to *syn*-**322** in 2:1 dr. The reaction of imine **323** with diazo **324a** at -78 °C afforded a 1:1 mixture of aziridine *cis*-**327** and *syn*-oxazolidine dione *syn*-**322** (Scheme 7). The *cis*-aziridine *cis*-**327** could be converted with triflic acid at -20 °C to *syn*-oxazolidine dione *syn*-**322** in 34% yield with no evidence for *anti*-oxazolidine dione *anti*-**322**.

Scheme 7. Isolation of Intermediate Aziridine and Conversion to Oxazolidine Dione

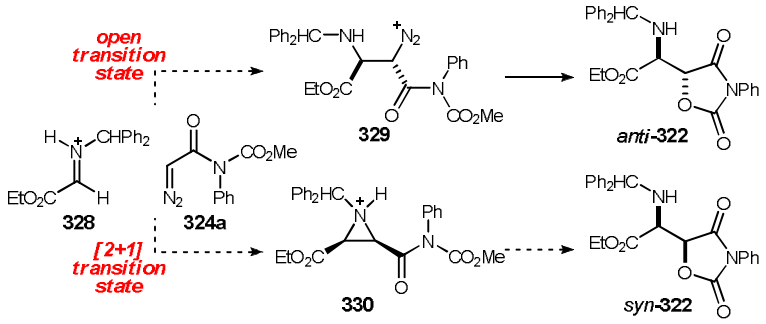


2. 5. Conclusions

A clearer picture of the mechanism of the diastereoselective aza-Darzens reaction and conversion of triazolines to aziridines has emerged as a result of analyzing the

stereochemical outcome of several reactions. Prior to this study little was known about the intermediates of either reaction, the stereochemical outcome of the acid promoted conversion of triazolines, and the orgin of diastereoselectivity of the aza-Darzens reaction. The isolation of *cis*-aziridine **305** and *vic*-diazoamine **306** from the thermal addition of ethyl diazo acetate to imine **304** (eq 105) suggests that a triazoline is not a critical intermediate in the diastereoselective aza-Darzens reaction since neither *vic*-diazoamine nor *trans*-triazoline have converted to *cis*-aziridine under thermal conditions. The conversion of *trans*-triazoline **310** to predominately *cis*-aziridine **305** in the presence of strong Brønsted acids (Table 3, entry 2) suggests that a *vic*-aminodiazonium ion is an intermediate in this conversion. This is supported by the observation that the *vic*-diazoamine **306** could be converted to **305** in the presence of a strong Brønsted acid (Table 4, entry 3). It would seem unlikely that a *trans*-triazoline would exist in any appreciable amount relative to the corresponding *vic*-aminodiazonium ion in this transformation. The conversion of *trans*-triazoline **310** to exclusively *vic*-diazoamine **306** in the presence of weak acids (Table 3, entry 6) would also suggest a *vic*-aminodiazonium ion as the intermediate. It seems that cyclization to aziridine is slower in the presence of weaker acids than proton loss. It is unlikely that a mechanism which involves 3-exo-tet cyclization to aziridine occurs, since this would result in a *trans*-aziridine (Scheme 4). The fact that chiral non-racemic triazolines undergo a stereospecific conversion to aziridines (eq 112-115) establishes that this intermediate aminodiazonium ion is not epimerized by proton exchange or a retro-Mannich process.

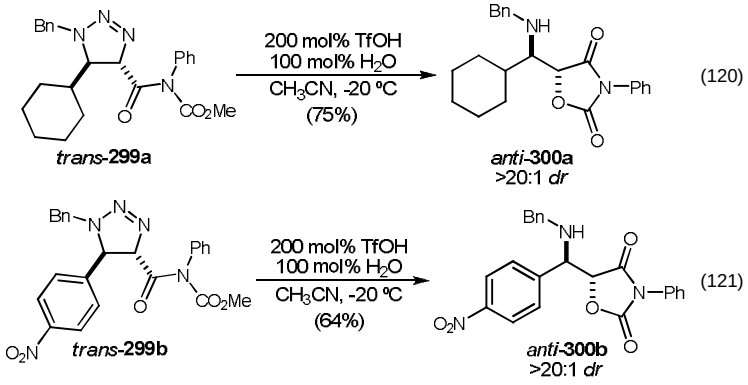
Scheme 8. Mechanistic Understanding of the Addition of Diazos to Imines



The addition of an imide as a source of oxygen nucleophile to the reagents was also informative in elucidating the mechanisms of these reactions (Scheme 8). The intermediate *vic*-aminodiazonium ion **329** can form a *cis*-aziridine as discussed above. A *cis*-aziridine would lead to formation of *syn*-oxazolidine dione *syn*-**322** as a result of nucleophilic ring opening. However, the *vic*-aminodiazonium ion **329** could cyclize to *anti*-oxazolidine dione *anti*-**322** without involving an intermediate *cis*-aziridine. The conversion of *trans*-triazoline **315** to primarily *anti*-oxazolidine dione *anti*-**322** in the presence of a strong acid (eq 118) supports the assertion that a *vic*-aminodiazonium ion is the key intermediate. The lower diastereoselectivity for the conversion of triazoline *anti*-**322** to oxazolidine dione is likely due to competitive formation of *cis*-aziridine. Much higher diastereoselectivites are observed for this transformation when *N*-benzyl-triazolines are used. The higher diastereoselectivity is likely not a result of stereoelectronic factors since triazolines *trans*-**299a** and *trans*-**299b** can still be converted to *anti*-**300a** and *anti*-**300b** with high diastereoselectivity (*Figure 33*).[142] It is more likely that the increased sterics of the diphenylmethyl group destabilizes the triazoline. In general the *N*-benzyltriazolines are stable at room temperature and can be isolated without complication from competitive formation of *vic*-diazoamine. Furthermore, bond

rotation is required to place the diazonium ion leaving group antiperiplanar to the amine to allow for aziridination to occur. The increased sterics of the diphenylmethyl group may increase the rate of bond rotation and thereby increase the amount of aziridine formation.

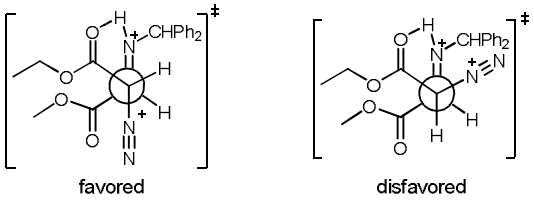
Figure 33. Examples of Conversion of *N*-Benzyltriazolines to *anti*-Oxazolidine Diones



The isolation of *vic*-diazoamine **326** from the reaction of *trans*-triazoline **315** with triflic acid at -78 °C (Scheme 6) and the isolation of *cis*-aziridine *cis*-**327** from the reaction of imine **323** with diazoimide **324a** at -78 °C (Scheme 7) suggest that the cyclization to oxazolidine dione is the rate limiting step. This result also indicates the key intermediates in the formation of both *syn*-oxazolidine dione and *anti*-oxazolidine dione. The conversion of *cis*-aziridine *cis*-**327** to *syn*-oxazolidine dione *syn*-**322** (Scheme 7) demonstrates the cyclization to oxazolidine dione via a nucleophilic ring opening of an aziridine is stereospecific. The stereospecificity of this transformation suggests that it is the most likely path for formation of *syn*-oxazolidine dione since epimerization of *anti*-oxazolidine dione to *syn*-oxazolidine dione has not been observed.

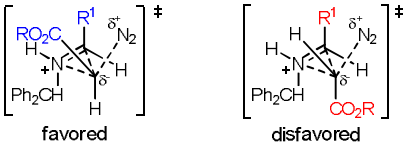
The conversion of *vic*-diazoamine **326** to oxazolidine dione (Scheme 6) again confirmed that a *vic*-aminodiazonium is a common intermediate in formation of *cis*-

Figure 34. Model for Diastereoselection in the Conversion of *vic*-Diazoamine to *cis*-Aziridine



aziridine and *anti*-oxazolidine dione. The fact that there was a slight preference for *syn*-oxazolidine dione *syn*-**322** in this reaction reaffirms that facial selectivity for protonation of the *vic*-diazoamine exists. It is conceivable that a highly selective protonation leads to a mixture of *cis*-aziridine and *vic*-aminodiazonium both of which in turn cyclize to *syn*-oxazolidine dione and *anti*-oxazolidine dione respectively. This highly selective protonation of the *vic*-diazoamine may be the result of a strong hydrogen bond forming between the amine and the neighboring ester (Figure 34). This hydrogen bond would restrict bond rotation and thus only protonation of one face of the diazo leads to an aminodiazonium ion in which the diazonium ion is antiperiplanar to the amine.

Figure 35. Model for Diastereoselection in a [2+1] Transition State Between Diazos and Imines



The addition of α-diazoimide **324a** to imine **323** afforded the *syn*-oxazolidine dione *syn*-**322** with high diastereoselectivity (eq 117). This result suggests that the two reactions in question may operate by different mechanisms. Specifically, the addition of α-diazoimide to imine might bypass formation of a discrete aminodiazonium ion, since this intermediate leads to the *anti*-oxazolidine dione. This suggests that the addition of α-

diazoimide to imines proceeds via a concerted transition state directly to the aziridinium (Figure 35). The implication thereof is that electrophiles can be activated by a Brønsted acid to elicit carbene like behavior from both ethyl diazoacetate and α-diazoimides. The decreased diastereoselectivity of ethyl glyoxylate imine **323** relative to methyl glyoxylate imine **304a** (eq 117 vs. 119) could be a result of increased steric repulsion in the [2+1] transition state. The effect of sterics on the diastereoselectivity of this reaction will be discussed further in the next chapter.

CHAPTER III

THE DEVELOPMENT OF THE SYN-GLYCOLATE MANNICH REACTION

3. 1. The Significance of 1,2-Aminoalcohols

There exist numerous examples of 1,2-aminoalcohols in natural products and pharmaceuticals, and they are also constituents of ligands and synthetic intermediates.[145] As a result they are the target of a variety of synthetic methods. Many of these examples are aryl or alkyl 1,2-aminoalcohols such as sphingosine,[146] anisomycin,[147] norephedrine,[148] cytoxazone,[149] the HIV protease inhibitor saquinavir,[150] and the aminoglycoside containing daunomycin.[151] Examples of β–hydroxy-α-amino acids are serine, threonine, and β-hydroxyaspartic acid.[152] The regioisomeric α-hydroxy-β-amino

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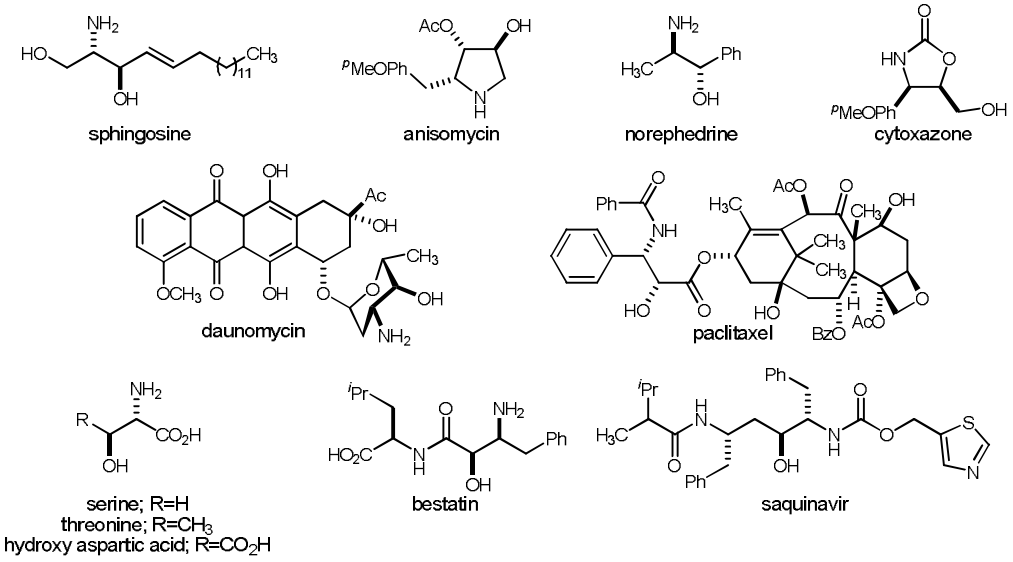
[145] Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.
[146] a) Mislow, K. *J. Am. Chem. Soc.* **1952**, *74*, 5155. b) Devant, R. M. *Kontakte (Darmstadt)* **1992**, 11. c) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075. d) Hannun, Y. A.; Linardic, C. M. *Biochim. Biophys. Acta* **1993**, *1154*, 223.
[147] a) Sobin, B. A.; Tanner, F. W. *J. Am. Chem. Soc.* **1954**, *76*, 4053. b) Schaefer, J. P.; Wheatley, P. J. *J. Org. Chem.* **1968**, *33*, 166. c) Grollman, A. P. *J. Biol. Chem.* **1967**, *242*, 3226. d) Hall, S. S.; Loebenberg, D.; Schumacher, D. P. *J. Med. Chem.* **1983**, *26*, 469. e) Dinman, J. D.; Ruiz-Echevarria, M. J.; Czaplinski, K.; Peltz, S. W. *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 6606. e) Hosoya, Y.; Kameyama, T.; Naganawa, H.; Okami, Y.; Takeuchi, T. *J. Antibiot.* **1993**, *46*, 1300. f) He, A. W. R.; Cory, J. G. *Anticancer Res.* **1999**, *19*, 421. g) Stadheim, T. A.; Kucera, G. L. *Leukemia Research* **2002**, *26*, 55.
[148] a) Kanao, S. *Ber. Dtsch. Chem. Ges.* **1930**, *63B*, 95. b) Reti, L., Ephedra bases. In *The Alkaloids*, Manske, R. H. F.; Holmes, H. L., Eds. Academic Press: New York, 1953; Vol. 3, pp 339.
[149] a) Kakeya, H.; Morishita, M.; Kobinata, K.; Osono, M.; Ishizuka, M.; Osada, H. *J. Antibiot.* **1998**, *51*, 1126. b) Kakeya, H.; Morishita, M.; Koshino, H.; Morita, T.; Kobayashi, K.; Osada, H. *J. Org. Chem.* **1999**, *64*, 1052.
[150] Ohta, Y.; Shinkai, I. *Bioorg. Med. Chem.* **1997**, *5*, 465.
[151] a) Di Marco, A.; Gaetani, M.; Orezzi, P.; Scarpinato, B. M.; Silvestrini, R.; Soldati, M.; Dasdia, T.; Valentini, L. *Nature* **1964**, *201*, 706. b) Zunino, F.; Gambetta, R.; DiMarco, A.; Luoni, G.; Zaccara, A. *Biochem. Biophys. Res. Commun.* **1976**, *69*, 744. c) Penco, S.; Angelucci, F.; Vigevani, A.; Arlandini, E.; Arcamone, F. *J. Antibiot.* **1977**, *30*, 764. d) El Khadem, H. S., *Anthracycline antibiotics.* Academic Press: New York, 1982; p 285. e) Lown, J. W., *Anthracycline and Anthracenedione-Based Anticancer Agents*. Elsevier: Amsterdam, 1988; p 753.
[152] a) Sallach, H. J.; Kornguth, M. L. *Biochim. Biophys. Acta* **1959**, *34*, 582. b) Kornguth, M. L.; Sallach, H. J. *Arch. Biochem. Biophys.* **1960**, *91*, 39. c) Mokotoff, M.; Bagaglio, J. F.; Parikh, B. S. *J. Med. Chem.* **1975**, *18*, 354.

acids are found in the side chain of the popular anticancer therapy, paclitaxel,[153] as well as the biologically active dipeptide bestatin.[154]

Figure 36. Examples of Biologically Important Small Molecules Containing 1,2 Aminoalcohols.



3. 2. Synthetic Methods for the Preparation of 1,2-Aminoalcohols

3. 2. 1. Functional Group Manipualtions

1,2-Aminoalcohols can often be prepared from natural amino acids. The synthesis of Evans' chiral auxiliaries often begins with the reduction of an amino acid.[155] Similarly, diphenyl prolinol is formed from a Grignard reaction with proline.[156]

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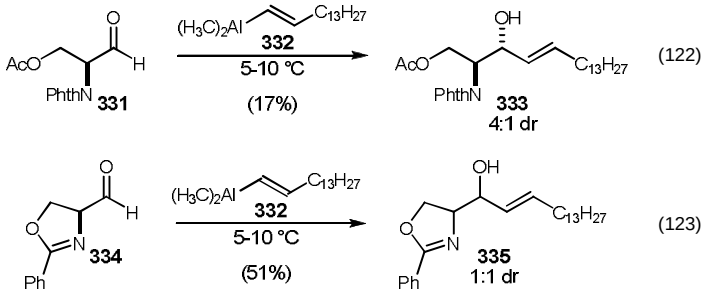
[153] a) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325. b) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem. Int. Ed.* **1994**, *33*, 15. c) Kingston, D. G. I. *J. Nat. Prod.* **2000**, *63*, 726.

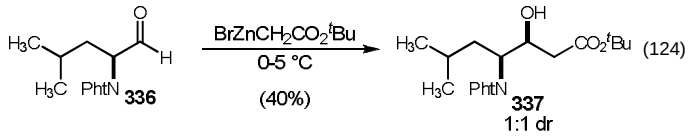
[154] a) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97. b) Nakamura, H.; Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H.; Iitaka, Y. *J. Antibiot.* **1976**, *29*, 102. c) Umezawa, H.; Ishizuka, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 857. d) Ino, K.; Goto, S.; Nomura, S.; Isobe, K. I.; Nawa, A.; Okamoto, T.; Tomoda, Y. *Anticancer Res.* **1995**, *15*, 2081.

[155] a) Feng, D.-Z.; Song, Y.-L.; Jiang, X.-H.; Chen, L.; Long, Y.-Q. *Org. Biomol. Chem.* **2007**, *5*, 2690. b) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 2471.

Figure 37. Additions of Vinylalanes to α–Amino Aldehydes

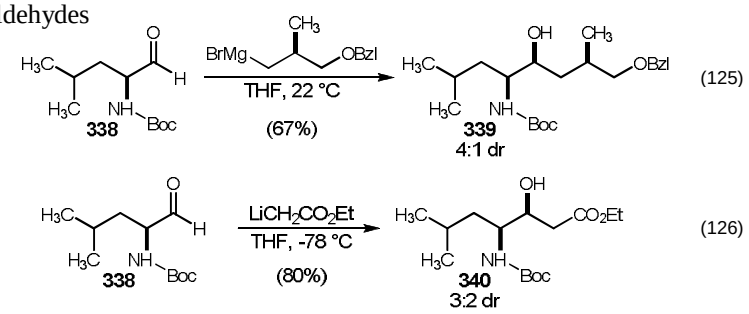


α–Amino aldehydes derived from amino acids can also be converted to 1,2-aminoalcohols. Newman reported the addition of vinyl alane **332** to phthaloyl protected amino aldehyde **331** in 1973 (eq 122).[157] Similarly, Thornton and coworkers



demonstrated the addition of vinyl alane **332** to the oxazolidine aldehyde **334** (eq 123).[158] A Reformatsky reaction with phthaloyl protected amino aldehyde **336** was

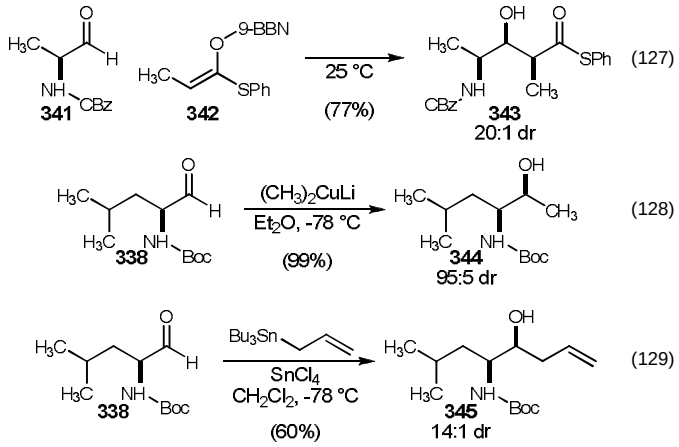
Figure 38. The Grignard and Aldol Reactions with Boc-Amino Aldehydes



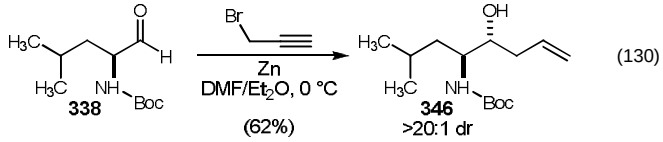
[156] Xavier, L. C.; Mohan, J. J.; Mathre, D. J.; Thompson, A. S.; Carroll, J. D.; Corley, E. G.; Desmond, R., *Org. Synth.*; Wiley & Sons: New York, 1998; Collect. Vol. No. 9, pp. 676.
[157] Newman, H. *J. Am. Chem. Soc*. **1973**, *95*, 4098.
[158] Tkaczuk, P.; Thornton, E. R. *J. Org. Chem.* **1981**, *46*, 4393.

disclosed by Glover (eq 124).[159] Rich and coworkers utilized Boc-leucinal (**338**) for both the Grignard and aldol reactions (Figure 38).[160] The same reactions were reported for similar aldehydes.[161]

Figure 39. Diastereoselective Additions to Boc-Leucinal



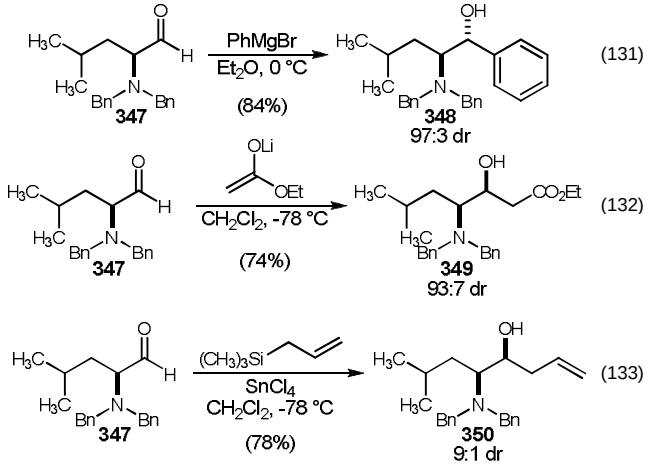
The preceding examples are limited by a lack of diastereoselectivity. Ohno and coworkers were able to achieve high levels of diastereoselectivity using a chiral boron enolate **342** with Cbz-alanal (**341**) (eq 127).[162] Reetz reported that the use of cuprates instead of the corresponding organolithium compounds allowed for significant



[159] Liu, W. S.; Glover, G. I. *J. Org. Chem.* **1978**, *43*, 754.
[160] a) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624. b) Holladay, M. W.; Rich, D. H. *Tetrahedron Lett.* **1983**, *24*, 4401.
[161] a) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399. b) Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133. c) Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921.
[162] Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M.; Umezawa, Y.; Morishima, H.; Saito, S. I.; Takita, T.; Umezawa, H. *Tetrahedron Lett.* **1982**, *23*, 525.

improvements in diastereoselectivity (eq 128).[163] Allylsilanes can also be added diastereoselectively to α–amino aldehydes in the presence of a Lewis acid.[164] Ghosh and coworkers were able to form the *syn*-1,2-amino alcohol **345** from the addition of either an allylstannane or an allylsilane to Boc-leucinal (**338)** in the presence of $SnCl_4$ (eq 129).[165] They isolated the *anti*-1,2-amino alcohol **346** exclusively as a result of the addition of propargyl bromide to Boc-leucinal (**338)** in the presence of zinc dust (eq 130). Allylchromium reagents can also add to α–amino aldehydes with significant diastereoselectivity.[166] α–Amino aldehydes are known to be configurationally unstable.[167] The examples shown may achieve high diastereoselecitivities in part due to the use of nucleophiles with decreased basicity.

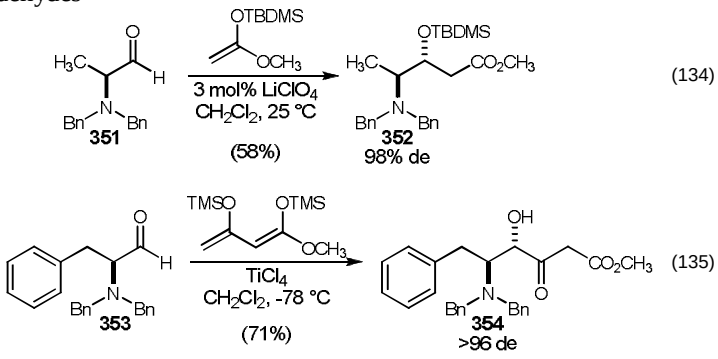
Figure 40. Diastereoselective Additions to *N,N'*-Dibenzylamino Aldehydes



Dialkyl protection of α–amino aldehydes allows for greater configurational stability,

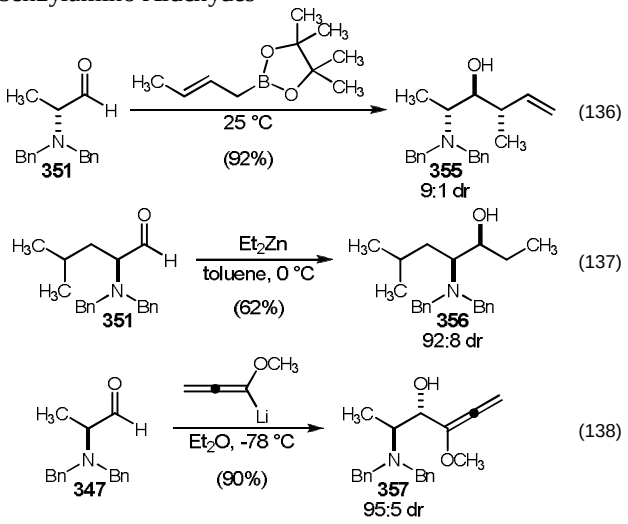
[163] Reetz, M. T.; Rolfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969.
[164] a) Daniello, F.; Mann, A.; Mattii, D.; Taddei, M. *J. Org. Chem.* **1994**, *59*, 3762. b) Jurczak, J.; Prokopowicz, P. *Tetrahedron Lett.* **1998**, *39*, 9835.
[165] Ghosh, A. K.; Cappiello, J. *Tetrahedron Lett.* **1998**, *39*, 8803.
[166] Ciapetti, P.; Falorni, M.; Taddei, M. *Tetrahedron* **1996**, *52*, 7379.
[167] Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

Figure 41. Mukiayama Aldol Reactions with *N,N'*-Dibenzylamino Aldehydes



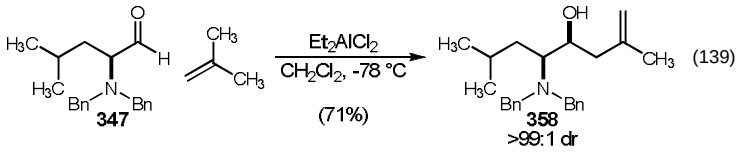
but not necessarily more diastereoselective Grignard or Aldol reactions.[168] Reetz and coworkers discovered that *N,N'*-dibenzylamino aldehydes **347** were capable of undergoing the addition of Grignard reagents with a high degree of diastereoselection (eq 131).[169] They also achieved high diastereoselectivity for the aldol reaction (eq 132). Interestingly, the addition of $SnCl_4$ to the reaction of allylsilanes to aldehyde **347** afforded the opposite diastereomer (eq 133). The use of $LiClO_4$ or $TiCl_4$ in the

Figure 42. Other Diastereoselective Additions to *N,N'*-Dibenzylamino Aldehydes



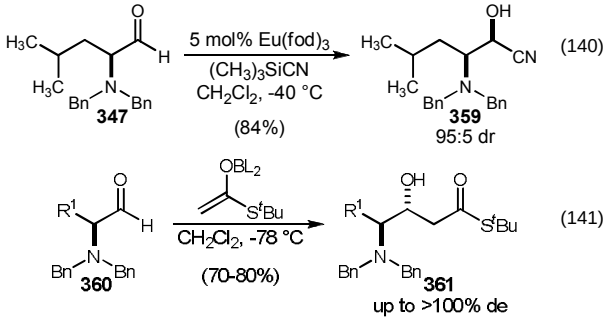
[168] Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.
[169] Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem. Int. Ed.* **1987**, *26*, 1141.

Mukiayama aldol reaction also afforded the *anti*-1,2 amino alcohol (Figure 41).[170]



Crotyl boronates,[171] lithiated methoxyallene,[172] and diethylzinc[173] have all been have utilized in diastereoselective additions to *N,N'*-dibenzylamino aldehydes **351** and **347** (Figure 42). Diastereoselective allylation of aldehyde **347** is also feasible by an aldehyde-ene reaction (eq 139).[174] Nakai and coworkers have demonstrated that cyanohydrins of aldehyde **347** can be formed diastereoselectively in the presence of a europium catalyst (eq 140).[175] The use of *N,N'*-dibenzylamino aldehydes has been extended to the asymmetric aldol reaction with chiral boron enolates (eq 141).[176]

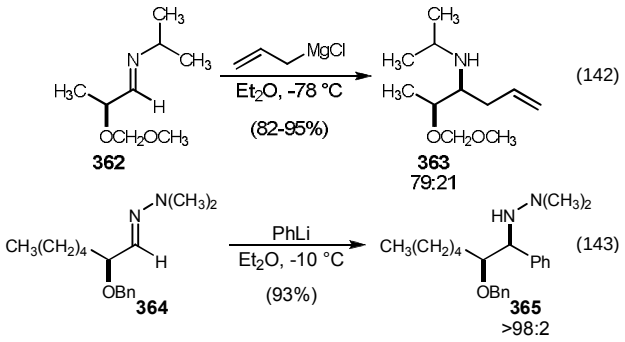
Figure 43. Diastereoselective Cyanohydrin formation and Aldol Reaction of *N,N'*-Dibenzylamino Aldehydes



[170] a) Reetz, M. T.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, *34*, 1119. b) Enders, D.; Burkamp, F.; Runsink, J. *Chem. Commun.* **1996**, 609.
[171] Brinkmann, H.; Hoffmann, R. W. *Chem. Ber.* **1990**, *123*, 2395.
[172] a) Hormuth, S.; Reissig, H. U. *Synlett* **1991**, 179. b) Hormuth, S.; Reissig, H. U. *J. Org. Chem.* **1994**, *59*, 67.
[173] Andres, J. M.; Barrio, R.; Martinez, M. A.; Pedrosa, R.; PerezEncabo, A. *J. Org. Chem.* **1996**, *61*, 4210.
[174] Mikami, K.; Kaneko, M.; Loh, T. P.; Terada, M.; Nakai, T. *Tetrahedron Lett.* **1990**, *31*, 3909.
[175] Gu, J. H.; Okamoto, M.; Terada, M.; Mikami, K.; Nakai, T. *Chem. Lett.* **1992**, 1169.
[176] a) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248. b) Gennari, C.; Moresca, D.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5593.

Garner's aldehyde is also configurationally stable.[177] However, most attempts utilizing Garner's aldehyde in a Grignard reaction have failed to achieve appreciable diastereoselectivity.[178] Roush and coworkers were able to achieve high diastereoselectivity for the allyboration of Garner's aldehyde.[179]

Figure 44. Grignard Reactions with α–Alkoxy Imines.



The corresponding α–hydroxyl imines can also be transformed to 1,2-aminoalcohols. Yamamoto and coworkers reported the diastereoselective addition of an allyl Grignard to α–alkoxy imine **362** (eq 142).[180] Claremon and coworkers successfully achieved higher diastereoselection using organolithiums and the analogous hydrazone **364** (eq 143).[181]

Then in 1994, Jäger and coworkers reported a more comprehensive study of Grignard reactions with α–alkoxy imines.[182] They demonstrated that higher diastereoselectivities were more consistently achieved with glyceraldehyde derived imines **366** (eq 144).[183]

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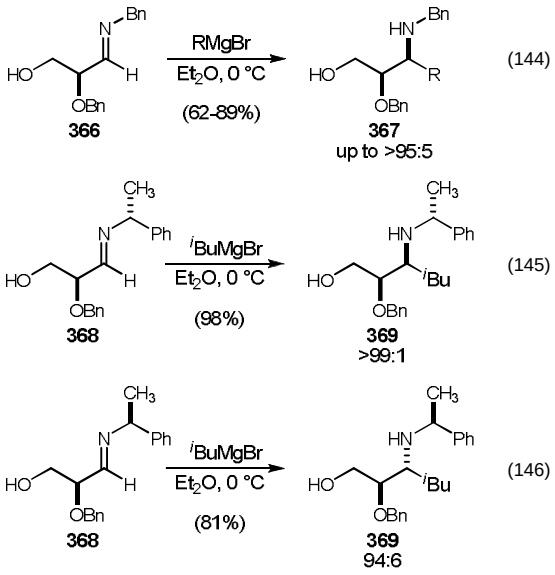
[177] Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.
[178] a) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. b) Laib, T.; Chastanet, J.; Zhu, J. P. *J. Org. Chem.* **1998**, *63*, 1709. c) Aoyagi, Y.; Inaba, H.; Hiraiwa, Y.; Kuroda, A.; Ohta, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3975.
[179] Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798.
[180] Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 814.
[181] Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265.
[182] Franz, T.; Hein, M.; Veith, U.; Jager, V.; Peters, E. M.; Peters, K.; Vonschnering, H. G. *Angew. Chem. Int. Ed.* **1994**, *33*, 1298.
[183] Veith, U.; Schwardt, O.; Jager, V. *Synlett* **1996**, 1181.

Figure 45. Jäger's Grignard Reactions of Glyceraldehyde Imines



Subsequently they showed that a chiral non-racemic auxiliary attached to the nitrogen of the imine allowed for higher diastereoselectivies as well as determing the preferred diastereomer (eqs 145 and 146).[184] Others have also utilized chiral non-racemic auxiliaries on the nitrogen of the imine with similar success.[185] The diastereoselective addition to α–alkoxy imines has been extended to *N*-phosphinoylimines,[186] nitrones,[187] *N*-acylimines,[188] and *N*-Boc imines[189] and a variety of nucleophiles such as diethyl zinc,[190] thiazole,[187] organoboronic acids,[191] cuprates,[188] silyl enol ethers,[192] nitromethane,[193] lithium and zinc enolates,[193] and allylzinc reagents.[193]

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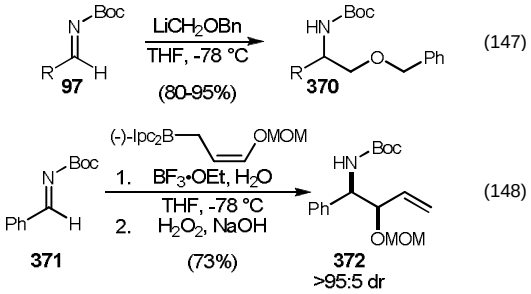
[184] Veith, U.; Leurs, S.; Jager, V. *Chem. Commun.* **1996**, 329.
[185] a) Enders, D.; Reinhold, U. *Angew. Chem. Int. Ed.* **1995**, *34*, 1219. b) Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948. c) Cooper, T. S.; Larigo, A. S.; Laurent, P.; Moody, C. J.; Takle, A. K. *Synlett* **2002**, 1730.
[186] Desrosiers, J. N.; Cote, A.; Charette, A. B. *Tetrahedron* **2005**, *61*, 6186.
[187] Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem.-Eur. J.* **1995**, *1*, 505.
[188] Ishimaru, K.; Tsuru, K.; Yabuta, K.; Wada, M.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1996**, *52*, 13137.
[189] Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275.
[190] Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409.
[191] Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798.
[192] Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron Lett.* **2003**, *44*, 9189.

Figure 46. Alternative Routes to 1,2-Amino Alcohols from Imines



A related technique for the synthesis of 1,2-amino alcohols was reported by Kim and coworkers involving the addition of benzyloxymethyl lithium to *N*-Boc imines **97** (eq 147).[194] Recently, Jäger and coworkers reported a similar reaction using an allyl borane (eq 148).[195]

These methods rely on relative stereocontrol to establish the *vic*-aminoalcohol chirality. Complementary to this approach is one that is based on stereospecific transformations. For example, Curtius and Hoffman rearrangements of β-hydroxy acids have also been used to prepare stereodefined 1,2-aminoalcohols.[196] The following section explores this approach through one of the most practiced stereospecific syntheses of *vic*-aminoalcohols.

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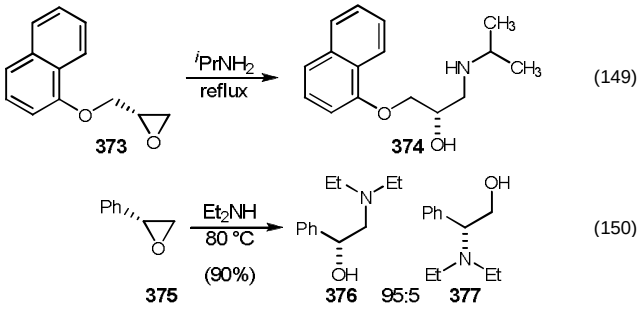
[193] Giri, N.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2004**, *69*, 7303.
[194] Jung, D. Y.; Ko, C. H.; Kim, Y. H. *Synlett* **2004**, 1315.
[195] Li, F.; Li, Z. M.; Yang, H.; Jager, V. *Z. Naturforsch., B: Chem. Sci.* **2008**, *63*, 431.
[196] a) Andruszkiewicz, R.; Wyszogrodzka, M. *Synlett* **2002**. b) Coelho, F.; Rossi, R. C. *Tetrahedron Lett.* **2002**, *43*, 2797. c) Hakogi, T.; Monden, Y.; Taichi, M.; Iwama, S.; Fujii, S.; Ikeda, K.; Katsumura, S. *J. Org. Chem.* **2002**, *67*, 4839. d) Bertau, M.; Burli, M.; Hungerbuhler, E.; Wagner, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2103. e) Ghosh, A. K.; Bischoff, A.; Cappiello, J. *Org. Lett.* **2001**, *3*, 2677. f) Roers, R.; Verdine, G. L. *Tetrahedron Lett.* **2001**, *42*, 3563. g) Yu, C. Z.; Jiang, Y. Y.; Liu, B.; Hu, L. Q. *Tetrahedron Lett.* **2001**, *42*, 1449. h) Wang, G.; Hollingsworth, R. I. *Tetrahedron: Asymmetry* **2000**, *11*, 4429. i) Garcia-Urdiales, E.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 721. j) Takacs, J. M.; Jaber, M. R.; Vellekoop, A. S. *J. Org. Chem.* **1998**, *63*, 2742. k) Oetting, J. H., J.; Meyer, H. H.; Pahl, A. *Tetrahedron: Asymmetry* **1997**, *8*, 477. l) Misiti, D. Z., G.; Delle Monache, G *Synth. Comm.* **1995**, 2285. m) Norman, B. H.; Morris, M. L. *Tetrahedron Lett.* **1992**, *33*, 6803. n) Grunewald, G. L.; Ye, Q. Z. *J. Org. Chem.* **1988**, *53*, 4021.

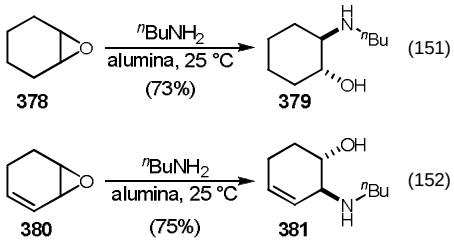
3. 2. 2. Ring Opening of Aziridines and Epoxides

Figure 47. Thermal Aminolysis of Epoxides.



Nucleophilic ring opening of aziridines or epoxides can also afford 1,2-aminoalcohols.[145,115] This ring opening typically proceeds via a S_N2 mechanism which is a stereospecific process with inversion of configuration. Thus, highly enantioselective syntheses of aziridines and epoxides in turn allow for the synthesis

Figure 48. Posner's Alumina Promoted Aminolysis of Epoxides

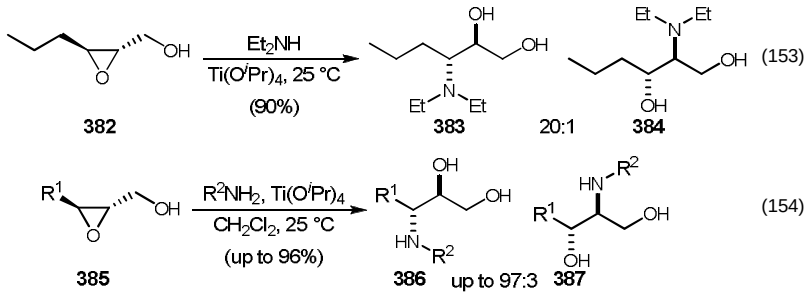


stereodefined 1,2-aminoalcohols. However, the control of regioselectivity in nucleophilic ring opening can be problematic. The aminolysis of an epoxide can be accomplished with excess amine at elevated temperatures but lacks any appreciable regioselecitivity.[197] Sharpless and Chini have reported a regioselective aminolysis of an epoxide by this route

[197] Moller, F., In *Methoden der Organische Chemie (Houben-Weyl)*, 4th ed.; Muller, E., Ed. Thieme Verlag: Stuttgart, 1957; Vol. 11/1, pp 311.

(Figure 47).[198] Posner and coworkers were the first to demonstrate that this aminolysis could be accomplished at ambient temperatures in the presence of alumina (eq 151).[199] They also demonstrated that this method was highly regioslective with vinyl and aryl epoxides (eq 152).[200]

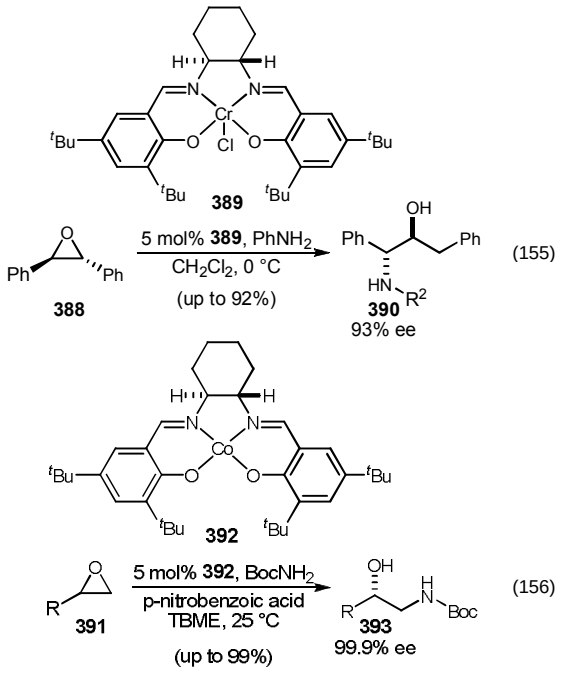
Figure 49. Titanium Promoted Aminolysis of Epoxides



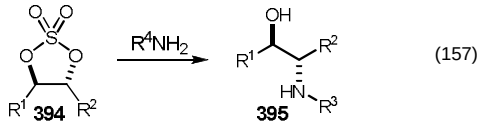
Then in 1985, Sharpless and coworkers reported that the inclusion of $Ti(O^iPr)_4$ in the aminolysis was more effective than the use of excess amine and higher temperatures (eq 153).[201] Primary amines initially failed to afford the desired product, but it was later determined that this reaction afforded 1,2-aminoalcohols regioselectively and in good yield (eq 154).[202] The use of $LiClO_4$,[198b] $Yb(OTf)_3$,[203] $SmCl_3$,[204] tosic acid,[205] and cyclodextrin[206] have all been proven effective for the aminolysis of epoxides. Yet the regioselectivity of these reactions is dependent on the stereoelectronic effects of the

[198] a) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710. b) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939.
[199] Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208.
[200] Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208.
[201] Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557.
[202] Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6931.
[203] a) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433. b) Meguro, M.; Asao, N.; Yoshimoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597.
[204] Fu, X. L.; Wu, S. H. *Synth. Comm.* **1997**, *27*, 1677.
[205] Lindstrom, U. M.; Franckowiak, R.; Pinault, N.; Somfai, P. *Tetrahedron Lett.* **1997**, *38*, 2027.
[206] Reddy, L. R.; Bhanumathi, N.; Rao, K. R. *Chem. Commun.* **2000**, 2321.

Figure 50. Asymmetric Aminolysis of Epoxides



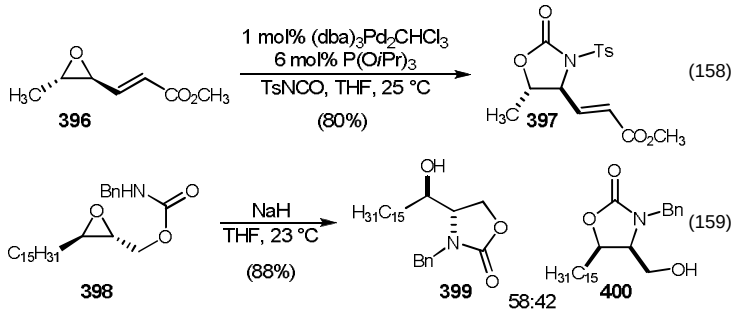
epoxide and the amine. Chiral nonracemic Lewis acids using BINOL as a ligand have met with limited success.[207] Chiral nonracemic Lewis acids bound to the Salen Ligand have proven to be the most effective for the stereo and regioselective aminolysis of epoxides (eq 155).[208] The reaction is equally effective with carbamate (eq 156)[209] and azides (eq 2)[3] as nucleophiles. A related approach is the aminolysis of cyclic sulfates **394** (eq 157).[210]



[207] a) Hou, X. L.; Wu, J.; Dai, L. X.; Xia, L. J.; Tang, M. H. *Tetrahedron: Asymmetry* **1998**, *9*, 1747. b) Sagawa, S.; Abe, H.; Hase, Y.; Inaba, T. *J. Org. Chem.* **1999**, *64*, 4962. c) Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 75.
[208] Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 2173.
[209] a) Kim, S. K.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2004**, *43*, 3952. b) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett.* **2004**, *6*, 3973.

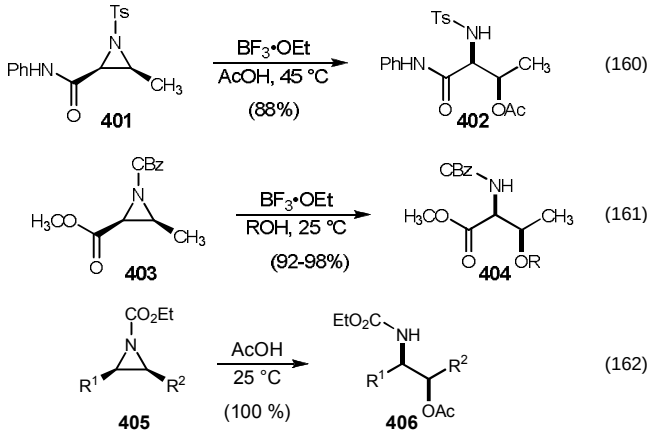
Epoxides can also experience intramolecular ring opening. Trost and coworkers reported the palladium catalyzed ring opening of epoxides in the presence of tosyl isocyanate resulting in oxazolidinone **397** (eq 158).[211] The isocyanate forms a carbamate

Figure 51. Examples of Intramolecular Ring Opening of Epoxides



with the oxygen of the epoxide while the palladium stabilizes the carbocation. Cyclization to the oxazolidinone then terminates the sequence. The carbamate can also

Figure 52. Examples of Acid Promoted Ring Opening of Activated Aziridines

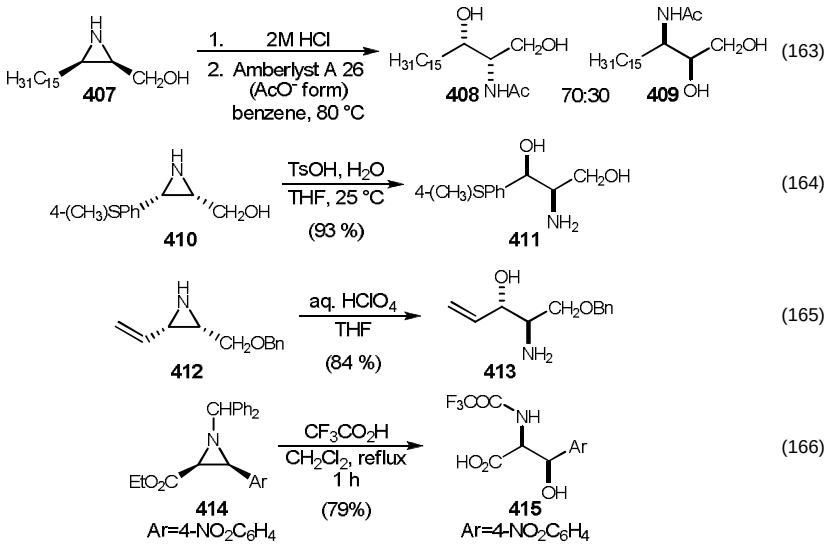


[210] Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623.
[211] Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792.

exist alpha to the epoxide and cyclize to oxazolidinone **400** affording the desired 1,2-amino alcohol (eq 159).[212]

Aziridines can be opened by oxygen nucleophiles to afford 1,2-amino alcohols. Typically these reactions require an activating group attached to the nitrogen of the aziridine. For example, *N*-tosyl aziridines **401** experience nucleophilic ring opening by carboxylic acids and alcohols in the presence of $BF_3 \cdot OEt_2$ (eq 160 and 161).[213] Acetic acid is also capable of promoting the nucleophilic attack of acetate or ethanol on the aziridine ring (eq 162).[214]

Figure 53. Examples of Acid Promoted Ring Opening of Unactivated Aziridines

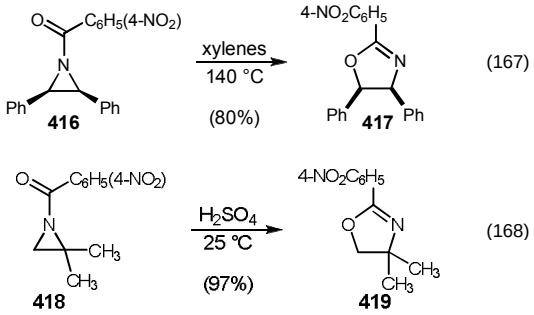


There are several examples of nucleophilic ring opening of unactivated aziridines.

[212] a) Wang, H.; Kozekov, I. D.; Harris, T. M.; Rizzo, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 5687. b) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752. c) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.
[213] a) Okawa, K.; Kinutani, T.; Sakai, K. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1353. b) Nakajima, K.; Neya, M.; Yamada, S.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3049. c) Tanaka, T.; Nakajima, K.; Maeda, T.; Nakamura, A.; Hayashi, N.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3579.
[214] Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 121.

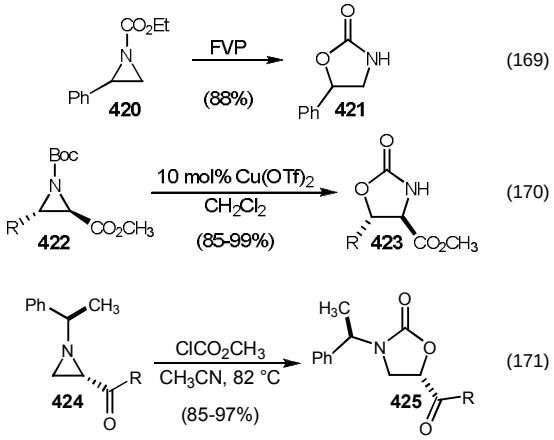
Cardillo and coworkers thermally hydrolyzed the hydrochloride salt of the *N*-H aziridine **407** (eq 163).[215] Davis and coworkers were able to hydrolyze the *N*-H aziridine **410** in the presence of tosic acid (eq 164).[216] *N*-H aziridines **412** have also been hydrolyzed by perchloric acid (eq 165).[217] Trifluoroacetic acid is also effective for aziridine ring opening reactions (eq 166).[218]

Figure 54. Oxazolines from *N*-Acylaziridines



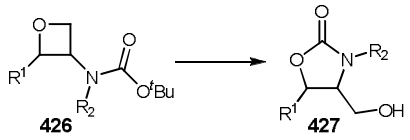
Intramolecular ring opening of *N*-acyl-aziridines has also been shown to afford

Figure 55. Oxazolidinones from Aziridines



[215] Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1339.
[216] Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525.
[217] Olofsson, B.; Khamrai, U.; Somfai, P. *Org. Lett.* **2000**, *2*, 4087.
[218] Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675.

1,2-aminoalcohols. Heine and coworkers demonstrated that *N*-acyl aziridines could be transformed to oxazolines using acid, sodium iodide, or simply thermal conditions (Figure 54).[219] Others have demonstrated that a variety of Brønsted and Lewis acids are equally effective.[220] Meanwhile, *N*-Boc aziridines **422** are efficiently converted to oxazolidinones **423** in the presence of a Lewis acid (eq 170)[221] or by flash vacuum pyrolysis (eq 169).[222] Lee and coworkers isolated oxazolidinones **425** by refluxing aziridine **424** in acetonitrile with methyl chloroformate present (eq 171).[223] Bach and coworkers have reported the analogous reaction with *N*-acyl aminooxetanes **426** (eq 172).[224]



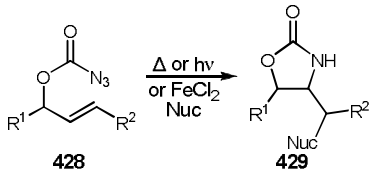
(172)

3. 2. 3. Additions to Olefins

Olefins can be converted to 1,2-aminoalcohols by aziridination, conjugate addition, electrophilic activation, direct amino hydroxylation, and via rearrangements. For example, the intramolecular aziridination of allylic azido formates followed by

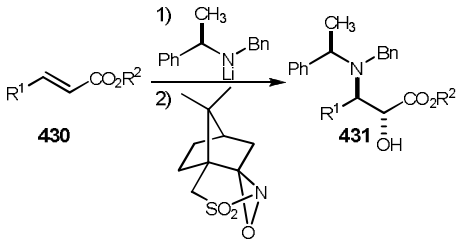
[219] a) Heine, H. W.; Fetter, M. E.; Nicholson, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 2202. b) Heine, H. W.; Kaplan, M. S. *J. Org. Chem.* **1967**, *32*, 3069.
[220] a) Allemann, S.; Vogel, P. *Synthesis* **1991**, 923. b) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *Tetrahedron Lett.* **1997**, *38*, 6953. c) Ferraris, D.; Drury, W. J.; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568.
[221] Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153.
[222] Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Hodgson, P. K. G.; Thomson, D. E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 961.
[223] Sim, T. B.; Kang, S. H.; Lee, K. S.; Lee, W. K.; Yun, H.; Dong, Y. K.; Ha, H. J. *J. Org. Chem.* **2003**, *68*, 104.
[224] Bach, T. *Synlett* **2000**, 1699.

intermolecular nucleophilic attack affords the desired aminoalcohol (eq 173).[225] The



(173)

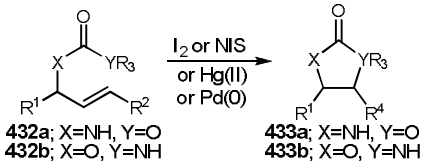
same overall transformation is realized by the generation of the acylnitrene from the carbamate form of **428** and rhodium(II) in the presence of either iodosobenzene or phenyl



(174)

iodoacetate.[226] The previously mentioned azide/olefin addition reaction is similar but does not seem to involve an aziridine as an intermediate.[138]

Davies and coworkers reported the conjugate addition of a chiral amide to

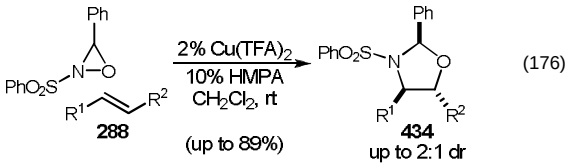


(175)

[225] a) Bach, T.; Schlummer, B.; Harms, K. *Chem.-Eur. J.* **2001**, *7*, 2581. b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449. c) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852. d) Kan, C.; Long, C. M.; Paul, M.; Ring, C. M.; Tully, S. E.; Rojas, C. M. *Org. Lett.* **2001**, *3*, 381. e) Churchill, D. G.; Rojas, C. M. *Tetrahedron Lett.* **2002**, *43*, 7225.

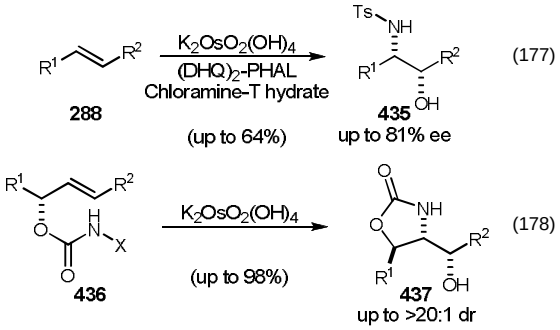
[226] a) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137. b) Levites-Agababa, E.; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863.

α,β-unsaturated ester **430** followed by electrophilic oxidation of the resulting enolate (eq 174).[227] Electrophilic activation by iodine or mercury(II) salts allows for the intramolecular cyclization with carbamates **432** (eq175).[228] The same transformation can be realized by activation of various olefins with palladium.[229]



(176)

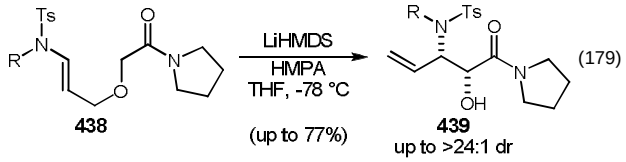
Recently, Yoon and coworkers reported a conceptually similar approach using a copper(II) Lewis acid and oxaziridine as the source of electrophilic oxygen and nucleophilic nitrogen (eq 176).[230] An asymmetric aminohydroxylation reaction utilizing an imidoosmium reagent was developed by Sharpless and coworkers (eq 177).[231]



(177)
(178)

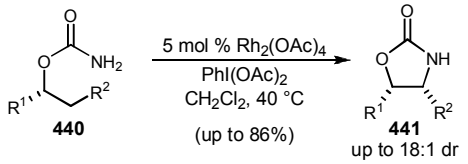
[227] Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2385.
[228] a) Zappia, G.; Gacs-Baitz, E.; Delle Monache, G.; Misiti, D.; Nevola, L.; Botta, B. *Current Organic Synthesis* **2007**, *4*, 81. b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321.
[229] a) Backvall, J. E.; Bjorkman, E. E. *J. Org. Chem.* **1980**, *45*, 2893. b) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. c) Liu, G. S.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179.
[230] a) Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 1866. b) Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 6610.
[231] Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207. Li, G. G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 451.

Donohoe and coworkers have demonstrated an intramolecular version of this aminohydroxylation reaction (eq 178).[232] Meyer and coworkers demonstrated the use of a [2,3]-Wittig rearrangement to synthesize 1,2-aminoalcohols (eq 179).[233] This motif has also been realized from the reaction of allylic amines with singlet oxygen and the hydroboration of enamines.



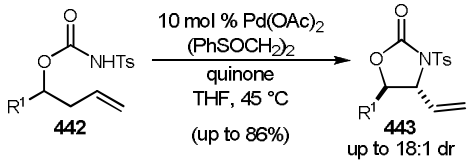
(179)

3. 2. 4. C-H Insertion



(180)

Another approach to 1,2 aminoalcohols is amination or oxidation of a C-H bond. There are some examples of α–oxidation of β–amino enolates[234] and α–amination of

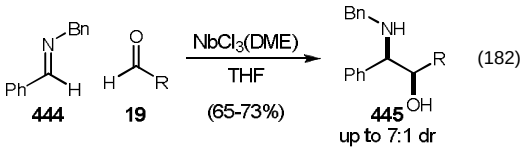


(181)

[232] Donohoe, T. J.; Bataille, C. J. R.; Gattrell, W.; Kloesges, J.; Rossignol, E. *Org. Lett.* **2007**, *9*, 1725.
[233] Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2007**, *9*, 3245.
[234] Hata, S.; Tomioka, K. *Tetrahedron* **2007**, *63*, 8514.

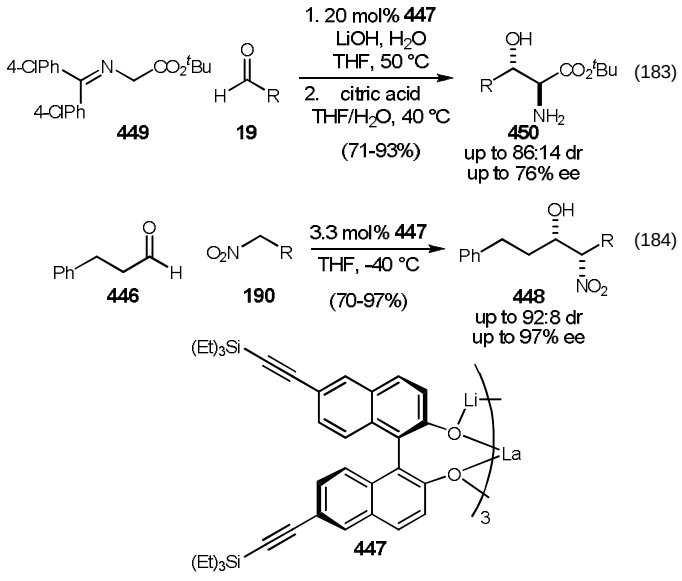
β-hydroxy enolates.[235] Du Bois has developed an intramolecular nitrene insertion in to a C-H bond to afford 1,2-aminoalcohols (eq 180).[236] White and co-workers synthesized 1,2-aminoalcohols via palladium catalyzed allylic C-H activation followed by intramolecular attack of a weak nitrogen nucleophile (eq 181).[237]

3. 2. 5. Coupling Reactions



1,2-Aminoalcohols can also be prepared by formation of the central C-C bond. For example, imines **444** and aldehydes **19** can be reductively coupled in an aza-pinacol

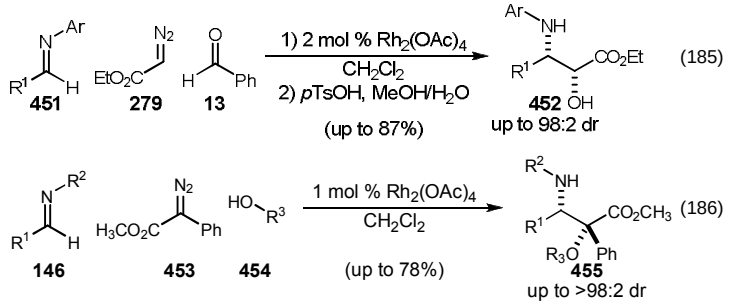
Figure 56. 1,2-Aminoalcohols via Henry and Aldol Reactions



[235] Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.
[236] Espino, C. G.; Du Bois, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598.
[237] Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274.

reaction (eq 182).[238] The nitroaldol reaction (the aza-Henry reaction) followed by reduction of the nitro group has been reported (eq 184).[239] The enolates of O'Donnell type imines **449** and related compounds have been shown to react with aldehydes **19** to form 1,2-aminoalcohols **450** (eq 183).[240] Hu and Somfai have both reported the reaction of oxonium ylides with imines (Figure 57).[241]

Figure 57. 1,2-Aminoalcohols from Oxonium Ylides



[238] a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc*. **1987**, *109*, 6551. b) Imamoto, T.; Nishimura, S. *Chem. Lett.* **1990**, 1141. c) Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. *Chem. Lett.* **1991**, 2191. d) Guijarro, D.; Yus, M. *Tetrahedron* **1993**, *49*, 7761. e) Murakami, M.; Ito, H.; Ito, Y. *J. Org. Chem.* **1993**, *58*, 6766. f) Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1995**, *36*, 5955. g) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397. h) Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 201. i) Bobo, S.; de Gracia, I. S.; Chiara, J. L. *Synlett* **1999**, 1551. j) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 4469.

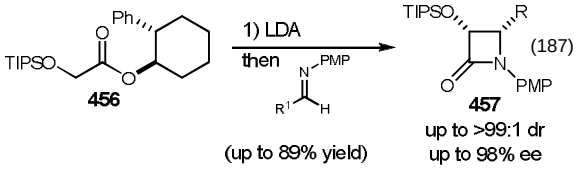
[239] a) Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388. b) Kudyba, I.; Raczko, J.; Jurczak, J. *J. Org. Chem.* **2004**, *69*, 2844.

[240] a) Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1991**, *32*, 2799. b) Hughes, P. F.; Smith, S. H.; Olson, J. T. *J. Org. Chem.* **1994**, *59*, 5799. c) Ferey, V.; Legall, T.; Mioskowski, C. *J. Chem. Soc., Chem. Commun.* **1995**, 487. d) Ding, C. Z. *Tetrahedron Lett.* **1996**, *37*, 945. e) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843. f) Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron* **2001**, *57*, 6615. g) Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 8289. h)MacMillan, J. B.; Molinski, T. F. *Org. Lett.* **2002**, *4*, 1883. i) Yamashita, A.; Norton, E. B.; Williamson, R. T.; Ho, D. M.; Sinishtaj, S.; Mansour, T. S. *Org. Lett.* **2003**, *5*, 3305. j) Thayumanavan, R.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2004**, *6*, 3541.

[241] a) Torssell, S.; Kienle, M.; Somfai, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 3096. b) Huang, H. X.; Guo, X.; Hu, W. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 1337.

3. 2. 6. The Asymmetric Glycolate Mannich Reaction

The use of α–hydroxy carbonyls in C-C bond forming reactions is well documented. Several examples exist of asymmetric catalytic glycolate aldol reactions.[242] The large body of knowledge on the diversity of substrates and the use of chiral auxiliaries and chiral Lewis acids for stereoinduction in the aldol reaction suggests the analogous



glycolate Mannich reaction is a desireable method for the rapid assembly of a diverse set of 1,2-aminoalcohols. Yet most of the progress in this area has occurred since 2000.[243] To the best of our knowledge the first use of a glycolate enolate in a Mannich reaction was demonstrated by Newcomb and coworkers in 1980.[244] Several others reported examples as part of broader studies on the reaction of ester enolates with imines.[245]

Motivated by the *syn*-1,2-aminoalcohol in the side chain of Taxol, Ojima reported the first asymmetric version of this reaction by using a nonracemic silyl ketene acetal for stereoinduction (eq 187).[246] Several others have used this technique or chiral

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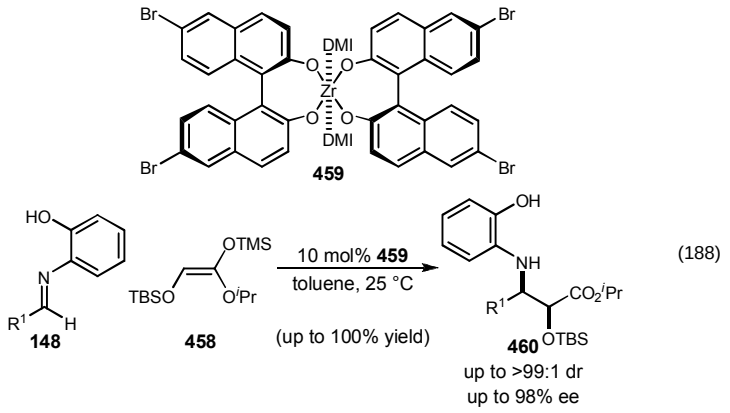
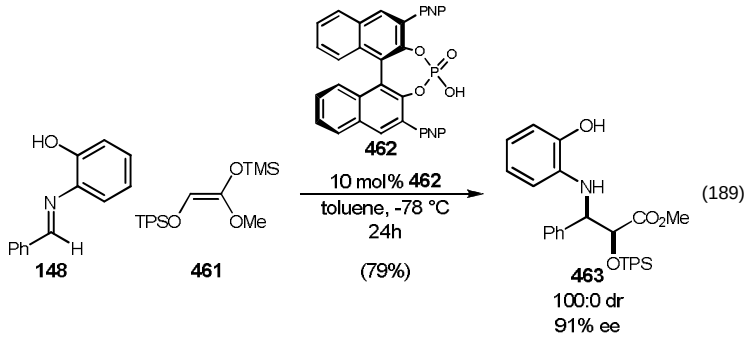
[242] Ley, S. V.; Sheppard, T. D.; Myers, R. M.; Chorghade, M. S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1451.
[243] Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447.
[244] Gluchowski, C.; Cooper, L.; Bergbreiter, D. E.; Newcomb, M. *J. Org. Chem.* **1980**, *45*, 3413.
[245] a) Ikeda, K.; Terao, Y.; Sekiya, M. *Chem. Pharm. Bull.* **1981**, *29*, 1747. b) Ojima, I.; Inaba, S. I.; Nagai, M. *Synthesis* **1981**, 545. c) Bose, A. K.; Khajavi, M. S.; Manhas, M. S. *Synthesis* **1982**, 407. d) Ikeda, K.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1983**, *24*, 4707. e) Colvin, E. W.; McGarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, 539. f) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157. g) Adrian, J. C.; Barkin, J. L.; Fox, R. J.; Chick, J. E.; Hunter, A. D.; Nicklow, R. A. *J. Org. Chem.* **2000**, *65*, 6264.
[246] Ojima, I.; Habus, I.; Zhao, M. Z.; Georg, G. I.; Jayasinghe, L. R. *J. Org. Chem.* **1991**, *56*, 1681.

nonracemic imines to achieve high diastereoselectivities in the glycolate Mannich reaction.[247]



(188)

Kobayashi and coworkers reported the first catalytic asymmetric glycolate Mannich reaction in 1998 (eq 188).[248] In 2004, Akiyama and cowokers demonstrated that a chiral Brønsted acid **148** could catalyze the glycolate Mannich reaction with excellent

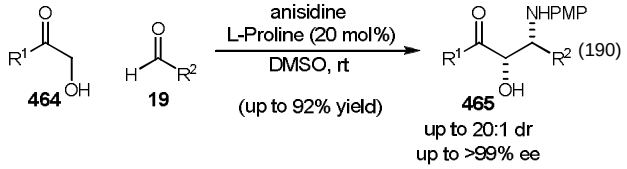


(189)

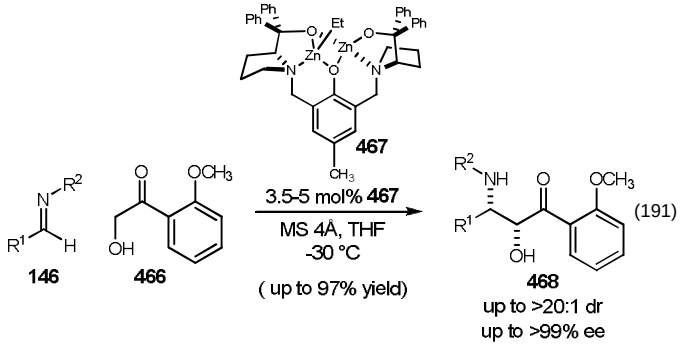
diastereo- and enantioselectivities (eq 189).[249] Both of these methods still relied on the

[247] a) Swindell, C. S.; Tao, M. *J. Org. Chem.* **1993**, *58*, 5889. b) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785. c) Arai, Y.; Yoneda, S.; Masuda, T.; Masaki, Y. *Chem. Pharm. Bull.* **2002**, *50*, 615. d) Hjelmgaard, T.; Faure, S.; Lemoine, P.; Viossat, B.; Aitken, D. J. *Org. Lett.* **2008**, *10*, 841.
[248] Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431.
[249] Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.

use of silyl ketene acetals.



The first direct catalytic asymmetric Mannich reaction using an α–hydroxy ketone **464** was developed independently by List[250] and Barbas[251] in 2002 (eq 190). Trost and coworkers were the first to report a direct catalytic asymmetric Mannich reaction using

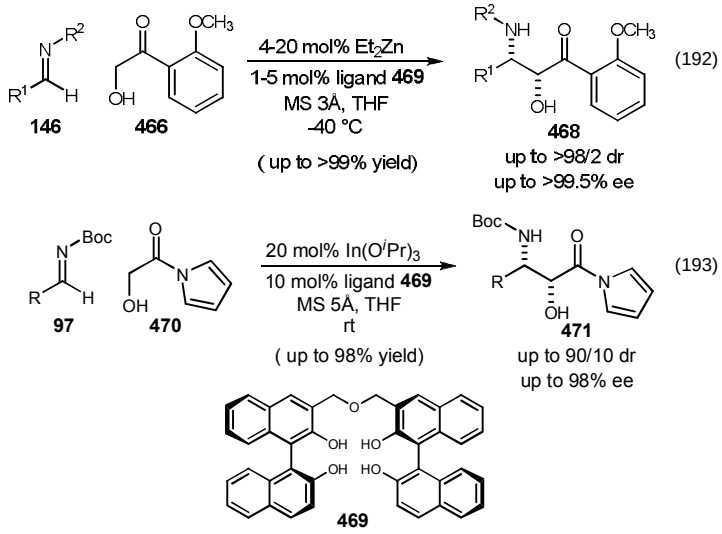


an α–hydroxy ketone **466** with a chiral nonracemic zinc lewis acid catalyst **467** (eq 191).[252] In this example the α–hydroxy ketone **466** is a phenyl ketone, which is functionally equivalent to a glycolate. More recently, Shibasaki and coworkers have devoted considerable attention to the further development of the direct catalytic

[250] List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827.
[251] b) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. *J. Am. Chem. Soc*. **2007**, *129*, 288. a) Cordova, A.; Notz, W.; Zhong, G. F.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842.
[252] a) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. b) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778.

asymmetric glycolate Mannich reaction, in order to expand the substrate scope.[253] They have utilized the α–hydroxy phenyl ketone **466** as well as the α–hydroxy acyl pyrrole **470** as glycolic acid equivalents (*Figure 58*).[254]

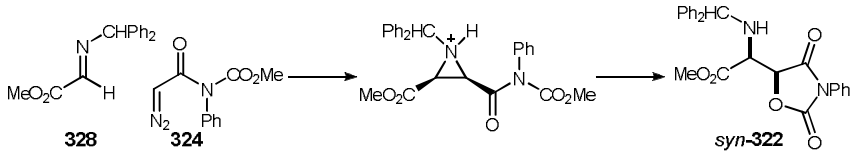
Figure 58. Shibasaki's Asymmetric Glycolate Mannich Reaction



3. 3. Development of a Novel *syn*-Glycolate Mannich Reaction

We proposed, as a result of out mechanistic studies outlined in the previous chapter, that the incorporation of a pendant nucleophile would facilitate the intramolecular

Scheme 9. Mechanistic Rationale for Development of a *syn*-Glycolate Mannich Reaction



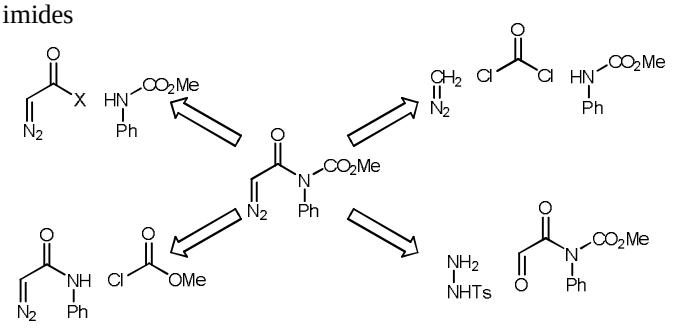
[253] a) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. b) Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339. c) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 3985.
[254] Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4365.

nucleophilic attack on the *cis*-azirdinium intermediate. We chose the imide nucleophile that had been so effective in the azide-olefin addition chemistry. As was shown in section 2. 4. 5 our hypothesis was correct and represented a novel synthesis of *syn*-oxazolidinediones. The reaction represents a short and direct Route to *syn*-1,2-aminoalcohols while establishing two key stereocenters.

3. 3. 1. Preparation of the Key α-Diazo Imide Reagent

We then sought to demonstrate the utility of this *syn*-glycolate Mannich reaction, which required the efficient synthesis of the α-diazo imide. From the outset, we

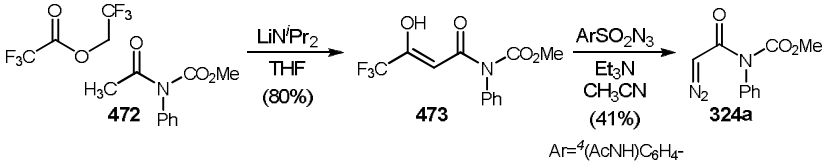
Scheme 10. Bond Disconnections for the Synthesis of A-diazo imides



considered several different approaches. Included were reactions of carbamate with activated diazoacetates, addition of diazo to the imido chloride, tosyl hydrazone formation, and reaction of chloroformate with α-diazo amide. Carbamate was deprotonated and reacted with ethyl diazoacetate, but none of the desired product was isolated. The succinimide ester and acid chloride were also used in this reaction with similar results. Attempts were also made using several coupling reagents with the carbamate and the tosyl hydrazone of glyoxylic acid. In all these cases, there was no detectable conversion leading to the isolation of the initial carbamate. Clearly the

carbamate is too weak a nucleophile for these reactions. However, the use of a stronger electrophile, like phosgene, still did not improve the outcome. The corresponding α-diazo amides were easily synthesized. Deprotonation of the α-diazo amide followed by exposure to methyl chloroformate afforded a product that appeared to be **324a** by ^{1}H NMR. However, the distinctive diazo stretch at 2100 cm^{-1} was absent from the IR.

Scheme 11. Doyle's Diazo Transfer Protocol for the Synthesis of α-Diazo Imides

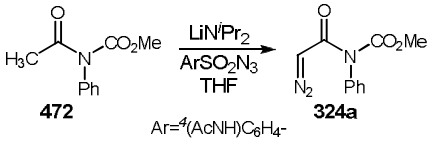


Installation of the diazo in the last step was determined to be the appropriate strategy. The imide of glyoxylic acid could not be synthesized which prevented any attempt to access the diazo from the tosyl hydrazone. Ultimately, the diazo transfer procedure of Doyle was successful (Scheme 11).[255] This procedure utilizes a Claisen condensation to afford a trifluoromethyl enol (**473**). Enol **473** is characterized by a singlet at ppm in the ^{1}H NMR. The enol **473** allows for diazo transfer to occur with a sulfonyl azide in the presence of a mild base to afford diazoimide **324a** which could be identified by a singlet at 6.61 ppm in the ^{1}H NMR and the distinctive diazo stretch at 2100 cm^{-1} in the IR. In contrast, direct diazo transfer to the enolate of **472** was inconsistent and would at best afford <10% yield of **324a** (eq 194).

Typically water was used for the removal of the trifluoroacetyl group, however it was found to be unnecessary in our case. The diazo transfer reaction with purified enol **473**

[255] Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663.

suffers from low yield. One of the major byproducts of the diazo transfer was found to be the carbamate. It is believed that this deacylation is facile and may be facilitated by the sulfonamide that results from the diazotransfer reagent. The presence of the trifluoroacetyl group likely consumes the sulfonamide and prevents it from cleaving the acyldiazo bond. The deacylation is not surprising considering the difficulties experienced with attempts to react the carbamate with various diazo acetates. Other weak nucleophiles, such as water, could also act as a nucleophile in this acyl-nitrogen bond cleavage.

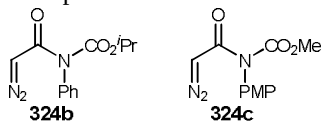


(194)

An additional practical complication was the difficulty in separating the *N*-acetyl carbamate **472** from the α-diazo imide **324a**. A slight excess of LDA was critical for full conversion to avoid mixtures of *N*-acetyl carbamate **472** and α-diazo imide **324a**. Initially the enol **473** was isolated using a wash with 50% acetic acid in water. However, complete removal of the acetic acid was difficult. The use of 1M hydrochloric acid allowed for the isolation of the enol as a light yellow solid without any purification. Allowing the extraction to stand, or leaving the isolated enol at ambient temperature for more than an hour resulted in significant amounts of carbamate formed. The enol could be purified by silica gel chromatography, but was found to be unnecessary. The enol can be prepared on a multigram scale and stored for long periods of time at -78 °C. The diazo transfer reaction was optimally kept at room temperature or below, even during solvent removal.

The byproduct of the diazo transfer reagent is removed by filtration in dichloromethane.

Figure 59. Examples of α-Diazo Imides Synthesized



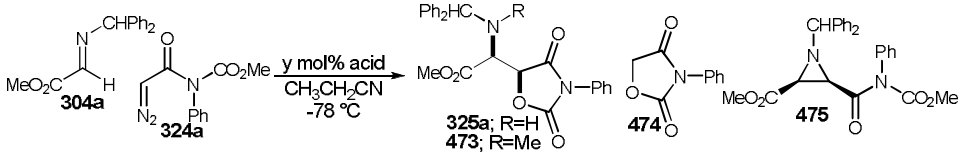
324b **324c**

The α-diazo imide is then isolated by silica gel chromatography at 0 °C. Cooler temperatures are required for the chromatography to avoid further decomposition of the α-diazo imide. It should be noted that contamination of α-diazo imide **324a** with imide **472** is a result of incomplete deprotonation in the enol formation and not from decomposition of enol or α-diazo imide. This procedure has been successfully applied to additional α-diazo imides (Figure 59).

3. 3. 2. Optimization of the syn-Glycolate Mannich Reaction

With the α-diazo imide **324a** in hand, we were able to demonstrate that the desired product **325a** was obtained by exposure of the α-diazo imide **324a** with imine **304a** in the presence of triflic acid. Not only was did this result represent a potentially useful

Table 5. Determination of Optimal Amount of Triflic Acid[a]

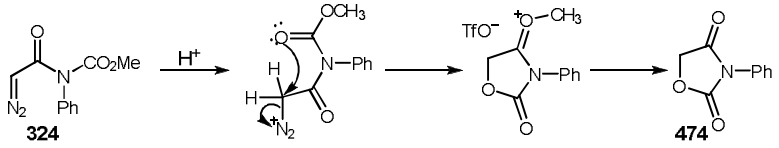


entry	y	**325a**:**473**:**474**:**475**[b]	%yield **325a**
1	50	4:3:1:1	nd
2	110	3:4:1:1	nd
3	150	7:0:3:0	61
4	200	5:0:2:0	50

[a]All reactions contained 1.2 eq of ethyl diazoacetate and were were 0.30 M in substrate and proceeded to complete conversion. [b]Ratios were measured by ^{1}H NMR.

methodology for the synthesis of *syn*-1,2-aminoalcohols, but it also was a validation of our mechanistic understanding of acid catalyzed reactions of imines with diazos. We then optimized the reaction and determine its substrate scope. The optimal amount of triflic acid for the *syn*-glycolate Mannich reaction was investigated first. Using 1.5 equivalents of acid afforded the highest yield of the desired product and the least amount of byproducts. Substoichiometric amount of acid suffered from low conversion and increased amounts of amounts of three byproducts. Perhaps the most insidious of the byproducts results from acid promoted self cyclization of the α-diazo imide **324a** to oxazolidine dione **474** (Scheme 12). We have found that product **325a** is quite stable and yields are not adversely affected by the length of the reaction. Therefore, it is most likely that byproduct **474** forms prior to addition to the imine. The relative amount of **474** increases as the amount of acid used increases. Clearly, the imine buffers the acid and slows the formation of **474**.

Scheme 12. Mechanism of Self Cyclization of α-Diazoimide

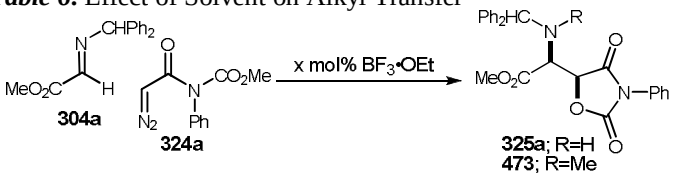


Another byproduct that was isolated is the *N*-methyl amine **473**. It would seem that this product is the result of alkyl transfer from the intermediate oxonium ion. While this is a validation of the proposed mechanism, it is an undesired product. Its formation could be eliminated by use of excess acid that ensures the evolving nucleophilic nitrogen will be protonated. It will be shown in later sections that this product is significantly reduced

by the addition of a nucleophilic scavenger or the use of an alkyl group which is more sterically hindered.

cis-Aziridine **475** can be isolated when substoichiometric amounts of acid are used. Previous work had demonstrated that turnover could be observed in the aziridine synthesis from ethyl diazoacetate,[134] but not in the preparation of α-amino-oxazolidine diones from azides.[138, 139] In the previous chapter it was shown that the *cis*-aziridine **327** could be converted to oxazolidine dione **322** with an excess of acid at higher

Table 6. Effect of Solvent on Alkyl Transfer[a]



entry	x	solvent	conc.	temp	time	**325a**:**473**[b]
1	30	DCM	0.1 M	-78 °C	96 h	1:1
2	150	CH_3CH_2CN	0.2 M	-20 °C	0.5 h	1:1
3	150	CH_3CH_2CN	0.1 M	-20 °C	0.5 h	1:1
4	150	toluene	0.1 M	-20 °C	1 h	1:1
5	150	THF	0.1 M	-20 °C	1 h[c]	1:1
6	150	EtOAc	0.1 M	-20 °C	1 h	1:1
7	150	DMF	0.1 M	0 °C	2 h[d]	-
8	150	DCM	0.1 M	-20 °C	0.5 h	1:1

[a]All reactions contained 1.2 eq of diazo and proceeded to complete conversion unless otherwise stated. [b]Ratio was determined by ^{1}H NMR. [c]Reaction did not go to completion. [d]No reaction occurred.

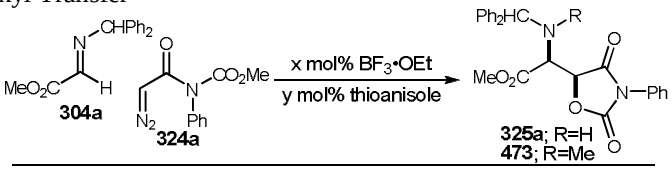
temperatures. Thus the isolation of *cis*-aziridine here may simply be the result of the intermediate not being converted to product.

An equivalent of protons from the Brønsted acid is consumed in the formation of oxazolidine dione **325a** as well as in the formation of the byproduct **474**. The mechanism of the *syn*-glycolate Mannich reaction (Scheme 8) suggests that only the protonated aziridine is capable of nucleophilic attack from the carbamate oxygen leading to the oxazolidine dione product. The conversion of this azirdinium to oxazolidine dione is

likely inhibited by a loss of a proton from the aziridinium. The amine of the oxazolidine dione is clearly nucleophilic enough to allow for methyl transfer. It is likely that this amine, by analogy, is also basic enough to remove a proton from the aziridinium, preventing its conversion to oxazolidine dione.

An initial screen of various nitrogen protecting groups for the imine found that only the benzhydryl imines provided any meaningful reactivity. It should be noted that many of these imines were found to be unstable and therefore were generated *in situ* and used without purification. A screen of various Brønsted and Lewis acids revealed that weaker acids were less effective. High conversions could be obtained with $BF_3 \cdot OEt_2$, however only if the $BF_3 \cdot OEt_2$ was freshly distilled and the reaction was kept scrupulously dry to prevent oxazolidine dione **474** formation. Even with these conditions, a 1:1 mixture of the desired product and the methyl transfer product **473** was isolated (Table 6, entry 3).

Table 7. Effect of Concentration and Nucleophilic Scavenger on Alkyl Transfer[a]



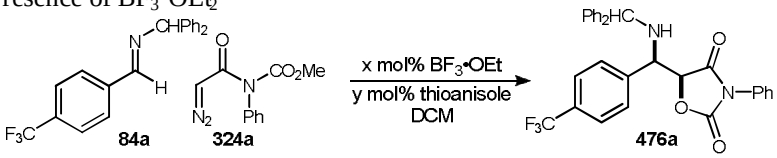
entry	x	y	solvent	conc.	temp	time	**325a**:**473**[b]
1	150	0	DCM	0.1 M	-20 °C	0.5 h	1:1
2	150	0	DCM	0.1 M	-78 °C	16 h	1:1
3	150	0	DCM	0.3 M	-78 °C	16 h	1:1
4	150	50	DCM	0.1 M	-20 °C	2 h[c]	3:1
5	150	100	DCM	0.1 M	-20 °C	4 h	6:1
6	200	100	DCM	0.1 M	-20 °C	4 h	5:1

[a]All reactions contained 1.2 eq of diazo and proceeded to complete conversion unless otherwise stated. [b]Ratio was determined by ^{1}H NMR. [c]Reaction did not go to completion. [d]No reaction occurred.

Different solvents were screened in the reaction to see if alkyl transfer was affected by less polar, aprotic solvents (Table 6). It is also possible that the nucleophilicity of the nitrile group facilitated the alkyl transfer, so non-nucleophilic solvents were also

compared (Table 6, entries 4 and 8). It was found that dichloromethane was the optimal solvent (Table 6, entry 8). Lower concentrations and lower temperature also reduced the amount of alkyl transfer (Table 6, entries 1-3). However, there were still significant amounts of the byproduct **473** forming, so the addition of nucleophilic scavengers was considered. The addition of thioanisole to the reaction, did indeed, nearly eliminate methyl transfer (Table 7, entry 5).

Table 8. The *syn*-Glycolate Mannich Reaction of Aryl imines in the Presence of $BF_3 \cdot OEt_2$[a]

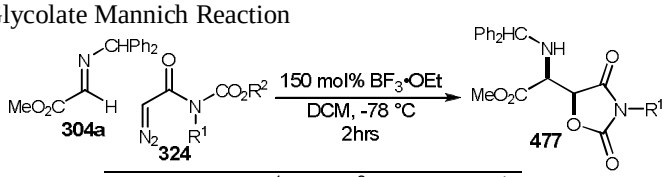


entry	x	y	temp	time	% conversion[b]
1	150	100	-20 °C	4 h	7.5
2	150	0	-20 °C to 0 °C	3 h	12
3[d,e]	100	0	-20 °C	0.5 h	19[c]

[a]All reactions contained 1.2 eq of diazo and were 0.1M in imine. [b]Determined by ^{1}H NMR. [c]Other unidentified products formed. [d]Slow addition of diazo to imine. [e]Reaction contained 1.2 eq of imine and was 0.1M in diazo.

We then attempted to apply these conditions to other substrates, however, these conditions were not effective with aryl imine **84a** (Table 8, entry 1). Although thioanisole was very effective in limiting alkyl transfer when very reactive imines were used (eg.**304a**), it might also attenuate the Lewis acid reactivity. Aryl aldimines such as **84a** are less reactive electrophiles and were not converted efficiently to oxazolidine dione even without thioanisole present (Table 8, entry 2). In an attempt to encourage binding of $BF_3 \cdot OEt_2$ to imine, hypothesizing that the α–diazo imide might be an inhibitor, the α-diazo imide was added slowly to a mixture of imine and $BF_3 \cdot OEt_2$, but no appreciable increase in conversion was observed (Table 8, entry 3). Unfortunately, warming the reaction only increased the amount of oxazolidine dione **474** formed.

Table 9. Determining the Optimal α-Diazo Imide for the *syn*-Glycolate Mannich Reaction

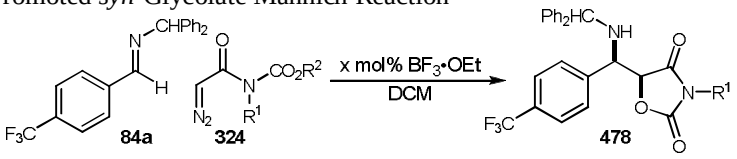


entry		R^1	R^2	conversion[b]
1	**a**	Ph	Me	64
2	**b**	Ph	iPr	66
3	**c**	PMP	Me	64
4	**d**	Bn	Me	70
5	**e**	Ph	iBu	51

[a]All reactions were 0.1 M. [b]Determined by ^{1}H NMR.

It was proposed that the amount of **474** that forms, increases as the rate of α-diazo imide addition to the imine decreases. We then investigated whether adding electron density to the α-diazo imide would improve its reactivity in this reaction. This might be

Table 10. Attempts to Increase the Conversion of the Lewis Acid Promoted *syn*-Glycolate Mannich Reaction[a]



entry		x	R^1	R^2	conc.	temp	time	% conversion[b]
1	**c**	150	PMP	Me	0.1 M	-20 °C	18 h	8
2[c]	**c**	100	PMP	Me	0.3 M	-78 °C	5 h	12
3[c]	**c**	50	PMP	Me	0.3 M	-78 °C	5 h	14
4[c]	**c**	20	PMP	Me	0.3 M	-78 °C	18 h	10
5[c]	**c**	50	PMP	Me	0.3 M	-78 °C to -20 °C	36 h	23[d]
6[c]	**b**	100	Ph	^{i}Pr	0.3 M	-20 °C	5 h	28

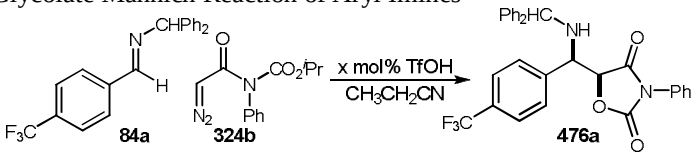
[a]All reactions contained 1.2 eq of diazo. [b]Determined by ^{1}H NMR. [c]Reaction contained 1.2 eq of imine. [d]Other unidentified products formed.

accomplished by homologating the imide nitrogen substituent from phenyl to benzyl, where the latter no longer has conjugation between the nitrogen and the aromatic ring. In order to reduce the possibility of carbamate alkyl transfer to the evolving sp^3-hybridized nitrogen, subsequent imides utilized an isopropyl carbamate instead of a methyl carbamate. Conversion of imine **304a** to oxazolidine dione **477** in the presence of α-diazo imides **324** and $BF_3 \cdot OEt_2$ was largely unaffected by these changes to the α-diazo imide

(Table 9). The same trend was observed with aryl imine **84a** and $BF_3 \cdot OEt_2$ (Table 10). However, alkyl transfer was eliminated from reactions which utilized α-diazo imide **324b**, even in the presence of one equivalent of acid. A slight improvement in conversion was realized at higher concentrations.

Since α-diazo imide **324b** was shown to have similar reactivity to α-diazo imide **324a** while preventing complications arising from alkyl transfer, we returned to studying the *syn*-glycolate Mannich reaction of aryl imines in the presence of triflic acid. The conversions with triflic acid were much higher than with $BF_3 \cdot OEt$, so different conditions were tried in order to optimize the reaction. In this example, concentration had little

Table 11. Optimization of the Triflic Acid Promoted *syn*-Glycolate Mannich Reaction of Aryl Imines



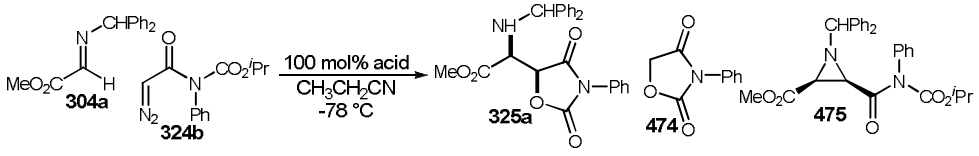
entry	x	conc.	temp	time	% conversion	%yield[a]
1[b]	100	0.3M	-78 °C	5 h	63	<53
2[b]	100	0.3M	-20 °C	2 h	53	41
3[c]	150	0.3M	-78 °C	4 h	48	-
4[b,d]	150	0.1M	-78 °C	2 h	42	-
5[c]	100	0.1M	-78 °C	18 h	62	35
6[b,e]	100	0.1M	-78 °C	18 h	70	35
7[c]	100	0.1M	-78 °C to -20 °C	18 h	36	-
8[c,f]	100	0.15M	-78 °C	15 h	100	52

[a]Determined by ^{1}H NMR. [b]Reactions contained 120 mol% of imine. [c]Reactions contained 120 mol% of diazo. [d]Acid added in 50 mol% portions every 30 min. [e]Slow addition of diazo to imine. [f]Imine was recrystallized before use.

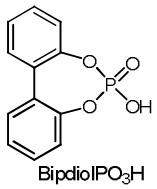
effect on the reaction and lower yields were typically a result of the consumption of α-diazo imide **324b** to formation of oxazolidine dione **474** (Table 11). It was thought that the use of excess imine might prevent formation of **474** by increasing the amount of protonated imine in solution. Excess imine **84b** neither increased the conversion of the reaction nor decreased the amount of **474** formed (Table 11, entry 1). As was true with

$BF_3 \cdot OEt$, higher temperatures also simply increased the decomposition of α–diazo imide **324b** to **474** (Table 11, entry 2). For the same reasons as mentioned above, a slow addition of α-diazo imide **324b** to a solution of imine **84a** and triflic acid was attempted, but failed to provide a meaningful improvement (Table 11, entry 6). Excess triflic acid was also tried, but in this instance only increased the amount of dione **474** formed (Table 11, entries 3 and 4).

Table 12. The Acid Screen for the *syn*-Glycolate Mannich Reaction[a]



entry	acid	time(h)	% conv	%yield	**325a:474:475**[b]
1	HBF_4	1	100	83	5:1:0
2	TfOH	1	100	76	7:1:1
3	$(CF_3SO_2)_2NH$	1	100	71	5:2.5:1
4	CF_3CO_2H	1	65	42	8:1:3
5	*p*TsOH	24	100	43	6:6:1
6	HCl[c]	4	55	40	4:8:1
7	H_3PO_4[c]	4	63	31	5:4:1
8	$BipdiolPO_3H$[c]	4	36	24	5:11:1
9	$PhCO_2H$[d]	24	<5	nd	-
10	CH_3CO_2H[d]	24	<5	nd	-
11	PPTS[c]	2	0	nd	-
12	NH_4Cl[d]	24	0	nd	0:0:0



$BipdiolPO_3H$

[a]All reactions contained 1.2 eq of diazo and were 0.15 M in substrate. [b]Ratios were measured by ^1H NMR. [c]Reactions were warmed to -20 °C for several hours. [d]Reactions were warmed to 25 °C for several hours.

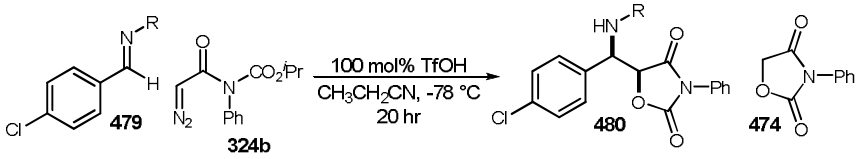
Full conversion could be accomplished with purified imines imines (Table 11, entry 8). Typically these imines are formed from equimolar amounts of the corresponding amines and aldehydes in the presence of molecular sieves and then used without any further purification.[49] No impurities are typically observed in the ^1H NMR, however the crude materials often appear colored. It was found that recrystallization of crystalline imines afforded the imines as colorless solids. It was these colorless solids that then allowed for full conversion in the *syn*-Glycolate Mannich reaction. It is possible that the

crude material contained some unreacted reagents or some other impurity in quantities that are undectable by ^{1}H NMR yet of sufficient quantity to buffer the Brønsted acid. The consequences of substoichiometric amounts of acid were discussed above and the requirement for an acid of sufficient strength will be discussed in the next section. It should be noted that further purification of non-crystalline imines was attempted by column chromatography, but did not afford imines of sufficient purity, in part due to decomposition of the imines on the silica gel adsorbant.

The optimal conditions were determined to be 100 mol% of triflic acid at -78 °C with a slight excess of α-diazo imide **324b**. With this knowledge in hand, a more thorough screen of acids was performed (Table 12). Imine **304a** was used since it had been found to be the most reactive imine in the *syn*-glycolate Mannich reaction. The data indicates that acids with pKa's below -10 afford the highest conversions and isolated yields. Acids with pKa's between 2 and -10 suffer from lower conversions and increased amounts of decomposition of the α-diazo imide **324b** to dione **474**. Interestingly, trifluoracetic acid gives an increased relative amount of the aziridine **475** (Table 12, entry 4). Finally, acids with pKa's above 3 failed to provide any conversion. Even the α-diazo imide **324b** was not decomposed, which indicates the formation of dione **474** is also dependent on acid strength.

A screen of various nitrogen protecting groups on the imine was also investigated (Table 13). For this study we utilized imines **479** derived from *p*-chlorobenzaldehyde, since the products were crystalline, easily recrystallized, and stable for a significant period of time under an inert atmosphere at ambient temperature. Conversions seem to decrease with increased steric hindrance (Table 13, entry 2). There would also seem to be

Table 13. The Imine Screen for the *syn*-Glycolate Mannich Reaction[a]



entry	R	product	%conv	%yield	dr	**480**:**474**[b]
1	Ph_2CH	**480a**	67	59	10:1	>20:1
2	Ph_3C	**480b**	0	0	NA	>1:20
3	$PhCH_2$	**480c**	52	19	10:1	1:1
4	$^{p}MeOPhCH_2$	**480d**	53	22	10:1	1:2
5	Ph	**480e**	71	50	10:1	1:1
6	$^{p}MeOPh$	**480f**	8	4	NA	1:10
7	$H_2C{=}CHCH_2$	**480g**	53	15	2:1	1:10
8	^{2}Py	**480h**	38	16	2:1	1:1
9	Boc	**480i**	100	80	2:1	4:1
10	CBz	**480j**	100	36	1:1	1:1

[a]All reactions contained 1.2 eq of diazo and were 0.15 M in substrate.
[b]Ratios were measured by ^{1}H NMR.

an electronic effect since the *p*-methoxyphenyl imine was observed to have very little conversion (Table 13, entry 6). In contrast, the *p*-methoxybenzyl imine and benzyl imine were found to be identical in conversion and isolated yield (Table 13, entries 3 and 4). The *N*-phenyl imine afforded nearly identical conversion and yield to the benzyhydryl imine (Table 13, entry 5). Full conversion and higher yields were realized with *N*-Boc imine, however the diastereoselectivity was significantly decreased (Table 13, entry 9). It has also been shown in separate studies that full conversion can be realized with both *N*-Boc imine and *N*-CBz imine using catalytic amounts of $Cu(OTf)_2$.[256]

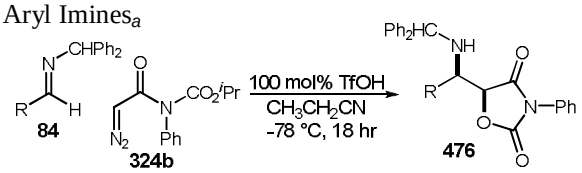
3. 3. 3. Scope of syn-Glycolate Mannich Reaction with Aryl Imines

The optimal conditions were then applied to a variety of aryl imines (Table 14). All the aryl imines used produced the desired oxazolidine dione in 10:1 dr. The lower diastereoselectivity for aryl imines may be a result of increased steric interactions by phenyl ring in the proposed [2+1] transition state (Figure 35). The increased steric

[256] Muchalski, H.; Johnston, J. N. *unpublished results.*

interaction could prevent the [2+1] transition state from being operable in favor of the open transition state of the *vic*-aminodiazonium which could cyclize to *anti*-oxazolidine dione prior to aziridine formation. If the [2+1] transition state is still operable, then the lower diastereoselectivity could be the result of a decrease in the difference in energy between the two possible possible transition states which allows for some *trans*-aziridine to be formed which in turn affords the *anti*-oxazolidine dione.

Table 14. The *syn*-Glycolate Mannich Reaction of Aryl Imines[a]



entry	R	product	%yield	dr
1	$^{p}CF_3C_6H_4$	**476a**	53	10:1
2	$^{p}NO_2C_6H_4$	**476b**	69	10:1
3	3,4-$F_2C_6H_4$	**476c**	55	10:1
4	$^{p}FC_6H_4$	**476d**	48	10:1
5	$^{p}CF_3OC_6H_4$	**476e**	51	10:1
6	3,4-$Cl_2C_6H_4$	**476f**	53	10:1
7	$^{p}BrC_6H_4$	**476g**	68	10:1
8	$^{p}ClC_6H_4$	**476h**	59	10:1
9	$^{m}PhOC_6H_4$	**476i**	37	10:1
10	$^{p}AcOC_6H_4$	**476j**	43	10:1
11	$^{p}CNC_6H_4$	**476k**	36	10:1

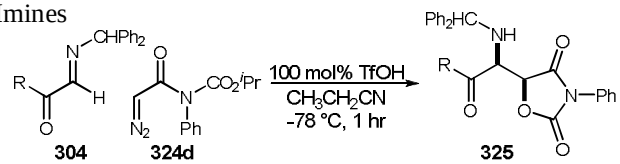
[a]Reactions contained 1.2 eq of diazo and were 0.15M in solvent. [b]Isolated by column chromatography.

In general, aryl imines were less reactive than glyoxal imines. The reaction times for aryl imines were significantly longer and vigorous nitrogen evolution is observed immediately upon addition of triflic acid to glyoxal imines, but not when added to aryl imines. This lower reactivity certainly contributes to increased amounts of byproduct **474**, but probably isn't responsible for the lower diastereoselectivity since imine **323** was highly reactive but still experienced lower diastereoselectivity. Moreover, there is no change in diastereoselectivity between electron rich and electron poor aryl imines. Higher

reactivity is observed amoung imines that have stronger electron withdrawing groups adjacent to the imine. If higher reactivity led to higher diastereoselectivity, then electron deficient aryl imines should have allowed for higher diastereoselection than electron rich aryl imines. Despite the diminished reactivity and decreased diastereoselectivity, a variety of aryl imines with various substituent patterns afforded the desired oxazolidine dione in adequate yields and high diastereoselectivity.

3. 3. 4. Scope of syn-Glycolate Mannich Reaction with Glyoxal Imines

Table 15. The *syn*-Glycolate Mannich Reaction of Glyoxal Imines



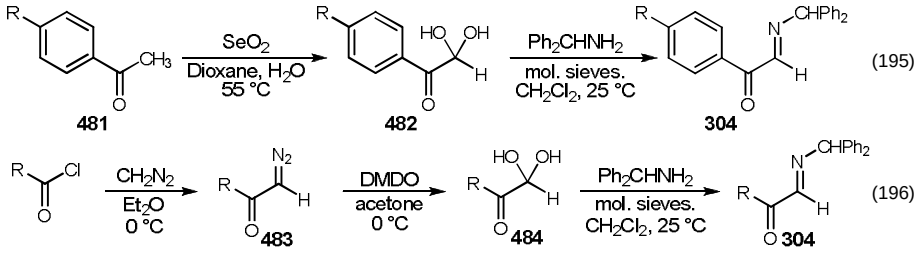
304 **324d** **325**

entry[a]	R	product	%yield	dr
1	OCH_3	**325a**	68	>20:1
2	C_6H_5	**325b**	77	>20:1
3	$^{p}CH_3C_6H_4$	**325c**	79	>20:1
4	$^{p}BrC_6H_4$	**325d**	69	>20:1
5	$^{p}FC_6H_4$	**325e**	81	>20:1
6	$^{p}CH_3OC_6H_4$	**325f**	70	>20:1
7	biphenyl	**325g**	81	>20:1
8	$^{p}CF_3OC_6H_4$	**325h**	64	>20:1
9	$^{p}AcOC_6H_4$	**325i**	66	>20:1
10	$^{p}CF_3C_6H_4$	**325j**	72	>20:1
11[c]	^{t}Bu	**325k**	88	4:1
12[c]	cyclopropyl	**325l**	98	4:1
13[c]	cyclohexyl	**325m**	97	1:1
14[c]	2-thiophenyl	**325n**	80	6:1

[a]Reactions contained 1.2 eq of diazo and were 0.15M in solvent. [b]Isolated by column chromatography. [c]Reactions performed by Hubert Muchalski.

Better yields and higher diastereoselectivities were obtained for a variety of aryl glyoxal imines. The aryl and alkyl glyoxal imines were synthesized from the corresponding hydrates (Scheme 13). The aryl glyoxal hydrates were realized from the oxidation of various acetophenone derivatives by selenium dioxide (eq 195). Alkyl glyoxal hydrates were obtained from the DMDO oxidation of diazos (eq 196). A variety

Scheme 13. The Synthesis of Glyoxal Imines

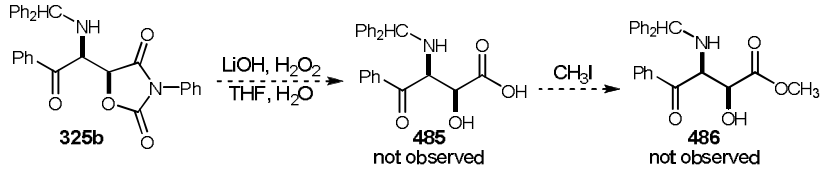


of electron rich and electron deficient phenyl glyoxal imines afforded the desired product in good yield and high diastereoselectivity (Table 15). Alkyl glyoxal imines also produced the desired products in good yield, however the diastereoselectivities were diminished (Table 15, entries 11-13). The increased steric bulk of the alkyl imines is likely the reason for erosion of the diastereoselectivity. These imines would be larger than the aryl imines and imine **323** which explains the more significant loss in diastereoselection. The alkyl glyoxal imines actually afforded the desired oxazolidine diones in greater yields. The greater yields allowed for enrichment of the major diastereomer by recrystallization in adequate yields. It is not exactly clear why the thiophenyl glyoxal imine (**325n**) afforded the desired oxazolidine dione with diminished diastereoselectivity (Table 15, entry 14). This is the only example of an imine substrate with an additional hydrogen bond acceptor. The additional hydrogen bond acceptor may in some way affect the reaction course and allow for more *anti*-oxazolidine dione to form.

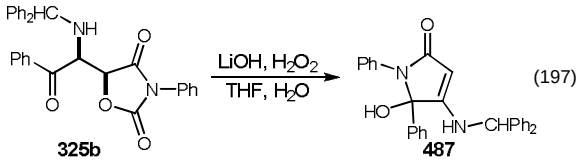
No alkyl imines were found to be crystalline which prevented any from being isolated in sufficiently high purity to be used in the *syn*-Glyclolate Mannich reaction.

3. 3. 5. Functionalization of syn-Oxazolidine Diones

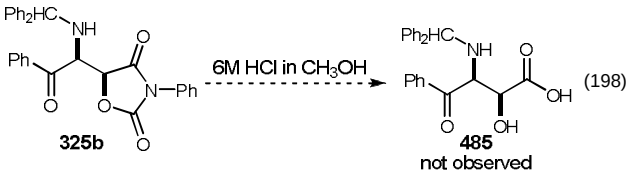
Scheme 14. The Azide-Olefin/Addition Reaction



To demonstrate the utility of the reaction we attempted to functionalize the oxazolidine dione products. Ring opening of the oxazolidine dione ring was complicated by the likely zwitterionic product being soluble in water. Ring opening was attempted by lithium peroxide and lithium hydroxide. Both reactions result in complete consumption of



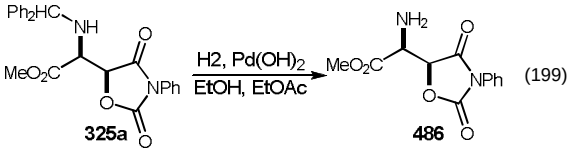
the oxazolidine dione **325b**. Initially, the crude reaction mixture was treated with methyl iodide to convert the desired carboxylic acid to the methyl ester in order to facilitate easy extraction in to an organic solvent. However, two major products were isolated from the organic layer and those products appeared to be similar with the exception of one being methylated and the other not. The reaction was repeated without any treatment with methyl iodide but the yield of the major product was still quite low. Analysis of the product would seem to indicate that oxalidine dione was opened to an amide which subsequently cyclized with the ketone to afford **487** after elimination of water (eq 197).



325b

485
not observed

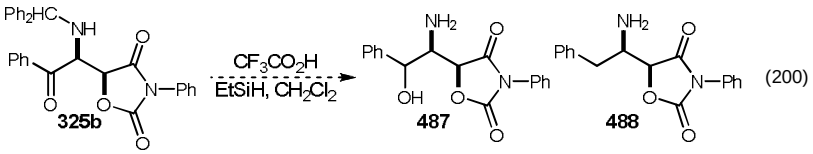
Ring opening was also attempted with refuxing 6M aqueous hydrochloric acid and also by refluxing in a methanolic solution of hydrochloric acid (eq 198). No recognizable product was isolated from either reaction and no starting material could be recovered.



325a

486

Removal of the benzhydryl group was accomplished with either trifluoracetic acid and triethyl silane or by hydrogenation with Pearlman's catalyst (eq 199).



325b

487

488

It is likely that the ketone in oxazolidine dione **325b** is likely interfering with the functionalization. One attempt was made at reducing the ketone to a methylene with trifluoroacetic acid and triethylsilane at elevated temperatures (eq 200). The benzhydryl group was removed as anticipated, but it was unclear whether the carbonyl was fully reduced to a methylene or a hydroxyl. Another reaction may have occurred at the elevated temperatures that resulted in the demise of oxazolidine dione **325b**, since attempts at ring opening with hydrochloric acid involved elevated temperatures.

3. 4. Conclusions

We have developed an effective synthesis of a novel α-diazoimide and demonstrated its utility in a novel *syn*-Glycolate Mannich Reaction. A thorough study of the synthesis of the α-diazoimide revealed that it is prone to deacylation and self-cyclization. Its ability to readily deacylate was a reflection of the weak nucleophilicity of the carbamate which prevented many of the attempted syntheses of the diazoimide form being successful. The mild diazo transfer protocol of Doyle was ultimately the best route. Facile deacylation and self-cyclization required anhydrous reaction conditions and removal of other nucleophiles from the reaction, lower reaction times, rapid isolation of the diazoimide from the reaction, and purification by silica gel column chromatography at 0 °C. This procedure ultimately could be extended to a variety of diazoimides.

Self-cyclization of the α-diazoimide was a persistent byproduct of the *syn*-Glycolate Mannich reaction. Oxazolidine dione **474** was most abundant with less reactive imines. Many of the Brønsted acids used in the reaction were capable of affecting this self-cyclization reaction. It is likely that when the *syn*-Glycolate Mannich reaction pathway is slowed then the competing self-cyclization pathway can predominate. The byproduct **474** could be eliminated by using Lewis acids under scrupulously dry conditions. Self-cyclization was also limited at -78 °C but was more significant at -20 °C. This temperature dependence indicates that the intramolecular cyclization is entropically favored over the intermolecular reaction between the diazoimide and imine.

Another unwanted byproduct of the *syn*-Glycolate Mannich reaction was N-alkylation of the desired product. This byproduct is the result of an alkyl transfer from the intermediate oxonium ion that exists after cyclization of the imide side chain. The alkyl

that transfers is the alkyl group on the carbamate incorporated in the diazoimide. The alkyl transfer could be eliminated by incorporation of a carbamate that would transfer a more substituted carbon. A slight increase in the amount of alkyl transfer was observed at higher concentrations, which suggests the alkyl transfer process is bimolecular. More alkyl transfer was observed when reduced amounts of acid were used and with $BF_3 \cdot OEt2$. The carbon boron bond is weak and would allow the nitrogen to be more nucleophilic. Greater amounts of Brønsted acids will reduce the nucleophilicity of the nitrogen since it will likely exist as an ammonium salt.

All of the results thus far suggest a concerted [2+1] transition state is key bond forming step which determines the diastereoselectivity of the syn-Glycolate Mannich reaction. The steric bulk of the groups attached to both the carbon and the amine of the imine have a pronounced effect on the diastereoselectivity of this reaction. Benzaldehyde derived imines experienced lower diastereoselection than their phenyl glyoxal counterparts. Benzaldehyde derived imines would place a phenyl ring directly attached to the proposed three membered transition state, whereas the phenylglyoxal derived imines have a carbonyl inserted between the transition state and the phenyl ring which allows for greater conformational freedom for the phenyl ring an less steric influence. The slight increase in size from a methyl to an ethyl group on the glyoxate imines also lowered the diastereoselection. The most pronounced effect was the use of secondary and tertiary carbons adjacent to the carbonyl in the glyoxal imines. It is likely that these examples are larger than the phenyl imines and the ethyl glyoxylate imines and consequently result in significantly lower diastereoselection.

The size of the group attached to the nitrogen of the imine had less of an effect on the diastereoselection of the reaction. However, larger groups were found to be less reactive. Groups that could increase the electron density on the nitrogen of the imine were less reactive as well. The most reactive imines were the glyoxylate and glyoxal imines, which have a carbonyl adjacent to the imine which can make the imine more electron deficient and thereby more electrophilic. An acid is required for the *syn*-Glycolate Mannich reaction which suggests that the LUMO of the imine must be lowered for reactions with diazos to occur. It is possible that protonation of electron rich imines is unsuccessful in lowering the LUMO enough for a favorable interaction with the HOMO of the diazoimide to occur. It should be noted that Wulff and coworkers reported that boron Lewis acids can activate the same aryl imines for reaction with ethyl diazoacetate that were virtually unreactive with our diazoimide. This suggests the HOMO of the diazoimide may be lower than the HOMO of ethyl diazoacetate. Attempts at raising the HOMO of the diazoimide did not have a dramatic effect on the outcome of the *syn*-Glycolate Mannich reaction.

Of the different acids used for the *syn*-Glycolate Mannich Reaction, triflic acid allowed for the broadest scope with the highest yields. Moreover the strength of the acid determined the distribution of products and percent conversion. Acids with pKa's lower than -10 were required to produce the desired oxazolidine dione as the major product in good yield. Acids with pKa's between -10 and 2 allowed and equal amount of the byproduct **474** to form in addition to the desired product. Trifluoroacetic acid was an exception in that less of **474** was produced, but it was less effective in converting the intermediate aziridine to oxazolidine dione. No reaction occurred with acids that had a

pKa higher than 3. It is likely that acids with pKa's less than -10 will fully protonate all the imine, but that acids with pKa's between -10 and 2 only establish an equilibrium between the protonated and non-protonated imines. An equilibrium could slow the reaction since only protonated form reacts with the diazoimide and only a certain fraction of the imine would be activated at any given time. This would explain why vigorous nitrogen evolution is observed immediately upon addition of the strongest acids, but the intermediate acids never demonstrated visible nitrogen evolution and often required higher temperatures in order to observe a reaction. It would appear that the protonated imine is not as an effective reagent for the formation of byproduct **474**. Very little of byproduct **474** is observed with the strongest acids, but in the cases where the imines are not fully protonated the acids are free to react with the diazoimide which results in the formation of increased amounts of **474**.

We have developed a new methodology using a rational design of a novel diazimide reagent as a result of our understanding of the mechanism of reactions between imines and diazos. The *syn*-Glycolate Mannich reaction affords the *syn*-1,2-aminoalcohol moiety in good yields and high diastereoselectivity for a broad range of aryl and glyoxal imines. This reaction represents a versatile and efficient synthesis of 1,2-aminoalcohols while establishing relative stereochemistry for two key stereocenters in one step. Studies are currently underway to establish an asymmetric version of this reaction.

CHAPTER IV

EXPERIMENTAL

All glassware used for reactions was flame-dried under vacuum. All reagents and solvents were commercial grade and purified prior to use when necessary. Diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), toluene ($CH_3C_6H_5$), and acetonitrile (CH_3CN) were dried by passage through a column of activated alumina as described by Grubbs.[257] Toluene was additionally passed through a column containing activated Q-5 reactant. All other solvents were distilled from calcium hydride before use or are otherwise indicated differently. All organic extracts were dried over $MgSO_4$ unless otherwise indicated.

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 µm) plates and flash chromatography utilized 230–400 mesh silica. Products were visualized using UV light, and either ceric ammonium molybdate, potassium permanganate, ninhydrin, *p*-anisaldehyde, phosphomolybdic acid, or potassium iodoplatinate solutions.

Melting points were recorded on a Laboratory Devices Mel-Temp capillary melting point apparatus or a Stanford Research Systems OptiMelt MPA100 and are reported uncorrected. IR spectra were recorded on a Nicolet Avatar 360 or a Thermo Electron (Nicolet) IR100/IR200 spectrophotometer and are reported in wavenumbers (cm^{-1}). Liquids and oils were analyzed as neat films on a NaCl plate (transmission), whereas solids were applied to a diamond plate (ATR) if a thin film could not be prepared.

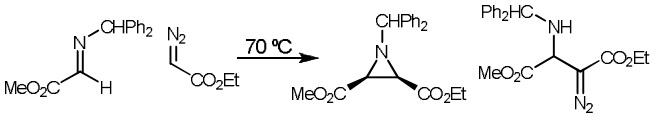
[257] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

Nuclear magnetic resonance spectra (NMR) were acquired on either a Varian instrument: INOVA-400 (400 MHz), VXR-400 (400 MHz) or Bruker instrument: AV-400 (400 MHz), DRX-500 (500 MHz), or AVII-600 (600 MHz). Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$) for ^1H and ^{13}C, respectively. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q) or combinations thereof while higher coupling patterns are not abbreviated. Mass spectra were obtained by use of chemical ionization (CI) or electrospray ionization (ESI) at Indiana University. Atlantic Microlabs, GA, performed all combustion analyses.

Methylglyoxylate,[258] ethylglyoxylate,[258] methyl 2-hydroxy-2-methoxyacetate,[259] ethyl 2-ethoxy-2-hydroxyacetate,[260] benzhydrylimino-acetic acid methyl ester (**304a**),[134] benzhydrylimino-acetic acid ethyl ester (**323**),[261] diphenylmethyl azide,[262] *p*-acetamidobenzenesulfonyl azide,[263] *N*-(4-nitrobenzylidene)benzhydrylamine (**84b**),[132] *N*-(4-fluorobenzylidene)benzhydrylamine (**84d**),[264] *N*-(4-trifluoromethoxybenzylidene)benzhydrylamine (**84e**),[265] *N*-(4-bromobenzylidene)benzhydrylamine (**84g**),[132] *N*-(4-chlorobenzylidene)benzhydrylamine (**84h**),[266] *N*-(4-acetoxybenzylidene)benzhydrylamine (**84j**),[132] *N*-(4-

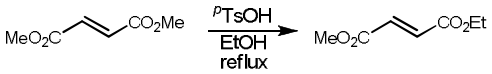
[258] Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891.
[259] Rodríguez-Borges, J. E.; García-Mera, X.; Fernández, F.; Lopes, V. H. C.; Magalhães, A. L.; Cordeiro, M. N. D. S. *Tetrahedron* **2005**, *61*, 10951.
[260] Schmidt, U.; Langner, J.; Kirschbaum, B.; Braun, C. *Synthesis* **1994**, 1138.
[261] Bailey, P. D.; Smith, P. D.; Pederson, F.; Clegg, W.; Rosair, G. M.; Teat, S. J. *Tetrahedron Lett.* **2002**, *43*, 1067.
[262] Ito, M.; Koyakumaru, K.; Ohta, T.; Takaya, H. *Synthesis* **1995**, 376.
[263] Davies, H. M. L.; Cantrell, W. R., Jr.; Romines, K. R.; Baum, J. S., *Org. Synth.*; Wiley&Sons: New York, 1998; Collect. Vol. No. 9, pp. 422.
[264] Brunner, B.; Stogaitis, N.; Lautens, M. *Org. Lett.* **2006**, *8*, 3473.
[265] Green, D. S. C.; Gruss, U.; Hägele, G.; Hudson, H. R.; Lindblom, L.; Pianka, M. *Phosphorous, Sulfur Silicon Relat.Elem.* **1996**, *113*, 179
[266] Lautens, M.; Tayama, E.; Nguyen, D. *Org. Lett.* **2004**, *6*, 345.

cyanobenzylidene)benzhydrylamine (**84k**),[267] *N*-(4-chlorobenzylidene)benzylamine (**484c**),[49] *N*-(4-chlorobenzylidene)-1-(4-methoxyphenyl)amine (**484f**),[268] *N*-(4-chlorobenzylidene)phenylamine (**484e**),[269] were prepared according to literature procedures.

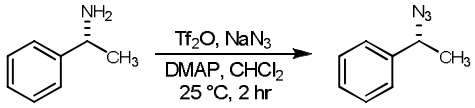


4-Ethyl 1-methyl 2-(benzyhydrylamino)-3-diazosuccinate (306). A vial was charged with the imine (57.2 mg, 0.226 mmol) and ethyl diazoacetate (221 mg, 1.94 mmol), and the resulting solution was stirred at 70 °C for 36 h. The excess diazomethane was removed *in vacuo*, and the resulting oil was purified by silica gel flash chromatography (5% ethyl acetate in hexanes) to afford the aziridine as a white solid (18 mg, 23%). Analytical data (^{1}H NMR, ^{13}C NMR) was identical to that reported. A separate fraction afforded the diazo ester as a yellow oil (16 mg, 19%). R_f = 0.17 (10% EtOAc/hexanes); IR (neat) 3341, 2981, 2093, 1734, 1685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 4H), 7.33-7.19 (m, 7H), 4.91 (s, 1H), 4.23 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.0, 142.8, 142.3, 128.7, 128.5, 127.5, 127.4, 127.34, 127.27, 64.7, 61.0, 55.3, 52.7, 14.4; HRMS (CI): Exact mass calcd for $C_{20}H_{22}N_3O_4$ $[M+H]^+$ 368.1610, found 368.1605.

[267] Siu, T.; Li, W.; Yudin, A. K. *J. Comb. Chem* **2001**, *3*, 554.
[268] Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665.
[269] Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2005**, *61*, 11148.

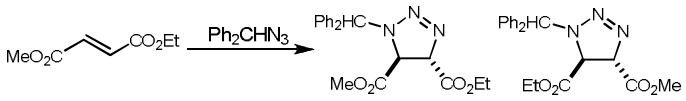


Ethyl methyl fumarate (*trans*-309). To a solution of dimethyl fumarate (14.4 g, 100 mmol) in EtOH (20 mL, 343 mmol) was added ^{p}TsOH (500 mg, 2.63 mmol) and the solution was heated to reflux for 16 h. The reaction mixture was condensed to an oil and purified by silica gel flash chromatography (5% ethyl acetate in hexanes) to afford the product as a colorless oil (4.75 g, 30%). R_f = 0.29 (1% EtOAc/hexanes); IR (neat) 2987, 1729, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.3, 164.8, 133.8, 133.0, 61.2, 52.1, 14.0; HRMS (CI): Exact mass calcd for $C_7H_{11}O_4$ $[M+H]^+$ 159.0651, found 159.0658.

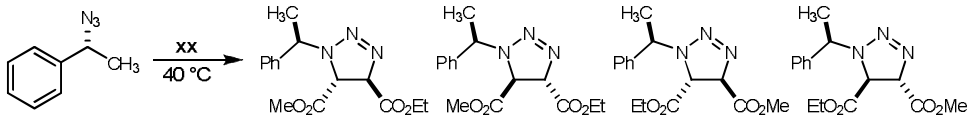


(*R*)-α-Methylbenzyl azide (312). To a cold solution (0 °C) of sodium azide (11.2 g, 172 mmol) in water (35 mL) was added CH_2Cl_2 (40 mL) and Tf_2O (6.0 mL, 35 mmol). The reaction was stirred for 2 hours and then extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and then added dropwise to a solution of (*R*)-α-methylbenzyl amine (1.12 g, 9.20 mmol) and DMAP (5.0 g, 41 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 2 h at ambient temperature, quenched with 5% aq HCl, and extracted with EtOAc. The organic layers were dried and concentrated to an oil that was purified by silica gel flash chromatography (2% diethyl ether in hexanes) to afford the product as a

colorless oil (1.04 g, 77%). R_f = 0.65 (2% Et_2O/hexanes); IR (neat) 2102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 4.63 (q, *J* = 6.8 Hz, 1H), 1.55 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 140.8, 128.7, 128.1, 126.3, 61.1, 21.5; HRMS (CI): Exact mass calcd for $C_8H_{10}N_3$ $[M+H]^+$ 147.0791, found 147.0791.



4-Ethyl 5-methyl 1-benzhydryl-[1,2,3]triazoline-4,5-dicarboxylate (310). A vial was charged with ethyl, methyl fumarate (859 mg, 5.43 mmol) and diphenylmethyl azide (842 mg, 4.02 mmol), and the solution was stirred at 40 °C for 24 h. The reaction mixture was purified by silica gel flash chromatography (20% ethyl acetate in hexanes) to afford the triazoline as a colorless oil (691 mg, 35%). IR (neat) 2976, 2099, 1745, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 20H), 6.07 (s, 1H), 6.06 (s, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 4.30-4.24 (m, 4H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.65 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.6, 167.4, 139.0, 137.7, 128.8, 128.7, 128.6, 128.4, 128.2, 127.8, 82.9, 67.8, 60.5, 53.2, 53.0; HRMS (ESI): Exact mass calcd for $C_{20}H_{22}N_3O_4$ $[M+H]^+$ 368.1605, found 368.1609.



4-Ethyl 5-methyl 1-(1-phenyl-ethyl)-[1,2,3]triazoline-4,5-dicarboxylate (313). A vial was charged with ethyl, methyl fumarate (796 mg, 5.03 mmol) and (*R*)-α-methylbenzyl azide (7.36 g, 50.0 mmol), and the solution was stirred at 45 °C for 12 h. The reaction mixture was purified by cold (0 °C) silica gel flash chromatography (10% ethyl acetate in hexanes) to afford a mixture of triazolines as a colorless oil (1.16 g, 75%). The triazolines were then separated by preparatory HPLC (15% ethyl acetate in hexanes at 20 mL/min).

Data for **313a**: R_f = 0.073 (15% EtOAc/hexanes); $[\alpha]_D^{20}$ -162.0 (*c* 0.0065, $CHCl_3$); IR (neat) 2984, 2101, 1745, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 3H), 7.21 (d, *J* = 7.0 Hz, 2H), 5.16 (d, *J* = 11.0 Hz, 1H), 4.92 (q, *J* = 7.0 Hz, 1H), 4.23 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.20 (dq, *J* = 10.5, 7.0 Hz, 1H), 4.07 (d, *J* = 11.0 Hz, 1H), 3.69 (s, 3H), 1.88 (d, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 169.5, 167.0, 139.6, 128.8, 128.1, 127.1, 82.6, 62.4, 59.6, 59.4, 52.9, 20.9, 14.0; HRMS (ESI): Exact mass calcd for $C_{15}H_{20}N_3O_4$ $[M+H]^+$ 306.1448, found 306.1447.

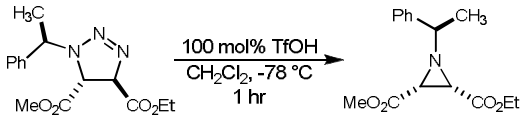
Data for **313b**: R_f = 0.13 (15% EtOAc/hexanes); $[\alpha]_D^{20}$ +143.0 (*c* 0.011, $CHCl_3$); IR (neat) 2921, 2091, 1735, 1686 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 5.17 (d, *J* = 11.2 Hz, 1H), 4.88 (q, *J* = 7.0 Hz, 1H), 4.28 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.11 (d, *J* = 11.2 Hz, 1H), 3.46 (s, 3H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.3, 167.1, 140.0, 128.6, 128.0, 127.3, 84.1, 62.5, 61.0, 60.8, 52.7, 20.4, 14.0; HRMS (ESI): Exact mass calcd for $C_{15}H_{20}N_3O_4$ $[M+H]^+$ 306.1448, found 306.1447.

Data for **313c**: R_f = 0.16 (15% EtOAc/hexanes); $[\alpha]_D^{20}$ -142.3 (*c* 0.019, $CHCl_3$); IR (neat) 2985, 2097, 1739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.26 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.21 (d, *J* = 7.0 Hz, 2H) 5.18 (d, *J* = 11.0 Hz, 1H), 4.92 (q, *J* = 7.0 Hz, 1H), 4.142 (q, *J* = 7.0 Hz, 1H), 4.139 (q, *J* = 7.0 Hz, 1H), 4.05 (d, *J* = 11.0 Hz, 1H), 3.77 (s, 3H), 1.88 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 168.8, 167.5, 139.6, 128.7, 128.1, 127.0, 82.3, 62.2, 59.6, 59.6, 53.1, 21.0, 14.0; HRMS (ESI): Exact mass calcd for $C_{15}H_{20}N_3O_4$ $[M+H]^+$ 306.1448, found 306.1447.

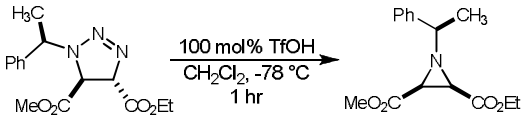
Data for **313d**: R_f = 0.12 (15% EtOAc/hexanes); $[\alpha]_D^{20}$ +167.0 (*c* 0.0185, $CHCl_3$); IR (neat) 2984, 2095, 1743, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 5.20 (d, *J* = 11.0 Hz, 1H), 4.91 (q, *J* = 7.0 Hz, 1H), 4.11 (d, *J* = 11.0 Hz, 1H), 3.96 (dq, *J* = 11.0, 7.0 Hz, 1H), 3.85 (dq, *J* = 11.0, 7.0 Hz, 1H), 3.81 (s, 3H), 1.75 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 169.7, 167.6, 140.0, 128.5, 128.0, 127.3, 83.8, 62.2, 61.1, 60.7, 53.2, 20.4, 13.7; HRMS (ESI): Exact mass calcd for $C_{15}H_{20}N_3O_4$ $[M+H]^+$ 306.1448, found 306.1447.

4-Ethyl 5-methyl 1-benzhydryl-[1,2,3]triazoline-4,5-dicarboxylate (315). A flask was charged with the unsaturated imide (1.39 g, 5.00 mmol) and diphenylmethyl azide (10.5 g, 21.5 mmol), and the solution was stirred at 45 °C for 12 h. The reaction mixture was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) at 0 °C to

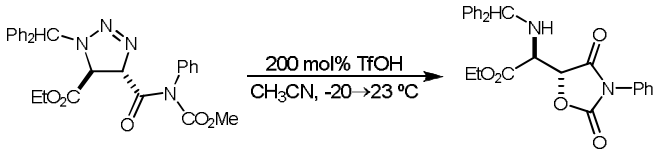
afford the triazoline as a colorless oil (86 mg, 4%). IR (neat) 2982, 1744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.28 (m, 13H), 7.16 (d, *J* = 7.2 Hz, 2H), 6.49 (d, *J* = 10.0 Hz, 1H), 6.09 (s, 1H), 4.56 (d, *J* = 10.0 Hz, 1H), 4.11 (dq, *J* = 10.7, 7.0 Hz, 1H), 4.07 (dq, *J* = 10.7, 7.0 Hz, 1H), 3.78 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 169.4, 168.4, 154.2, 139.3, 138.1, 137.4, 129.3, 128.9, 128.63, 128.60, 128.5, 128.3, 128.2, 128.0, 127.7, 127.3, 84.3, 67.7, 62.0, 60.5, 54.3, 14.0; HRMS (ESI): Exact mass calcd for $C_{27}H_{27}N_4O_5$ $[M+H]^+$ 487.1981, found 487.1982.



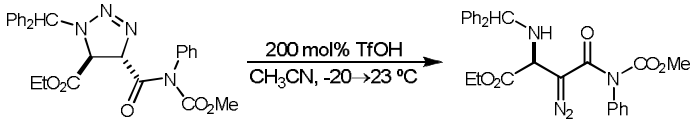
(2*S*,3*R*)-2-Ethyl 3-methyl 1-((*R*)-1-phenylethyl)aziridine-2,3-dicarboxylate (319a). To a cold (-78 °C) solution of triazoline (31 mg, 100 μmol) in dichloromethane (1 mL) was added TfOH (8.8 μL, 100 μmol), and the solution was stirred for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried and concentrated to a yellow oil that was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the aziridine as a colorless oil (12 mg, 43%). IR (neat) 2979, 2930, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 2H), 3.69 (s, 3H), 2.79 (q, *J* = 6.5 Hz, 1H), 2.58 (d, *J* = 7.0 Hz, 1H), 2.47 (d, *J* = 7.0 Hz, 1H), 1.52 (d, *J* = 6.5 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 167.8, 167.5, 142.2, 128.5, 127.5, 126.8, 69.3, 61.6, 52.3, 44.2, 42.7, 23.2, 14.1; HRMS (CI): Exact mass calcd for $C_{15}H_{20}NO_4$ $[M+H]^+$ 278.1387, found 278.1380.



(2*R*,3*S*)-2-Ethyl 3-methyl 1-((*R*)-1-phenylethyl)aziridine-2,3-dicarboxylate (319b). To a cold (-78 °C) solution of triazoline (29 mg, 95 μmol) in dichloromethane (1 mL) was added TfOH (8.4 μL, 95 μmol), and the solution was stirred for 1 h. The reaction was quenched with satd aq $NaHCO_3$, warmed to rt, and extracted with ethyl acetate. The organic layers were dried, and concentrated to a yellow oil that was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the aziridine as a white solid (10 mg, 38%). IR (neat) 2979, 2929, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 4.17 (dq, *J* = 7.5, 6.5 Hz, 1H), 4.15 (dq, *J* = 7.5, 6.5 Hz, 1H), 3.78 (s, 3H), 2.80 (q, *J* = 6.5 Hz, 1H), 2.60 (d, *J* = 6.8 Hz, 1H), 2.46 (d, *J* = 6.8 Hz, 1H), 1.52 (d, *J* = 6.5 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 168.0, 167.2, 142.2, 128.4, 127.4, 126.8, 69.2, 61.4, 52.6, 44.0, 42.9, 23.2, 14.1; HRMS (CI): Exact mass calcd for $C_{15}H_{20}NO_4$ $[M+H]^+$ 278.1387, found 278.1378. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.88; H, 7.06; N, 4.95.

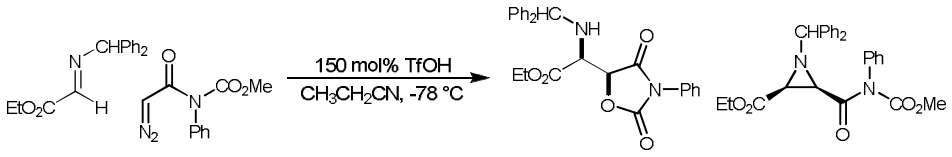


***anti*-Ethyl 2-(benzhydrylamino)-2-(2,4-dioxo-3-phenyloxazolidin-5-yl)acetate (*anti*-322)**. To a cold (-20 °C) solution of triazoline (86 mg, 180 μmol) in acetonitrile (1.77 mL) was added TfOH (31.3 μL, 354 μmol), and the solution was then allowed to warm to 25 °C and stirred for 1.5 h. The reaction was quenched with triethylamine (49 μL, 350 μmol) and concentrated to a yellow oil that was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless oil (49 mg, 62%). R_f = 0.27 (20% EtOAc/hexanes); IR (neat) 3328, 3058, 3017, 2982, 1821, 1751 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49-7.22 (m, 15H), 5.28 (d, *J* = 2.5 Hz, 1H), 5.09 (d, *J* = 4.6 Hz, 1H), 4.33 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.25 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.98 (dd, *J* = 8.4, 2.5 Hz, 1H), 2.75 (dd, *J* = 8.4, 4.6 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 169.7, 169.0, 154.2, 142.7, 141.8, 130.8, 129.5, 129.3, 129.1, 129.0, 128.7, 128.6, 128.5, 127.7, 127.6, 127.58, 127.55, 127.3, 127.2, 125.6, 125.5, 80.4, 66.2, 62.5, 59.2, 14.1; HRMS (ESI): Exact mass calcd for $C_{26}H_{24}NaN_2O_5$ $[M+Na]^+$ 467.1583, found 467.1581.



Ethyl 2-(benzhydrylamino)-3-diazo-4(methoxycarbonyl(phenyl)amino)-4-oxobutanoate (326). To a cold (-78 °C) solution of triazoline (78 mg, 160 μmol) in

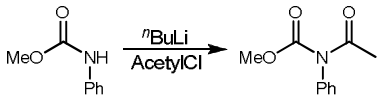
propionitrile (800 μL) was added TfOH (21.2 μL, 240 μmol), and the solution was then stirred for 1 h. The reaction was quenched with triethylamine (44 μL, 320 μmol) and concentrated to a yellow oil that was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the α-α-diazo imide as a yellow oil (39 mg, 50%). IR (neat) 3334, 3028, 2956, 2096, 1736, 1665 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.40-7.20 (m, 13H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.97 (s, 1H), 4.25 (s, 1H), 4.21 (dq, *J* = 10.7, 7.2 Hz, 1H), 4.17 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.80 (s, 3H), 2.70 (br s, 1H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.9, 166.1, 154.0, 142.8, 142.0, 129.2, 128.7, 128.5, 127.9, 127.5, 127.4, 127.3, 64.4, 62.0, 56.2, 53.9, 14.1; HRMS (CI): Exact mass calcd for $C_{27}H_{27}N_4O_5$ $[M+H]^+$ 487.1981, found 487.1968.



***syn*-Ethyl 2-(benzhydrylamino)-2-(2,4-dioxo-3-phenyloxazolidin-5-yl)acetate (*syn*-322)**. To a cold solution (-78 °C) of imine (44 mg, 160 μmol) and α-diazo imide (40.2 mg, 183 μmol) in propionitrile (0.75 mL) was added TfOH (20 μL, 230 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (27 mg, 37%) and the aziridine as a colorless solid (24 mg, 32%).

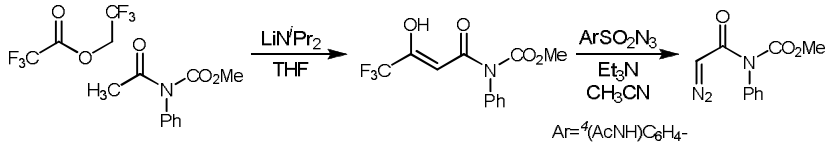
Data for *syn*-**322**: mp 119.6-120.6 °C; R_f = 0.25 (20% EtOAc/hexanes); IR (neat) 3314, 3060, 3023, 2982, 1821, 1750 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.55-7.21 (m, 15H), 5.28 (d, *J* = 2.0 Hz, 1H), 5.00 (d, *J* = 3.8 Hz, 1H), 4.30 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.26 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.95 (dd, *J* = 10.9, 2.0 Hz, 1H), 2.69 (dd, *J* = 10.9, 3.8 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 169.9, 169.6, 154.0, 143.0, 141.1, 130.8, 129.5, 129.4, 129.2, 129.1, 128.8, 128.7, 128.6, 127.7, 127.66, 127.5, 127.3, 127.2, 125.6, 125.56, 80.2, 65.6, 62.3, 58.3, 14.2; HRMS (ESI): Exact mass calcd for $C_{26}H_{24}NaN_2O_5$ $[M+Na]^+$ 467.1583, found 467.1586.

Data for *cis*-**327**: R_f = 0.14 (20% EtOAc/hexanes); IR (neat) 3068, 3021, 2973, 2956, 1746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.3 Hz, 2H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.43-7.37 (m, 3H), 7.33-7.21 (m, 6H), 7.16 (d, *J* = 7.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.10 (s, 1H), 3.67 (s, 3H), 3.50 (d, *J* = 6.7 Hz, 1H), 2.80 (d, *J* = 6.6 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 168.2. 154.5, 141.8, 141.7, 137.2, 129,4, 129.1. 128.5, 128.4, 128.3, 127.7, 127.5, 127.4, 127.2, 76.6, 61.3, 53.8, 48.2, 44.1, 14.1; HRMS (ESI): Exact mass calcd for $C_{27}H_{26}NaN_2O_5$ $[M+Na]^+$ 481.1739, found 481.1725.



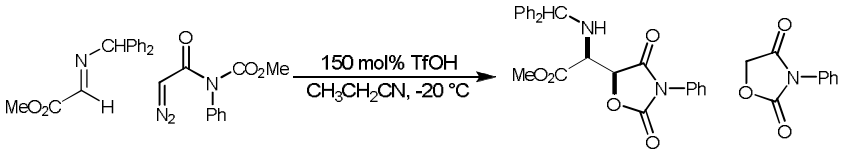
Methyl *N*-(acetyl)-*N'*-(phenyl)carbamate (472a). To a cold (-78 °C) solution of methyl *N*-(phenyl)carbamate (7.75 g, 51.2 mmol) in tetrahydrofuran (120 mL) was added *n*-butyllithium (22.0 mL, 55.0 mmol, 2.5 M). The solution was stirred at -78 °C for 1 h, at

which time acetyl chloride (3.8 mL, 43 mmol) was added. The solution was stirred at -78 °C an additional 5 hours, and then quenched with water and extracted with EtOAc. The organic layers were dried and concentrated to a brown solid that was purified by recrystallization (toluene) to afford the acetyl carbamate as a colorless crystalline solid (7.84 g, 95%). Mp 108-109 °C; R_f = 0.18 (10% EtOAc/hexanes); IR (neat) 3051, 3012, 2961, 1750, 1703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 2H), 3.69 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 172.8, 154.6, 138.0, 129.1, 128.2, 53.8, 26.4; HRMS (EI): Exact mass calcd for $C_{10}H_{11}NO_3$ $[M]^+$ 193.0733. Found 193.0729.



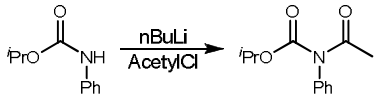
Methyl *N*-(diazoacetyl)-*N*'-(phenyl)carbamate (324a). To a cold (-78 °C) solution of diisopropylamine (15.5 mL, 111 mmol) in THF (176 mL) was added *n*-butyllithium (42.0 mL, 105 mmol, 2.5M). The solution was then warmed to 0 °C and stirred for 30 m. The solution was cooled to -78 °C and a solution of methyl *N*-(phenyl)carbamate (19.3 g, 100 mmol) in THF (200 mL) was added via canula. The solution was stirred at -78 °C for 1 h at which time trifluoroethyl trifluoroacetate (27.8 mL, 208 mmol) was added. The solution was stirred 5 m and then quenched with satd aq NH_4Cl and extracted with EtOAc. The organic layers were dried and concentrated to a brown solid that was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford a mixture of the keto and enol tautomers as a brown solid (23.5 g, 81%). To a cold solution (0 °C) of

the brown solid (2.97 g, 10.3 mmol) in acetonitrile (6.5 mL) was added triethylamine (2.1 mL, 15 mmol) and PABSA (2.31 g, 10.1 mmol). The reaction was stirred at 0 °C for 1 h, diluted with dichloromethane, filtered through a pad of Celite, and condensed to a brown oil. The oil was diluted in DCM and filtered and condensed to a brown oil that was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) at 0 °C to afford the diazoacetyl carbamate as a light yellow solid (922 mg, 41%). Mp 96-99 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (neat) 2114, 1735, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.0 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 2H), 6.61 (s, 1H), 3.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 166.7, 154.3, 137.2, 129.0, 128.6, 128.3, 53.8, 51.8; HRMS (EI): Exact mass calcd for $C_{10}H_9NO_3$ $[M-N_2]^+$ 191.0577. Found 191.0580.

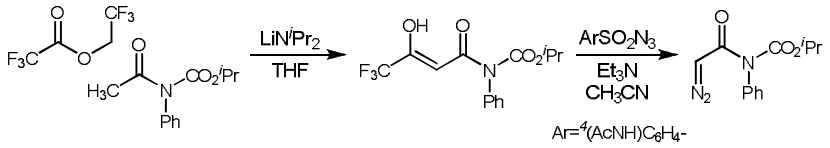


3-Phenyloxazolidine-2,4-dione (474). To a cold solution (-20 °C) of imine (39 mg, 150 μmol) and α-diazo imide (67 mg, 310 μmol) in acetonitrile (0.5 mL) was added of TfOH (20 μL, 230 μmol), and the solution was stirred at -20 °C for 1 h. The reaction was quenched with triethylamine and concentrated, and the resulting oil was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the oxazolidine dione acetate as a colorless solid (26 mg, 40%) and the oxazolidine dione as a white solid (10 mg, 18%). Mp 111-112 °C; R_f = 0.16 (20% EtOAc/hexanes); IR (neat) 1742, 1408, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.45-7.43 (m, 3H), 4.88 (s, 2H);

^{13}C NMR (125 MHz, $CDCl_3$) ppm 169.2, 154.5, 130.6, 129.4, 129.1, 125.5; HRMS (CI): Exact mass calcd for $C_9H_8NO_3$ $[M+H]^+$ 178.0499, found 178.0496.

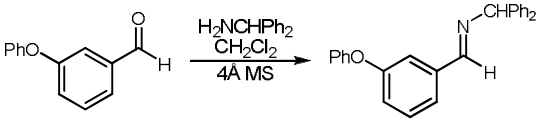


Isopropyl *N*-(acetyl)-*N'*-(phenyl)carbamate (472b). To a cold (-78 °C) solution of isopropyl *N*-(phenyl)carbamate (44.8 g, 250 mmol) in tetrahydrofuran (750 mL) was added *n*-butyllithium (120 mL, 300 mmol, 2.5M). The solution was stirred at -78 °C for 45 m after which acetyl chloride (30.5 mL, 310 mmol) was added. The solution was stirred at -78 °C an additional 5 h and then quenched with water and extracted with EtOAc. The organic layers were dried and concentrated to a brown solid that was purified by silica gel flash chromatography (5% ethyl acetate in hexanes) to afford the acetyl carbamate as a colorless crystalline solid (31.4 g, 57%). Mp 84.9-85.9 °C; R_f = 0.38 (20% EtOAc/hexanes); IR (neat) 2983, 1738, 1711, 1262 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 2H), 4.97 (sept, *J* = 6.3 Hz, 1H), 2.60 (s, 3H), 1.16 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 172.9, 153.7, 138.3, 129.0, 128.2, 128.0, 71.1, 26.5, 21.5; HRMS (ESI): Exact mass calcd for $C_{12}H_{15}NaNO_3$ $[M+Na]^+$ 244.0950, found 244.0954.

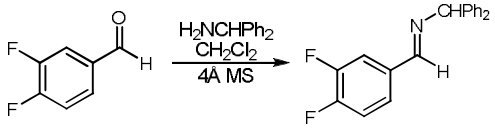


Isopropyl *N*-(diazoacetyl)-*N'*-(phenyl)carbamate (324b). To a cold (-78 °C) solution of the carbamate (1.086 g, 4.908 mmol) in THF (20 mL) was added a freshly prepared solution of lithium diispropylamide in THF (13.5 mL, 6.08 mmol, 0.45 M). The solution was stirred at -78 °C for 30 m at which time trifluoroethyl trifluoroacetate (1.40 mL, 10.5 mmol) was added. The solution was stirred 15 m and then quenched with satd aq NH_4Cl and extracted with Et_2O. The combined organic layers were washed with 50% acetic acid in water and brine, dried, and concentrated to a brown oil. To a solution of the brown oil in acetonitrile (3.4 mL) was added PABSA (1.172 g, 5.136 mmol) and then triethylamine (1.0 mL, 7.2 mmol). The reaction was stirred at ambient temperature for 1 h and then diluted in dichloromethane, filtered through a pad of Celite, and condensed to a brown oil that was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) at 0 °C to afford the diazoacetyl carbamate as a light yellow solid (165 mg, 14%). Mp 61.5-62.5 °C; R_f = 0.38 (20% EtOAc/hexanes); IR (neat) 2983, 2115, 1729 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.35 (m, 3H), 7.13-7.10 (m, 2H), 6.61 (s, 1H), 4.94 (sept, *J* = 6.0 Hz, 1H). 1.14 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 166.9, 153.4, 137.6, 129.0, 128.9, 128.6, 128.1, 71.9, 51.8, 21.5; HRMS (ESI): Exact mass calcd for $C_{12}H_{13}NaN_3O_3$ $[M+Na]^+$ 270.0855, found 270.0859.

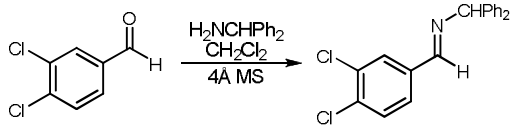
General Procedure for aldimine synthesis. All imines were prepared according to the procedure reported by Jacobsen.[49]



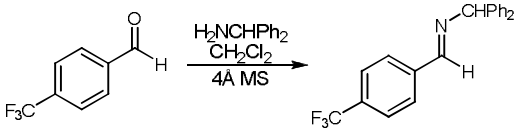
***N*-(3-Phenoxybenzylidene)benzhydrylamine (84i).** Colorless crystals. Mp 109.3-109.9 °C; IR (neat) 3060, 3026, 2848, 1643, 1580, 1489, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.57 (s, 1H), 7.34-7.33 (m, 11H), 7.26 (dd, *J* = 7.5, 7.0 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 2H), 5.62 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 160.0, 157.4, 157.1, 143.8, 138.3, 129.83, 129.78, 128.4, 127.6, 127.0, 123.4, 123.3, 121,2, 118.8, 118.7, 77.9; HRMS (ESI): Exact mass calcd for $C_{26}H_{22}NO$ $[M+H]^+$ 364.1701, found 364.1705.



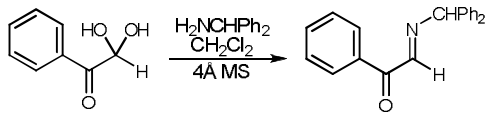
***N*-(3,4-Difluorobenzylidene)benzhydrylamine (84c).** Colorless crystals. Mp 75.4-75.9 °C; IR (neat) 3061, 3027, 2850, 1645, 1606, 1515, 1282 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.81 (dd, *J* = 8.5, 8.5 Hz, 1H), 7.53-7.49 (m, 1H), 7.43 (d, *J* = 6.7, 4H), 7.37 (dd, *J* = 7.2, 7.2 Hz, 4H), 7.28 (t, *J* = 7.0 Hz, 2H), 7.22 (dd, *J* = 17.6, 8.5 Hz, 1H), 5.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.3, 152.6 (dd, *J* = 138.9, 13.0 Hz), 150.1 (dd, *J* = 135.0, 13.1 Hz), 143.5, 133.5 (dd, *J* = 5.2, 3.7 Hz), 128.5, 127.6, 127.1, 125.2 (dd, *J* = 6.7, 3.4 Hz), 117.3 (d, *J* = 17.8 Hz), 116.4 (d, *J* = 17.9 Hz), 77.7; HRMS (CI): Exact mass calcd for $C_{22}H_{15}F_2N$ $[M]^+$ 307.1167, found 307.1172.



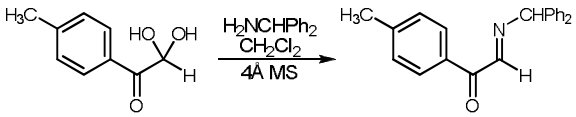
***N*-(3,4-Dichlorobenzylidene)benzhydrylamine (84f).** Colorless crystals. Mp 84.0-84.6 °C; IR (neat) 3061, 3026, 2849, 1642, 1557, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.01 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.47-7.27 (m, 10H), 5.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 158.2, 143.4, 136.1, 134.7, 133.0, 130.5, 129.7, 128.5, 127.5, 127.1, 77.8; HRMS (CI): Exact mass calcd for $C_{20}H_{15}Cl_2N$ $[M]^+$ 339.0582, found 339.0560.



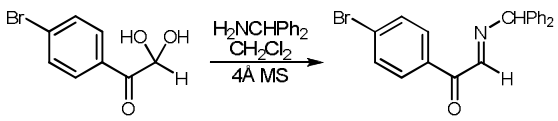
***N*-(4-Trifluorobenzylidene)benzhydrylamine (84a).** Colorless crystals. Mp 82.4-82.7 °C; IR (neat) 3062, 3027, 2848, 1643, 1493, 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 4H), 7.38 (dd, *J* = 7.4, 7.4 Hz, 4H), 7.29 (t, *J* = 6.9 Hz, 2H), 5.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.3, 143.5, 139.4, 132.3 (q, *J* = 32.5 Hz), 128.6, 128.5, 127.6, 127.2, 125.5 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.3 Hz), 77.9; HRMS (ESI): Exact mass calcd for $C_{21}H_{16}F_3N$ $[M]^+$ 339.1229, found 339.1217.



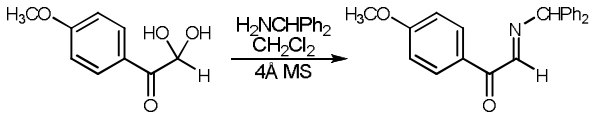
2-(Benzhydrylimino)-1-phenylethanone (304b). Colorless crystals. Mp 92.8-93.5 °C; IR (neat) 3061, 3027, 2862, 1662, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.2 Hz, 2H), 8.24 (s, 1H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.51 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.34-7.33 (m, 8H), 7.32 (dd, *J* = 6.8, 6.8 Hz, 2H), 5.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 190.6, 159.6, 142.1, 135.0, 133.5, 130.7, 128.6, 128.2, 127.5, 127.4, 78.6; HRMS (ESI): Exact mass calcd for $C_{21}H_{17}NaNO$ $[M+Na]^+$ 322.1208, found 322.1197.



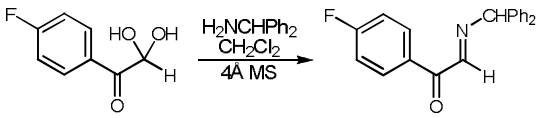
2-(Benzhydrylimino)-1-(4-methylphenyl)ethanone (304c). Colorless crystals. Mp 71.0-72.0 °C; IR (neat) 3061, 3028, 2861, 1658, 1604, 1492, 1295 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.2 Hz, 2H), 8.19 (s, 1H), 7.40-7.34 (m, 8H), 7.30-7.27 (m, 4H), 5.66 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 190.3, 159.8, 144.5, 142.2, 132.6, 130.8, 129.1, 128.7, 127.6, 127.4, 78.6, 21.7; HRMS (ESI): Exact mass calcd for $C_{22}H_{19}NaNO$ $[M+Na]^+$ 336.1364, found 336.1352.



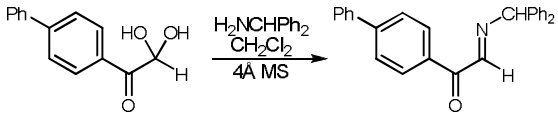
2-(Benzhydrylimino)-1-(4-bromophenyl)ethanone (304d). Colorless crystals. Mp 101.5-102.5 °C; IR (neat) 3061, 3028, 2863, 1663, 1584, 1492, 1290 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.5 Hz, 2H), 8.19 (s, 1H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.41-7.31 (m, 10H), 5.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 189.5, 159.4, 141.9, 133.7, 132.2, 131.6, 128.9, 128.7, 127.5, 127.4, 78.6; HRMS (ESI): Exact mass calcd for $C_{21}H_{16}BrNaNO$ $[M]^+$ 400.0313, found 400.0333.



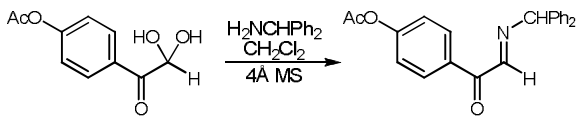
2-(Benzhydrylimino)-1-(4-methoxyphenyl)ethanone (304f). Colorless crystals. Mp 91.5-92.5 °C; IR (neat) 3061, 3027, 2934, 2840, 1655, 1597, 1572, 1259 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.9 Hz, 2H), 8.19 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 4H), 7.38 (dd, *J* = 7.7, 7.7 Hz, 4H), 7.30 (t, *J* = 6.9 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 1H), 5.66 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 188.9, 164.0, 160.0, 142.3, 133.1, 128.6, 128.0, 127.6, 127.4, 113.6, 78.6, 55.4; HRMS (ESI): Exact mass calcd for $C_{22}H_{19}NaNO_2$ $[M+Na]^+$ 352.1313, found 352.1305.



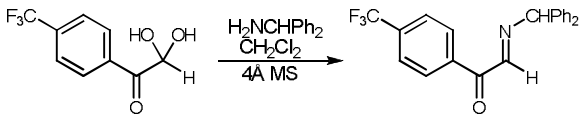
2-(Benzhydrylimino)-1-(4-fluorophenyl)ethanone (304e). Colorless crystals. Mp 107.1-107.6 °C; IR (neat) 3062, 3028, 2864, 1663, 1597 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 8.0, 5.8 Hz, 2H), 8.18 (s, 1H), 7.39-7.30 (m, 10H), 7.16 (t, *J* = 8.7 Hz, 2H), 5.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 188.9, 167.4, 164.8, 159.7, 142.0, 133.6, 133.5, 131.4, 128.7, 127.6, 127.5, 115.6, 115.4, 78.6; HRMS (ESI): Exact mass calcd for $C_{21}H_{16}FNaNO$ $[M+Na]^+$ 340.1114, found 340.1127.



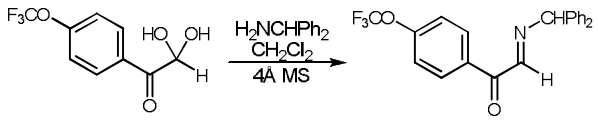
2-(Benzhydrylimino)-1-(4-phenylphenyl)ethanone (304g). Colorless crystals. Mp 122.1-123.1 °C; IR (neat) 3059, 3029, 2862, 1659, 1602 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 6.8 Hz, 2H), 8.27 (s, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 6.0 Hz, 2H), 7.54-7.29 (m, 14H), 5.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 190.1, 159.8, 146.1, 142.1, 139.8, 133.8, 131.3, 128.9, 128.7, 128.2, 127.54, 127.47, 127.2, 126.9, 78.6; HRMS (ESI): Exact mass calcd for $C_{27}H_{21}NaNO$ $[M+Na]^+$ 398.1521, found 398.1533.



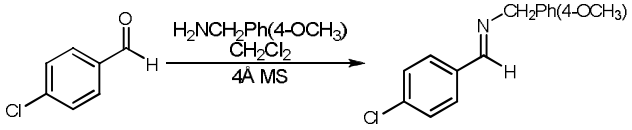
2-(Benzhydrylimino)-1-(4-acetoxyphenyl)ethanone (304i). Colorless crystals. Mp 97.7-98.7 °C; IR (neat) 3062, 3028, 2865, 1762, 1662, 1598, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.6 Hz, 2H), 8.18 (s, 1H), 7.38-7.27 (m, 10H), 7.23 (d, *J* = 8.7 Hz, 2H), 5.67 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 189.2, 168.7, 159.6, 154.7, 142.1, 132.6, 132.5, 128.7, 127.5, 121.5, 78.7, 21.1; HRMS (ESI): Exact mass calcd for $C_{23}H_{19}NaNO_3$ $[M+Na]^+$ 380.1263, found 380.1266.



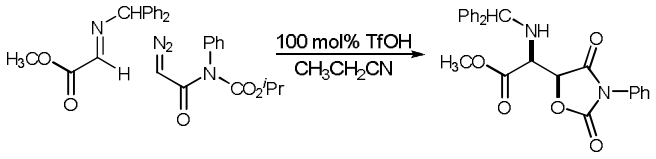
2-(Benzhydrylimino)-1-(4-trifluoromethylphenyl)ethanone (304j). Colorless crystals. Mp 95.5-96.4 °C; IR (neat) 3063, 3029, 2865, 1666, 1601, 1259, 1222, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.9 Hz, 2H), 8.20 (s, 1H), 7.41-7.32 (m, 12H), 5.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 189.0, 159.6, 152.9, 141.9, 133.2, 132.9, 128.7, 127.6, 127.5, 119.9, 119.3 (q, *J* = 258.9 Hz), 78.7; HRMS (ESI): Exact mass calcd for $C_{22}H_{16}F_3NaNO$ $[M+Na]^+$ 390.1082, found 390.1091.



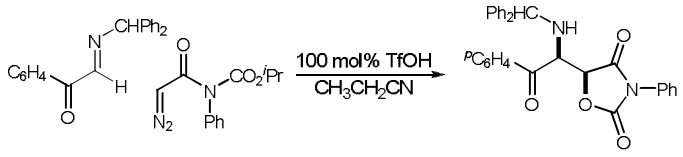
2-(Benzhydrylimino)-1-(4-trifluoromethoxyphenyl)ethanone (304h). Colorless crystals. Mp 50.5-51.5 °C; IR (neat) 3063, 3029, 2866, 1670, 1642, 1325 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.0 Hz, 2H), 8.21 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.41-7.31 (m, 10H), 5.71 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 189.7, 159.3, 141.9, 137.8, 134.5 (q, *J* = 32.7 Hz), 131.1, 128.8, 127.6, 127.5, 125.2 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.8 Hz), 78.6; HRMS (ESI): Exact mass calcd for $C_{22}H_{16}F_3NaNO_2$ $[M+Na]^+$ 406.1031, found 406.1024.



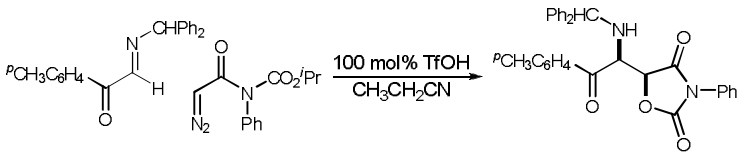
***N*-(4-Chlorobenzylidene)-1-(4-methoxyphenyl)methanamine (479d).** Colorless crystals. Mp 56.0-56.8 °C; IR (neat) 3000, 2932, 2834, 1644, 1511, 1247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.77 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 160.1, 158.7, 136.6, 134.6, 131.1, 129.4, 129.2, 128.8, 113.9, 64.4, 55.2; HRMS (CI): Exact mass calcd for $C_{15}H_{14}ClNO$ $[M]^+$ 259.0758, found 259.0754.



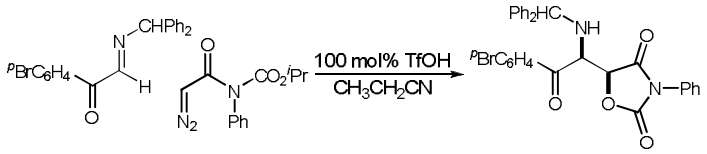
Methyl 2-(benzhydrylamino)-2-(2,4-dioxo-3-phenyloxazolidin-5-yl)acetate (325a). To a cold (-78 °C) solution of imine (39 mg, 150 μmol) and α-diazo imide (48.9 mg, 198 μmol) in propionitrile (1.0 mL) was added dry TfOH (13 μL, 150 μmol), and the solution was stirred at -78 °C for 3 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (44 mg, 68%). Mp 120.5-121.5 °C; R_f = 0.07 (10% EtOAc/hexanes); IR (film) 3323, 3028, 2954, 1820, 1749, 1503 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55-7.34 (m, 5H), 7.34-7.22 (m, 10H), 5.27 (d, *J* = 1.9 Hz, 1H), 5.00 (d, *J* = 3.4 Hz, 1H), 3.98 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.82 (s, 3H), 2.70 (dd, *J* = 10.9, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.4, 169.5. 153.9, 142.9, 141.0, 130.8, 129.5, 129.4, 129.1, 129.0, 128.7, 128.6, 127.73, 127.68, 127.6, 127.2, 125.6, 125.5, 80.1, 65.5, 58.2, 53.0; HRMS (CI): Exact mass calcd for $C_{25}H_{23}N_2O_5$ $[M+H]^+$ 431.1607, found 431.1608. Anal Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.15; N, 6.51. Found: C, 69.70; H, 5.16; N, 6.48. Relative stereochemistry determined by X-ray diffraction of a crystal grown from toluene in a chamber containing petroleum ether.



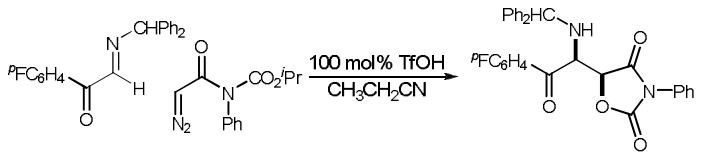
***syn*-5-(1-(Benzhydrylamino)-2-oxo-2-phenylethyl)-3-phenyloxazolidine-2,4-dione (325b)**. To a cold (-78 °C) solution of imine (46 mg, 150 μmol) and α-diazo imide (47.4 mg, 192 μmol) in propionitrile (1.0 mL) was added dry TfOH (13 μL, 150 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (54 mg, 77%). Mp 133-133.5 °C; R_f = 0.089 (10% EtOAc/hexanes); IR (film) 3312, 3062, 1823, 1749, 1686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.4 Hz, 2H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.55-7.45 (m, 8H), 7.35-7.20 (m, 9H), 5.13 (d, *J* = 2.1 Hz, 1H), 4.88-4.87 (m, 2H), 3.24 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 196.3, 169.9, 153.8, 142.7, 141.6, 134.4, 134.1, 130.8, 129.4, 129.1, 129.0, 128.9, 128.62, 128.57, 128.4, 127.6, 127.5, 127.3, 125.7, 78.9, 65.5, 60.1; HRMS (ESI): Exact mass calcd for $C_{30}H_{24}N_2NaO_4$ $[M+Na]^+$ 499.1634, found 499.1645. Anal Calcd for $C_{30}H_{24}N_2O_4$: C, 75.61; H, 5.08; N, 5.88. Found: C, 75.25; H, 5.04; N, 5.85.



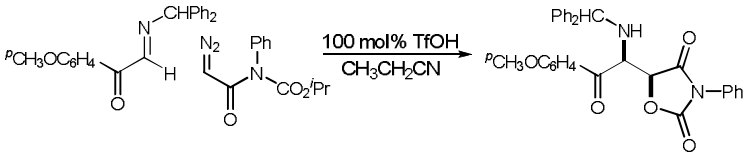
***syn*-5-(1-(Benzhydrylamino)-2-oxo-2-*p*-tolylethyl)-3-phenyloxazolidine-2,4-dione (325c)**. To a cold (-78 °C) solution of imine (50.4 mg, 161 μmol) and α-diazo imide (47.3 mg, 191 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (59 mg, 79%). Mp 138.5-139.5 °C; R_f = 0.091 (10% EtOAc/hexanes); IR (film) 3311, 3061, 3026, 1823, 1751, 1685 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.53 (dd, *J* = 8.6, 7.4 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.31-7.21 (m, 11H), 5.12 (d, *J* = 2.2 Hz, 1H), 4.87-4.85 (m, 2H), 3.24 (br s, 1H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 195.7, 170.0, 153.9, 145.4, 142.9, 141.7, 131.9, 130.9, 129.8, 129.5, 129.1, 128.7, 128.6, 127.7, 127.6, 127.5, 127.3, 125.7, 79.2, 65.5, 59.9, 21.8; HRMS (ESI): Exact mass calcd for $C_{31}H_{27}N_2O_4$ $[M+H]^+$ 491.1965, found 491.1967.



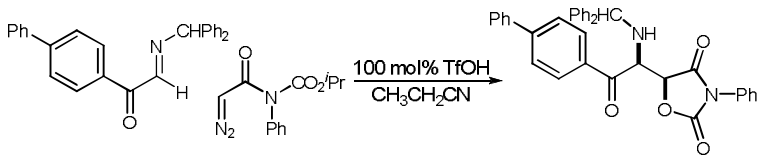
***syn*-5-(1-(Benzhydrylamino)-2-(4-bromophenyl)-2-oxoethyl)-3-phenyloxazolidine-2,4-dione (325d)**. To a cold (-78 °C) solution of imine (59.3 mg, 157 μmol) and α-diazo imide (44.9 mg, 182 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless oil (60 mg, 69%). R_f = 0.11 (10% EtOAc/hexanes); IR (film) 3307, 3061, 3024, 1822, 1749, 1686 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 7.9, 7.6 Hz, 2H), 7.47 (d, *J* = 7.0 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.31-7.22 (m, 9H), 5.09 (d, *J* = 2.4 Hz, 1H), 4.88 (s, 1H), 4.82 (br s, 1H), 3.21 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 195.4, 170.0, 153.8, 142.5, 141.5, 133.1, 132.5, 130.8, 129.9, 129.6, 129.5, 129.1, 128.72, 128.69, 127.8, 127.7, 127.6, 127.4, 125.7, 78.4, 65.6, 60.0; HRMS (ESI): Exact mass calcd for $C_{30}H_{24}BrN_2O_4$ $[M+H]^+$ 555.0914, found 555.0908.



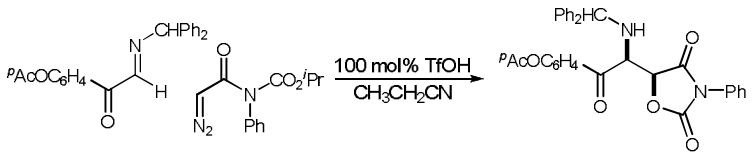
***syn*-5-(1-(Benzhydrylamino)-2-(4-fluorophenyl)-2-oxoethyl)-3-phenyloxazolidine-2,4-dione (325e)**. To a cold (-78 °C) solution of imine (48 mg, 150 μmol) and α-diazo imide (46.8 mg, 189 μmol) in propionitrile (1.0 mL) was added dry TfOH (13 μL, 150 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (59 mg, 81%). Mp 146.5-147 °C; R_f = 0.091 (5% EtOAc/hexanes); IR (film) 3309, 3063, 3024, 1824, 1750, 1688 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.5, 5.2 Hz, 2H), 7.54 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.47 (dd, *J* = 7.4, 7.4 Hz, 1H) 7.33 (d, *J* = 7.2 Hz, 2H), 7.31-7.27 (m, 7H), 7.22 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 5.10 (d, *J* = 2.3 Hz, 1H), 4.88 (br s, 1H), 4.84 (dd, *J* = 6.0, 2.3 Hz, 1H), 3.23 (br d, *J* = 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 194.7, 170.0, 167.2, 165.4, 153.8, 142.6, 141.6, 131.3, 131.2, 130.8, 129.5, 129.1, 128.70, 128.67, 127.7, 127.64, 127.61, 127.4, 125.7, 116.4 (d), 78.5, 65.5, 59.9; HRMS (ESI): Exact mass calcd for $C_{30}H_{24}FN_2O_4$ $[M+H]^+$ 495.1715, found 495.1719.



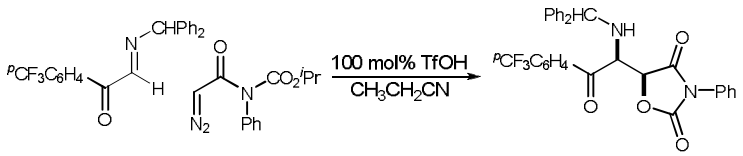
***syn*-5-(1-(Benzhydrylamino)-2-(4-methoxyphenyl)-2-oxoethyl)-3-phenyloxazolidine-2,4-dione (325f)**. To a cold (-78 °C) solution of imine (50 mg, 150 μmol) and α-diazo imide (45.1 mg, 182 μmol) in propionitrile (1.0 mL) was added dry TfOH (13 μL, 150 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (52 mg, 70%). Mp 126-127 °C; R_f = 0.056 (10% EtOAc/hexanes); IR (film) 3307, 3027, 2933, 1823, 1751, 1678 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 9.1 Hz, 2H), 7.54 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.0 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.31-7.24 (m, 7H), 7.21 (d, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 9.1 Hz, 2H), 5.12 (d, *J* = 2.3 Hz, 1H), 4.85 (d, *J* = 1.4 Hz, 1H), 4.83 (dd, *J* = 10.1, 1.4 Hz, 1H), 3.88 (s, 3H), 3.24 (dd, *J* = 10.1, 2.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 194.4, 170.1, 164.4, 153.9, 142.9, 141.7, 130.9, 129.5, 129.0, 128.63, 128.59, 127.7, 127.6, 127.5, 127.3, 127.2, 125.7, 114.3, 79.2, 65.5, 59.6, 55.6; HRMS (ESI): Exact mass calcd for $C_{31}H_{27}N_2O_5$ $[M+H]^+$ 507.1914, found 507.1922.



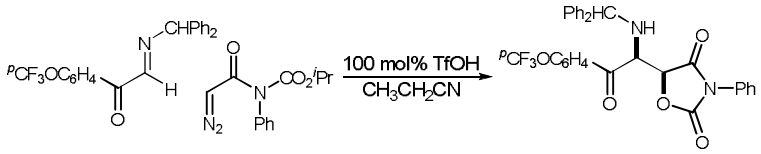
***syn*-5-(1-(Benzhydrylamino)-2-(biphenyl-4-yl)-2-oxoethyl)-3-phenyloxazolidine-2,4-dione (325g)**. To a cold (-78 °C) solution of imine (57 mg, 150 μmol) and α-diazo imide (45.1 mg, 182 μmol) in propionitrile (1.0 mL) was added dry TfOH (13 μL, 150 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (66 mg, 81%). Mp 181.5-183 °C; R_f = 0.11 (10% EtOAc/hexanes); IR (film) 3309, 3029, 1823, 1750, 1685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.54 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.50-7.47 (m, 5H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 2H), 7.33-7.27 (m, 7H), 7.22 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.18 (d, *J* = 2.2 Hz, 1H), 4.92 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.91 (d, *J* = 4.1 Hz, 1H), 3.27 (dd, *J* = 10.5, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 195.8, 170.0, 153.9, 147.0, 142.8, 141.7, 139.4, 133.0, 130.9, 129.5, 129.09, 129.06, 128.7, 128.64, 128.60, 127.7, 127.6, 127.4, 127.3, 125.8, 79.0, 65.6, 60.1; HRMS (ESI): Exact mass calcd for $C_{36}H_{29}N_2O_4$ $[M+H]^+$ 553.2122, found 553.2123.



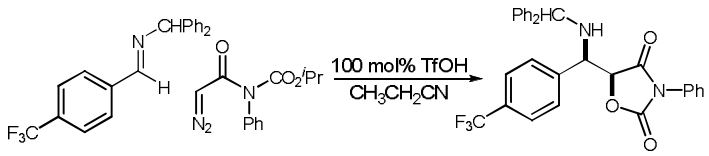
***syn*-5-(1-(Benzhydrylamino)-2-(4-acetoxyphenyl)-2-oxoethyl)-3-phenyloxazolidine-2,4-dione (325i)**. To a cold (-78 °C) solution of imine (53 mg, 150 μmol) and α-diazo imide (44.9 mg, 182 μmol) in propionitrile (1.0 mL) was added dry TfOH (13 μL, 150 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (15% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (52 mg, 66%). Mp 98-100 °C; R_f = 0.023 (10% EtOAc/hexanes); IR (film) 3308, 3063, 3028, 2925, 1823, 1752, 1688 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.54 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.31-7.24 (m, 7H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 5.12 (d, *J* = 2.3 Hz, 1H), 4.87 (br s, 1H), 4.85 (br d, *J* = 9.4 Hz, 1H), 3.23 (br d, *J* = 7.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 195.0, 169.9, 168.6, 155.2, 153.8, 142.7, 141.6, 131.9, 130.9, 130.2, 129.5, 129.1, 128.70, 128.66, 127.71, 127.66, 127.6, 127.3, 125.7, 122.4, 78.7, 65.6, 60.0, 21.1; HRMS (ESI): Exact mass calcd for $C_{32}H_{27}N_2O_6$ $[M+H]^+$ 535.1864, found 535.1872.



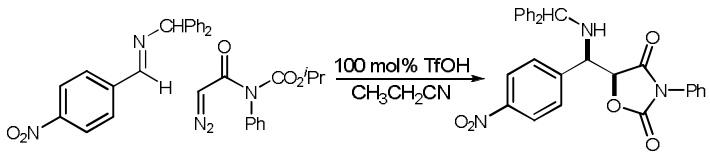
***syn*-5-(1-(Benzhydrylamino)-2-(4-trifluormethylphenyl)-2-oxoethyl)-3-phenyloxazolidine-2,4-dione (325j)**. To a cold (-78 °C) solution of imine (58 mg, 160 μmol) and α-diazo imide (45.6 mg, 184 μmol) in propionitrile (1.0 mL) was added dry TfOH (13 μL, 150 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (58 mg, 72%). Mp 160.5-161 °C; R_f = 0.11 (10% EtOAc/hexanes); IR (film) 3314, 3064, 3029, 1824, 1751, 1696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.54 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.49-7.46 (m, 3H), 7.34 (d, *J* = 7.1 Hz, 2H), 7.31-7.27 (m, 7H), 7.24 (t, *J* = 7.1 Hz, 1H), 5.09 (d, *J* = 2.4 Hz, 1H), 4.92 (br s, 1H), 4.87 (br d, *J* = 8.0 Hz, 1H), 3.22 (br d, *J* = 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 195.8, 169.9, 153.7, 142.4, 141.5, 137.3, 135.4 (d), 130.8, 129.5, 129.2, 128.83, 128.76, 128.7, 127.82, 127.77, 127.6, 127.4, 126.2 (d), 125.7, 78.0, 65.6, 60.5; HRMS (ESI): Exact mass calcd for $C_{31}H_{24}F_3N_2O_4$ $[M+H]^+$ 545.1683, found 545.1680. Anal calcd for $C_{31}H_{23}F_3N_2O_4$: C, 68.38; H, 4.26; N, 5.14. Found: C, 68.12; H, 4.26; N, 4.99.



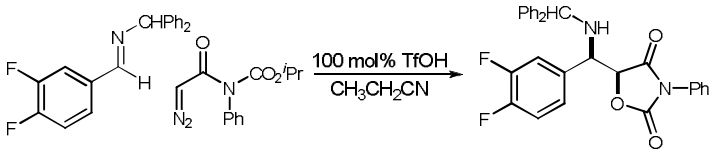
***syn*-5-(1-(Benzhydrylamino)-2-(4-trifluormethoxyphenyl)-2-oxoethyl)-3-phenyloxazolidine-2,4-dione (325h)**. To a cold (-78 °C) solution of imine (59.7 mg, 153 μmol) and α-diazo imide (45.0 mg, 182 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 1 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (55 mg, 64%). Mp 148-150 °C; R_f = 0.095 (10% EtOAc/hexanes); IR (film) 3324, 3064, 2924, 2853, 1824, 1750, 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.54 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.49-7.45 (m, 3H), 7.34 (d, *J* = 7.4 Hz, 2H), 7.31-7.22 (m, 10H), 5.10 (d, *J* = 2.2 Hz, 1H), 4.90 (d, *J* = 3.6 Hz, 1H), 4.85 (dd, *J* = 10.5, 1.9 Hz, 1H), 3.23 (dd, *J* = 10.5, 3.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 195.0, 169.9, 153.8, 153.3, 142.5, 141.5, 132.6, 130.8, 130.6, 129.5, 129.4 129.1, 128.72, 128.69, 127.8, 127.7, 127.6, 127.4, 125.7, 120.8 78.3, 65.6, 60.1; HRMS (ESI): Exact mass calcd for $C_{31}H_{23}F_3N_2NaO_5$ $[M+Na]^+$ 583.1457, found 583.1445. Anal Calcd for $C_{31}H_{23}F_3N_2O_5$: C, 66.43; H, 4.14; N, 5.00. Found: C, 66.03; H, 4.20; N, 4.89.



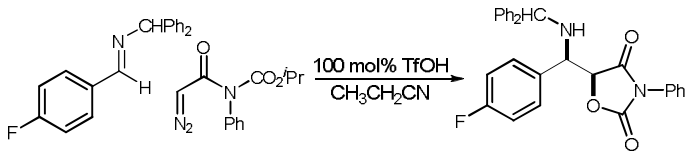
***syn*-5-(1-(Benzhydrylamino)(4-trifluoromethylphenyl)methyl))-3-phenyloxazolidine-2,4-dione (476a)**. To a cold (-78 °C) solution of imine (47 mg, 150 μmol) and α-diazo imide (47 mg, 190 μmol) in propionitrile (1.0 mL) was added dry TfOH (13 μL, 150 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (40 mg, 53%). Mp 173-174 °C; R_f = 0.14 (10% EtOAc/hexanes); IR (film) 3324, 3065, 3028, 1819, 1751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.58-7.45 (m, 5H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.34-7.19 (m, 10H), 5.048 (d, *J* = 2.1 Hz, 1H), 4.63 (s, 1H), 4.35 (dd, *J* = 10.2, 2.1 Hz, 1H), 2.63 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.1, 154.1, 143.2, 141.4, 141.1, 131.1, 130.8, 130.7, 129.6, 129.2, 128.8, 128.1, 127.8, 127.6, 127.5, 126.8, 126.0 (t), 125.6, 82.4, 63.9, 58.9; HRMS (CI): Exact mass calcd for $C_{30}H_{23}F_3N_2NaO_3$ $[M+Na]^+$ 539.1558, found 539.1585. Anal Calcd for $C_{30}H_{23}F_3N_2O_3$: C, 69.76; H, 4.49; N, 5.42. Found: C, 69.47; H, 4.62; N, 5.15.



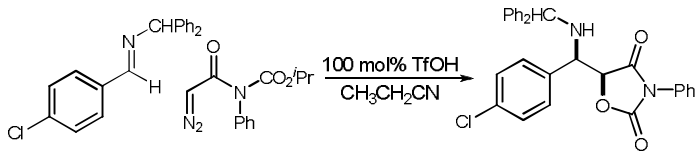
***syn*-5-(1-(Benzhydrylamino)(4-nitrophenyl)methyl))-3-phenyloxazolidine-2,4-dione (476b)**. To a cold (-78 °C) solution of imine (48.4 mg, 153 μmol) and α-diazo imide (44.8 mg, 181 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (52 mg, 69%). Mp 126.5-128 °C; R_f = 0.048 (10% EtOAc/hexanes); IR (film) 3324, 3062, 3028, 2927, 2853, 1817, 1750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.6 Hz, 2H), 7.60-7.50 (m, 5H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.36-7.22 (m, 10H), 5.06 (d, *J* = 2.2 Hz, 1H), 4.60 (s, 1H), 4.42 (dd, *J* = 12.3, 1.8 Hz, 1H), 2.64 (d, *J* = 12.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 169.9, 154.0, 148.1, 144.8, 143.0, 140.8, 130.6, 129.6, 129.3, 128.9, 128.8, 128.7, 127.9, 127.7, 127.4, 126.8, 125.6, 124.3, 124.0, 82.0, 64.1, 58.8; HRMS (CI): Exact mass calcd for $C_{29}H_{24}N_3O_5$ $[M+H]^+$ 494.1716, found 494.1694. Anal Calcd for $C_{29}H_{23}N_2O_5$: C, 70.58; H, 4.70; N, 8.51. Found: C, 69.60; H, 4.69; N, 8.26.



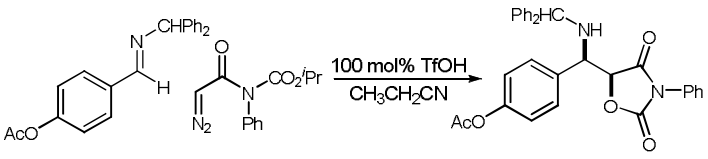
***syn*-5-(1-(Benzhydrylamino)(3,4-difluorophenyl)methyl))-3-phenyloxazolidine-2,4-dione (476c)**. To a cold (-78 °C) solution of imine (46.1 mg, 150 μmol) and α-diazo imide (44.7 mg, 181 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (40 mg, 55%). Mp 143-143.5 °C; R_f = 0.12 (10% EtOAc/hexanes); IR (film) 3322, 3063, 3028, 2924, 1820, 1749, 1518 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.35-7.18 (m, 12H), 7.06-7.04 (m, 1H), 5.03 (d, *J* = 2.1 Hz, 1H), 4.63 (s, 1H), 4.25 (br d, *J* = 11.3 Hz, 1H), 2.50 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.1, 154.1, 150.6 (dd, *J* = 250, 41.8 Hz), 150.5 (dd, *J* = 250, 41.0 Hz) 143.2, 141.1, 134.6, 130.7, 129.6, 129.2, 128.8, 127.8, 127.6, 127.5, 126.8, 125.6, 123.8, 117.9 (d, *J* = 17.1 Hz), 116.7 (d, *J* = 17.4 Hz), 82.4, 63.9, 58.5; HRMS (CI): Exact mass calcd for $C_{29}H_{22}F_2N_2NaO_3$ $[M+Na]^+$ 507.1496, found 507.1476. Anal Calcd for $C_{29}H_{22}F_2N_2O_3$: C, 71.89; H, 4.51; N, 5.72. Found: C, 71.88; H, 4.51; N, 5.72.



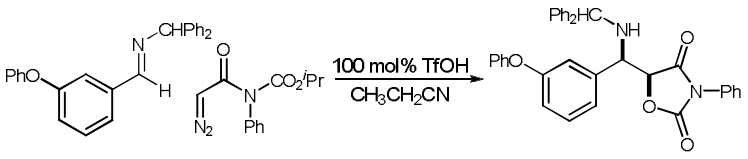
***syn*-5-(1-(Benzhydrylamino)(4-fluorophenyl)methyl))-3-phenyloxazolidine-2,4-dione (476d)**. To a cold (-78 °C) solution of imine (43.8 mg, 151 μmol) and α-diazo imide (44.9 mg, 182 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (34 mg, 48%). Mp 147.5-148.5 °C; R_f = 0.13 (10% EtOAc/hexanes); IR (film) 3308, 3056, 3022, 2921, 1818, 1749, 1601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.33-7.18 (m, 12H), 7.11 (dd, *J* = 8.0, 8.0 Hz, 2H), 5.04 (d, *J* = 2.0 Hz, 1H), 4.62 (s, 1H), 4.25 (br s, 1H), 2.54 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.4, 154.2, 143.5, 141.3, 133.0, 130.8, 129.5, 129.43, 129.37, 129.1, 128.7, 127.7, 127.6, 127.5, 126.8, 125.6, 116.0 (d), 82.7, 63.8, 58.7; HRMS (CI): Exact mass calcd for $C_{29}H_{23}FN_2NaO_3$ $[M+Na]^+$ 489.1590, found 489.1581. Anal Calcd for $C_{29}H_{23}FN_2O_3$: C, 74.66; H, 4.97; N, 6.00. Found: C, 74.65; H, 4.91; N, 5.94.



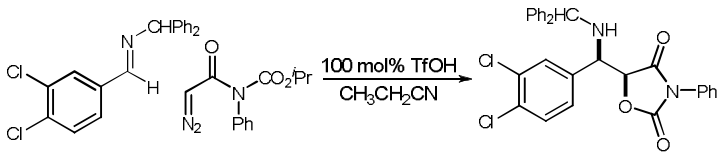
***syn*-5-(1-(Benzhydrylamino)(4-chlorophenyl)methyl))-3-phenyloxazolidine-2,4-dione (476h)**. To a cold (-78 °C) solution of imine (45.2 mg, 148 μmol) and α-diazo imide (44.9 mg, 182 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (42 mg, 59%). Mp 125-126 °C; R_f = 0.34 (20% EtOAc/hexanes); IR (film) 3322, 3059, 3027, 1817, 1749, 1492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.33-7.18 (m, 12H), 5.04 (d, *J* = 2.1 Hz, 1H), 4.63 (s, 1H), 4.26 (br s, 1H), 2.57 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.3, 154.2, 143.4, 141.2, 135.8, 134.6, 130.7, 129.5, 129.3, 129.1, 129.0, 128.7, 128.2, 127.7, 127.5, 126.8, 125.6, 125.2, 82.5, 63.8, 58.7; HRMS (CI): Exact mass calcd for $C_{29}H_{24}ClN_2O_3$ $[M+H]^+$ 483.1475, found 483.1474. Anal Calcd for $C_{31}H_{23}F_3N_2O_4$: C, 68.38; H, 4.26; N, 5.14. Found: C, 68.12; H, 4.26; N, 4.99.



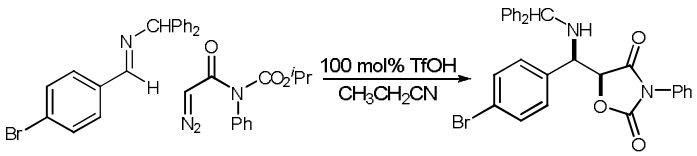
***syn*-5-(1-(Benzhydrylamino)(4-acetoxyphenyl)methyl))-3-phenyloxazolidine-2,4-dione (476j)**. To a cold (-78 °C) solution of imine (51.2 mg, 155 μmol) and α-diazo imide (44.5 mg, 180 μmol) in propionitrile (1.0 mL) was added dry TfOH (14.0 μL, 158 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (34 mg, 43%). Mp 171-171.5 °C; R_f = 0.16 (20% EtOAc/hexanes); IR (film) 3322, 3028, 2924, 2853, 1817, 1749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.32-7.18 (m, 10H), 7.16 (d, *J* = 8.5 Hz, 2H), 5.05 (d, *J* = 2.2 Hz, 1H), 4.67 (s, 1H), 4.28 (br s, 1H), 2.57 (br s, 1H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.4, 169.3, 154.3, 150.8, 143.5, 141.4, 134.8, 130.8, 129.5, 129.1, 128.7, 127.64, 127.58, 127.5, 126.8, 125.8, 122.2, 82.7, 63.7, 58.7, 29.7; HRMS (CI): Exact mass calcd for $C_{31}H_{26}N_2NaO_5$ $[M+Na]^+$ 529.1739, found 529.1722.



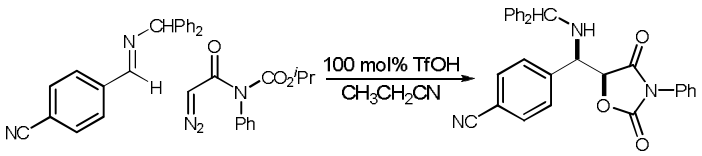
***syn*-5-(1-(Benzhydrylamino)(3-phenoxyphenyl)methyl))-3-phenyloxazolidine-2,4-dione (476i)**. To a cold (-78 °C) solution of imine (54.8 mg, 151 μmol) and α-diazo imide (44.3 mg, 179 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (30 mg, 37%). Mp 164-165 °C; R_f = 0.32 (20% EtOAc/hexanes); IR (film) 3310, 3056, 3027, 2922, 1820, 1749, 1583 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.6, 7.6 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.31-7.20 (m, 10H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 3H), 6.97 (s, 1H), 5.08 (d, *J* = 2.1 Hz, 1H), 4.70 (s, 1H), 4.23 (br s, 1H), 2.58 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.4, 158.0, 156.7, 154.2, 143.5, 141.3, 139.3, 130.8, 130.5, 129.9, 129.5, 129.1, 128.71, 128.68, 127.6, 127.5, 126.9, 125.7, 123.7, 122.0, 119.2, 118.7, 118.0, 82.6, 63.8, 59.1; HRMS (CI): Exact mass calcd for $C_{35}H_{28}N_2NaO_4$ $[M+Na]^+$ 563.1947, found 563.1921.



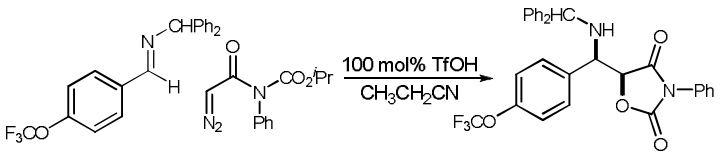
***syn*-5-(1-(Benzhydrylamino)(3,4-dichlorophenyl)methyl))-3-phenyloxazolidine-2,4-dione (476f)**. To a cold (-78 °C) solution of imine (52.0 mg, 153 μmol) and α-diazo imide (45.4 mg, 184 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (42 mg, 53%). Mp 105.5-106.5 °C; R_f = 0.33 (20% EtOAc/hexanes); IR (film) 3322, 3062, 3027, 2924, 1817, 1750, 1502 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.9, 7.9 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.35-7.21 (m, 10H), 7.18 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.02 (d, *J* = 2.3 Hz, 1H), 4.62 (s, 1H), 4.25 (br s, 1H), 2.54 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.0, 154.1, 143.2, 141.0, 137.8, 133.4, 132.9, 131.1, 130.7, 129.6, 129.2, 128.81, 128.79, 127.8, 127.6, 127.5, 127.0, 126.8, 125.6, 82.3, 63.9, 58.4; HRMS (CI): Exact mass calcd for $C_{29}H_{23}Cl_2N_2O_3$ $[M+H]^+$ 517.1086, found 517.1096.



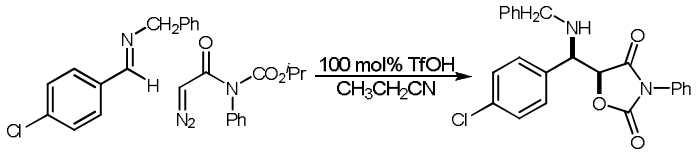
***syn*-5-(1-(Benzhydrylamino)(4-bromophenyl)methyl))-3-phenyloxazolidine-2,4-dione (476g)**. To a cold (-78 °C) solution of imine (52.9 mg, 151 μmol) and α-diazo imide (44.9 mg, 195 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 20 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (54 mg, 68%). Mp 139-139.5 °C; R_f = 0.35 (20% EtOAc/hexanes); IR (film) 3320, 3052, 3027, 2921, 2850, 1817, 1749, 1503 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 6.5, 6.5 Hz, 2H), 7.57 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.34-7.20 (m, 10H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.04 (d, *J* = 2.2 Hz, 1H), 4.63 (s, 1H), 4.25 (br s, 1H), 2.57 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.2, 154.2, 143.4, 141.2, 136.3, 132.2, 130.7, 129.6, 129.4, 129.2, 128.8, 127.7, 127.5, 126.8, 125.6, 122.7, 82.5, 63.8, 58.8; HRMS (CI): Exact mass calcd for $C_{29}H_{24}BrN_2O_3$ $[M+H]^+$ 527.0970, found 527.0968.



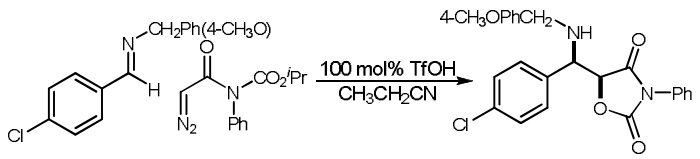
***syn*-5-(1-(Benzhydrylamino)(4-cyanophenyl)methyl))-3-phenyloxazolidine-2,4-dione (476k)**. To a cold (-78 °C) solution of imine (44.7 mg, 151 μmol) and α-diazo imide (45.0 mg, 182 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (26 mg, 36%). Mp 170-171 °C; R_f = 0.18 (20% EtOAc/hexanes); IR (film) 3305, 3062, 3026, 2923, 1817, 1749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.57 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.35-7.21 (m, 10H), 5.04 (d, *J* = 2.2 Hz, 1H), 4.59 (s, 1H), 4.35 (d, *J* = 10.0, 1H), 2.60 (br d, *J* = 11.2, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 169.9, 154.0, 143.0, 142.8, 140.9, 132.8, 130.6, 129.6, 129.2, 128.8, 128.5, 127.9, 127.7, 127.4, 126.7, 125.5, 118.2, 112.7, 82.0, 64.0, 59.0; HRMS (CI): Exact mass calcd for $C_{30}H_{23}N_3NaO_3$ $[M+Na]^+$ 496.1637, found 496.1659.



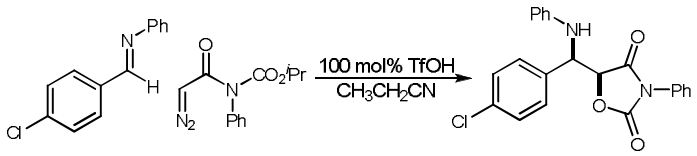
***syn*-5-(1-(Benzhydrylamino)(4-trifluoromethoxyphenyl)methyl))-3-phenyloxazolidine-2,4-dione (476e)**. To a cold (-78 °C) solution of imine (53.3 mg, 150 μmol) and α-diazo imide (44.6 mg, 180 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 15 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (41 mg, 51%). Mp 104.5-105.5 °C; R_f = 0.35 (20% EtOAc/hexanes); IR (film) 3323, 3063, 3027, 2924, 1818, 1749, 1504 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.33-7.20 (m, 12H), 5.06 (d, *J* = 2.3 Hz, 1H), 4.65 (s, 1H), 4.31 (br d, *J* = 5.4 Hz, 1H), 2.59 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.2, 154.2, 143.3, 141.3, 136.0, 130.7, 129.6, 129.2, 128.8, 127.7, 127.5, 126.8, 125.6, 121.5, 82.5, 63.9, 58.7; HRMS (CI): Exact mass calcd for $C_{30}H_{24}F_3N_2O_4$ $[M+H]^+$ 533.1688, found 533.1664.



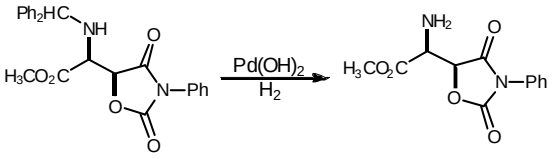
***syn*-5-(1-(Benzylamino)(4-chlorophenyl)methyl))-3-phenyloxazolidine-2,4-dione (480c)**. To a cold (-78 °C) solution of imine (35.0 mg, 152 μmol) and α-diazo imide (45.5 mg, 184 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 20 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (12 mg, 19%). Mp 158.9-159.9 °C; R_f = 0.28 (20% EtOAc/hexanes); IR (film) 3339, 3029, 2924, 2852, 1815, 1747, 1407 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.41 (d, *J* = 6.7 Hz, 2H), 7.35-7.27 (m, 7H), 7.22 (d, *J* = 6.6 Hz, 2H), 5.03 (d, *J* = 2.4 Hz, 1H), 4.28 (d, *J* = 2.3 Hz, 1H), 3.80 (d, *J* = 13.1 Hz, 1H), 3.59 (d, *J* = 13.1 Hz, 1H), 2.17 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.5, 154.2, 138.7, 136.1, 134.5, 130.7, 129.4, 129.2, 129.1, 128.9, 128.5, 128.2, 127.5, 125.7, 82.4, 60.6, 51.0; HRMS (ESI): Exact mass calcd for $C_{23}H_{20}ClN_2O_3$ $[M+H]^+$ 407.1162, found 407.1165.



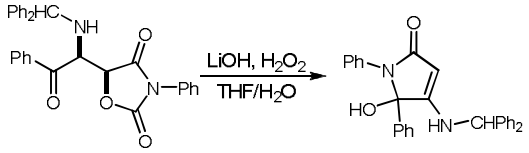
***syn*-5-(1-(4-Methoxybenzylamino)(4-chlorophenyl)methyl))-3-phenyloxazolidine-2,4-dione (480d)**. To a cold (-78 °C) solution of imine (43.1 mg, 166 μmol) and α-diazo imide (46.9 mg, 190 μmol) in propionitrile (1.0 mL) was added dry TfOH (14.5 μL, 164 μmol), and the solution was stirred at -78 °C for 20 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (15.5 mg, 22%). R_f = 0.17 (20% EtOAc/hexanes); IR (film) 3339, 2924, 2852, 1814, 1747 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.333 (d, *J* = 8.5 Hz, 2H), 7.329 (d, *J* = 7.3 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.02 (d, *J* = 2.4 Hz, 1H), 4.27 (d, *J* = 2.3 Hz, 1H), 3.79 (s, 3H), 3.73 (d, *J* = 12.8 Hz, 1H), 3.52 (d, *J* = 12.9 Hz, 1H), 2.15 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 170.5, 159.0, 154.3, 136.2, 134.5, 130.7, 129.42, 129.38, 129.2, 129.1, 128.9, 125.7, 119.8, 113.9, 82.5, 60.4, 55.3, 50.4; HRMS (ESI): Exact mass calcd for $C_{24}H_{22}ClN_2O_4$ $[M+H]^+$ 437.1268, found 437.1264.



***syn*-5-(1-(Phenylamino)(4-chlorophenyl)methyl))-3-phenyloxazolidine-2,4-dione (480e)**. To a cold (-78 °C) solution of imine (33.8 mg, 157 μmol) and α-diazo imide (45.3 mg, 183 μmol) in propionitrile (1.0 mL) was added dry TfOH (13.5 μL, 153 μmol), and the solution was stirred at -78 °C for 20 h. The reaction was quenched with satd aq $NaHCO_3$ and extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting solid was purified by silica gel flash chromatography (10% ethyl acetate in hexanes) to afford the oxazolidine dione as a colorless solid (30 mg, 50%). Mp 189.0-190.0 °C; R_f = 0.29 (10% EtOAc/hexanes); IR (film) 3377, 3055, 1814, 1742, 1603, 1497, 1409 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44-7.34 (m, 7H), 7.17 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.06 (d, *J* = 7.0 Hz, 2H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 2H), 5.27 (d, *J* = 3.0 Hz, 1H), 5.21 (d, *J* = 7.1 Hz, 1H), 4.69 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 170.4, 153.7, 145.1, 134.9, 134.8, 130.1, 129.5, 129.4, 129.3, 128.5, 125.6, 119.7, 114.7, 80.4, 57.2; HRMS (ESI): Exact mass calcd for $C_{22}H_{18}ClN_2O_3$ $[M+H]^+$ 393.1006, found 393.1009.



Methyl 2-amino(2,4-dioxo-3-phenyloxazolidin-5-yl)acetate (486). To a solution of oxazolidine dione (430 mg, 999 μmol) in ethanol (10.0 mL) and ethyl acetate (1.0 mL) was added $Pd(OH)_2$ (171 mg, 100 μmol, 20% on carbon, 50% H_2O). The flask was put under an atmosphere of H2 and the solution was stirred at ambient temperature for 5 h. The reaction was filtered through Celite, and concentrated, and the resulting solid was purified by silica gel flash chromatography (30% ethyl acetate in hexanes) to afford the amine as a colorless solid (235 mg, 89%). Mp 112.0-113.0 °C; $R_f = 0.078$ (30% EtOAc/hexanes); IR (film) 3400, 3338, 2956, 1817, 1746, 1410 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.0, 8.0 Hz, 2H), 7.44-7.41 (m, 3H), 5.34 (d, *J* = 1.7 Hz, 1H), 4.16 (d, *J* = 1.8 Hz, 1H), 3.85 (s, 3H), 1.77 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 171.3, 170.3, 154.1, 130.8, 129.4, 129.1, 125.7, 80.3, 54.5, 53.2; HRMS (CI): Exact mass calcd for $C_{12}H_{13}N_2O_5$ $[M+H]^+$ 265.0819, found 265.0810.



3-(Benzhydrylamino)-2-hydroxy-4-oxo-*N*,4-diphenybutanamide (487). To a cold (0 °C) solution of oxazolidine dione (245 mg, 514 μmol) in tetrahydrofuran (5.0 mL, 3:1 in H_2O) was added hydrogen peroxide (113 μL, 997 μmol, 30% in H_2O) and lithium

hydroxide (33mg, 1.4 mmol), and the solution was stirred at 0 °C for 1 h. The reaction was extracted with ethyl acetate. The organic layers were dried, concentrated, and the resulting oil was purified by silica gel flash chromatography (30% ethyl acetate in hexanes) to afford the amide as a colorless solid (89 mg, 38%). R_f = 0.022 (30% EtOAc/hexanes); IR (film) 3403, 3200, 3062, 3030, 2925, 1664, 1633, 1600, 1496, 1363 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 7.0 Hz, 2H), 7.27-7.16 (m, 11H), 6.99-6.97 (m, 3H), 6.74-6.73 (m, 2H), 6.46 (br s, 1H), 4.78 (d, *J* = 5.0 Hz, 1H), 4.61 (d, *J* = 4.4 Hz, 1H), 4.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) ppm 173.6, 164.9, 140.9, 139.6, 137.2, 128.7, 128.5, 128.4, 128.3, 127.9, 127.4, 126.7, 125.9, 124.1, 123.4, 91.8, 88.5, 62.4; HRMS (ESI): Exact mass calcd for $C_{29}H_{25}N_2O_2$ $[M\text{-}OH]^+$ 433.1911, found 433.1906.

Appendix

1-(1-Phenyl-ethyl)-aziridine-2,3-dicarboxylic acid 2-ethyl ester 3 methyl ester (319a).

Table 1. Crystal data and structure refinement for 06155.

Empirical formula	C15 H19 N O4	
Formula weight	277.31	
Crystal color, shape, size	colorless block, $0.20 \times 0.20 \times 0.15$ mm^3	
Temperature	130(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1$	
Unit cell dimensions	a = 5.5539(10) Å	α= 90°.
	b = 9.0119(17) Å	β= 98.460(4)°.
	c = 14.952(3) Å	γ = 90°.
Volume	740.2(2) Å^3	
Z	2	
Density (calculated)	1.244 Mg/m^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	296	

Data collection

Diffractometer	SMART6000 Platform CCD, Bruker
Theta range for data collection	2.65 to 26.55°.
Index ranges	-6<=h<=6, -11<=k<=11, -18<=l<=18
Reflections collected	10076
Independent reflections	3050 [R(int) = 0.0573]
Observed Reflections	2449
Completeness to theta = 26.55°	99.6 %

Solution and Refinement

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9866 and 0.9822
Solution	Direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting scheme	$w = [\sigma^2 Fo^2 + AP^2]^{-1}$, with $P = (Fo^2 + 2\,Fc^2)/3$, A = 0.079900
Data / restraints / parameters	3050 / 1 / 184
Goodness-of-fit on F^2	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0508, wR2 = 0.1235
R indices (all data)	R1 = 0.0689, wR2 = 0.1354
Absolute structure parameter*	-0.9(14)
Largest diff. peak and hole	0.386 and -0.222 e.Å^{-3}

Goodness-of-fit = $[\Sigma[w(F_o^2 - F_c^2)^2]/N_{observns} - N_{params})]^{1/2}$, all data.

R1 = $\Sigma(|F_o| - |F_c|) / \Sigma |F_o|$.

*w*R2 = $[\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2]]^{1/2}$.

* The absolute structure parameter is meaningless for a light atom structure. Here, the absolute structure is based on a known stereo center.

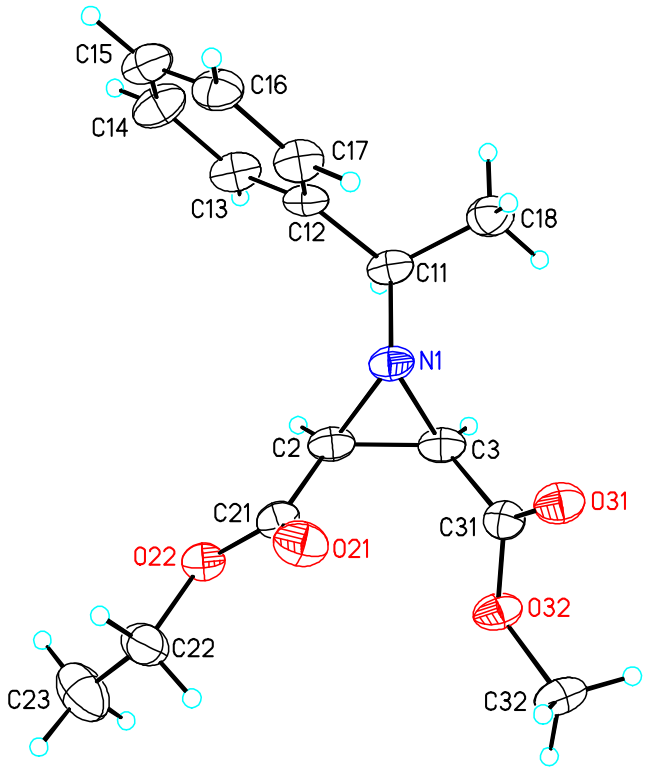


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 06155. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N1	615(4)	8473(2)	8127(2)	27(1)
C2	-85(4)	9666(3)	7462(2)	28(1)
C3	693(4)	9993(3)	8444(2)	28(1)
C11	-1496(5)	7611(3)	8358(2)	29(1)
C12	-1935(5)	6305(3)	7722(2)	27(1)
C13	-4171(5)	6115(3)	7183(2)	34(1)
C14	-4599(5)	4875(4)	6628(2)	40(1)
C15	-2794(5)	3835(3)	6601(2)	36(1)
C16	-572(5)	4014(3)	7131(2)	34(1)
C17	-138(5)	5249(3)	7684(2)	33(1)

C18	-922(6)	7135(3)	9339(2)	39(1)
O21	3796(3)	9708(2)	6946(1)	37(1)
C21	1668(5)	9986(3)	6818(2)	29(1)
O22	515(3)	10675(2)	6081(1)	31(1)
C22	2070(6)	11112(3)	5421(2)	40(1)
C23	655(8)	12089(4)	4742(2)	57(1)
O31	4841(3)	10017(2)	9199(1)	33(1)
C31	3129(5)	10644(3)	8780(2)	27(1)
O32	3112(3)	12101(2)	8575(1)	33(1)
C32	5311(5)	12919(3)	8904(2)	38(1)

Table 3. Bond lengths [Å] and angles [°] for 06155.

N1-C3	1.448(3)	N1-C2	1.477(3)
N1-C11	1.489(3)	C2-C21	1.496(4)
C2-C3	1.497(4)	C2-H2A	1.0000
C3-C31	1.492(4)	C3-H3A	1.0000
C11-C12	1.509(4)	C11-C18	1.516(4)
C11-H11A	1.0000	C12-C17	1.387(4)
C12-C13	1.389(4)	C13-C14	1.391(4)
C13-H13A	0.9500	C14-C15	1.378(4)
C14-H14A	0.9500	C15-C16	1.375(4)
C15-H15A	0.9500	C16-C17	1.387(4)
C16-H16A	0.9500	C17-H17A	0.9500
C18-H18A	0.9800	C18-H18B	0.9800
C18-H18C	0.9800	O21-C21	1.196(3)
C21-O22	1.341(3)	O22-C22	1.458(3)
C22-C23	1.480(5)	C22-H22A	0.9900
C22-H22B	0.9900	C23-H23A	0.9800
C23-H23B	0.9800	C23-H23C	0.9800
O31-C31	1.200(3)	C31-O32	1.348(3)
O32-C32	1.449(3)	C32-H32A	0.9800
C32-H32B	0.9800	C32-H32C	0.9800
C3-N1-C2	61.53(17)	C3-N1-C11	113.9(2)
C2-N1-C11	113.4(2)	N1-C2-C21	116.3(2)
N1-C2-C3	58.27(16)	C21-C2-C3	118.2(2)
N1-C2-H2A	117.0	C21-C2-H2A	117.0
C3-C2-H2A	117.0	N1-C3-C31	117.6(2)
N1-C3-C2	60.20(17)	C31-C3-C2	121.7(2)
N1-C3-H3A	115.4	C31-C3-H3A	115.4
C2-C3-H3A	115.4	N1-C11-C12	108.7(2)

N1-C11-C18	108.1(2)	C12-C11-C18	112.3(2)
N1-C11-H11A	109.2	C12-C11-H11A	109.2
C18-C11-H11A	109.2	C17-C12-C13	118.6(3)
C17-C12-C11	120.7(2)	C13-C12-C11	120.7(2)
C12-C13-C14	120.4(2)	C12-C13-H13A	119.8
C14-C13-H13A	119.8	C15-C14-C13	120.2(3)
C15-C14-H14A	119.9	C13-C14-H14A	119.9
C16-C15-C14	119.9(3)	C16-C15-H15A	120.1
C14-C15-H15A	120.1	C15-C16-C17	120.1(3)
C15-C16-H16A	120.0	C17-C16-H16A	120.0
C12-C17-C16	120.8(3)	C12-C17-H17A	119.6
C16-C17-H17A	119.6	C11-C18-H18A	109.5
C11-C18-H18B	109.5	H18A-C18-H18B	109.5
C11-C18-H18C	109.5	H18A-C18-H18C	109.5
H18B-C18-H18C	109.5	O21-C21-O22	124.8(2)
O21-C21-C2	125.3(2)	O22-C21-C2	109.9(2)
C21-O22-C22	114.9(2)	O22-C22-C23	108.5(3)
O22-C22-H22A	110.0	C23-C22-H22A	110.0
O22-C22-H22B	110.0	C23-C22-H22B	110.0
H22A-C22-H22B	108.4	C22-C23-H23A	109.5
C22-C23-H23B	109.5	H23A-C23-H23B	109.5
C22-C23-H23C	109.5	H23A-C23-H23C	109.5
H23B-C23-H23C	109.5	O31-C31-O32	123.7(2)
O31-C31-C3	126.9(2)	O32-C31-C3	109.3(2)
C31-O32-C32	116.2(2)	O32-C32-H32A	109.5
O32-C32-H32B	109.5	H32A-C32-H32B	109.5
O32-C32-H32C	109.5	H32A-C32-H32C	109.5
H32B-C32-H32C	109.5		

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for 06155. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
N1	27(1)	18(1)	37(1)	-1(1)	9(1)	2(1)
C2	23(1)	18(1)	43(1)	3(1)	7(1)	3(1)
C3	25(1)	17(1)	43(1)	1(1)	12(1)	5(1)
C11	25(1)	22(1)	42(2)	-2(1)	11(1)	-1(1)
C12	27(1)	18(1)	38(1)	2(1)	11(1)	-1(1)
C13	25(1)	27(2)	52(2)	-1(1)	11(1)	2(1)
C14	28(1)	34(2)	60(2)	-8(2)	7(1)	-5(1)

C15	37(2)	27(2)	49(2)	-7(1)	16(1)	-7(1)
C16	39(2)	22(1)	44(2)	1(1)	13(1)	7(1)
C17	27(1)	28(2)	44(2)	0(1)	7(1)	3(1)
C18	44(2)	34(2)	41(2)	-3(1)	16(1)	-8(1)
O21	25(1)	40(1)	49(1)	7(1)	10(1)	1(1)
C21	30(1)	22(1)	34(1)	-2(1)	5(1)	-2(1)
O22	31(1)	26(1)	36(1)	1(1)	6(1)	-1(1)
C22	50(2)	33(2)	38(2)	4(1)	16(1)	-3(1)
C23	80(3)	47(2)	47(2)	11(2)	23(2)	18(2)
O31	30(1)	23(1)	44(1)	1(1)	7(1)	3(1)
C31	28(1)	23(1)	31(1)	-1(1)	8(1)	3(1)
O32	32(1)	19(1)	48(1)	1(1)	5(1)	1(1)
C32	33(2)	24(2)	55(2)	-1(1)	5(1)	-7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 06155.

	x	y	z	U(eq)
H2A	-1857	9771	7226	33
H3A	-645	10285	8788	33
H11A	-2973	8259	8281	35
H13A	-5416	6835	7192	41
H14A	-6141	4745	6267	49
H15A	-3084	2995	6216	44
H16A	667	3291	7118	41
H17A	1411	5373	8041	39
H18A	-2228	6493	9491	58
H18B	-789	8014	9729	58
H18C	621	6590	9432	58
H22A	2625	10221	5122	48
H22B	3521	11645	5727	48
H23A	1649	12350	4276	85
H23B	195	12995	5038	85
H23C	-817	11570	4463	85
H32A	5101	13961	8722	56
H32B	6683	12494	8648	56
H32C	5636	12855	9565	56

Table 6. Torsion angles [°] for 06155.

C3-N1-C2-C21	108.3(2)	C11-N1-C2-C21	-146.2(2)
C11-N1-C2-C3	105.5(2)	C2-N1-C3-C31	-112.5(3)
C11-N1-C3-C31	142.7(2)	C11-N1-C3-C2	-104.7(2)
C21-C2-C3-N1	-105.0(2)	N1-C2-C3-C31	105.9(2)
C21-C2-C3-C31	0.9(3)	C3-N1-C11-C12	158.8(2)
C2-N1-C11-C12	90.9(3)	C3-N1-C11-C18	-79.0(3)
C2-N1-C11-C18	-146.9(2)	N1-C11-C12-C17	59.7(3)
C18-C11-C12-C17	-59.9(3)	N1-C11-C12-C13	-122.2(3)
C18-C11-C12-C13	118.2(3)	C17-C12-C13-C14	1.1(4)
C11-C12-C13-C14	-177.1(3)	C12-C13-C14-C15	-0.9(5)
C13-C14-C15-C16	0.7(5)	C14-C15-C16-C17	-0.8(4)
C13-C12-C17-C16	-1.1(4)	C11-C12-C17-C16	177.1(2)
C15-C16-C17-C12	1.0(4)	N1-C2-C21-O21	-23.3(4)
C3-C2-C21-O21	43.1(4)	N1-C2-C21-O22	158.6(2)
C3-C2-C21-O22	-135.0(2)	O21-C21-O22-C22	-1.1(4)
C2-C21-O22-C22	177.1(2)	C21-O22-C22-C23	-169.6(3)
N1-C3-C31-O31	-36.3(4)	C2-C3-C31-O31	-106.7(3)
N1-C3-C31-O32	146.3(2)	C2-C3-C31-O32	75.9(3)
O31-C31-O32-C32	-0.9(4)	C3-C31-O32-C32	176.5(2)

Methyl 2-(benzhydrylamino)-2-(2,4-dioxo-3-phenyloxazolidin-5-yl)acetate (325a).

Table 1. Crystal data and structure refinement for 07022.

Empirical formula	C25 H22 N2 O5	
Formula weight	430.45	
Crystal color, shape, size	colorless block, $0.30 \times 0.23 \times 0.22$ mm^3	
Temperature	130(2) K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a = 10.0853(3) Å	α= 90°.
	b = 16.6495(6) Å	β= 109.0620(9)°.
	c = 13.6635(5) Å	γ = 90°.
Volume	2168.50(13) Å^3	
Z	4	
Density (calculated)	1.318 Mg/m^3	
Absorption coefficient	0.093 mm^{-1}	
F(000)	904	

Data collection

Diffractometer	SMART6000 Platform CCD, Bruker
Theta range for data collection	2.00 to 27.54°
Index ranges	-13<=h<=13, -21<=k<=21, -17<=l<=17
Reflections collected	33553
Independent reflections	4997 [R(int) = 0.0342]
Observed Reflections	4204
Completeness to theta = 27.54°	99.8 %

Solution and Refinement

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9799 and 0.9727
Solution	Direct methods
Refinement method	Full-matrix least-squares on F^2
Weighting scheme	$w = [\sigma^2 Fo^2 + AP^2 + BP]^{-1}$, with
	$P = (Fo^2 + 2\,Fc^2)/3$, A = 0.0402, B = 0.8004
Data / restraints / parameters	4997 / 0 / 315
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0354, wR2 = 0.0866
R indices (all data)	R1 = 0.0439, wR2 = 0.0940
Largest diff. peak and hole	0.300 and -0.184 e.Å^{-3}

Goodness-of-fit = $[\Sigma[w(F_o^2 - F_c^2)^2]/N_{observns} - N_{params})]^{1/2}$, all data.

$R1 = \Sigma(|F_o| - |F_c|) / \Sigma |F_o|$.

$wR2 = [\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2]]^{1/2}$.

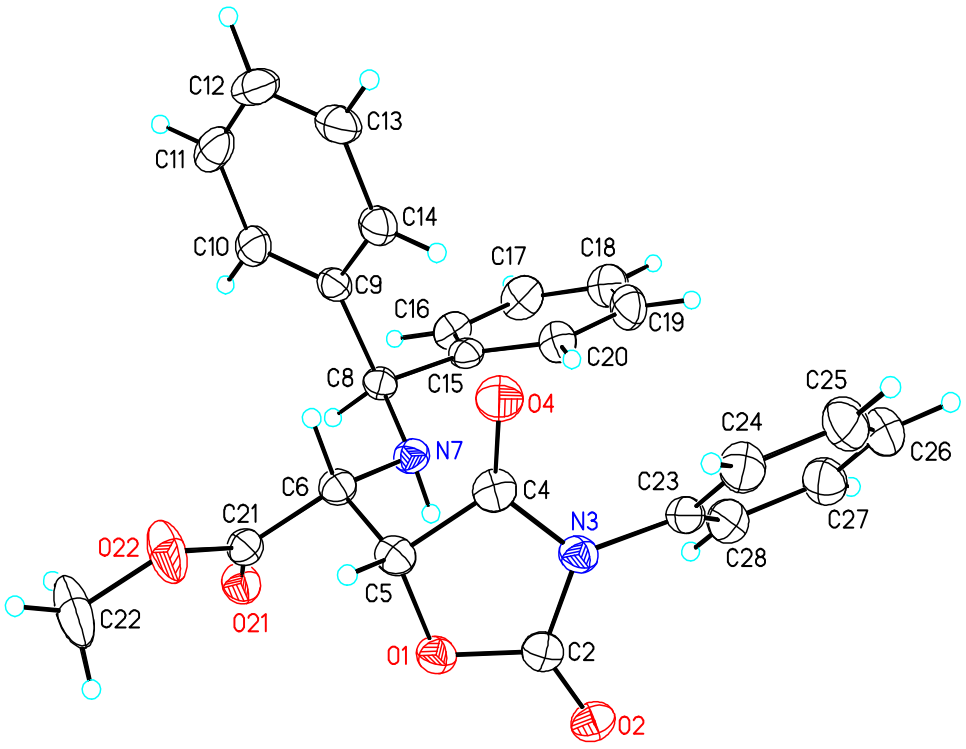


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 07022. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O1	5724(1)	-1451(1)	6024(1)	25(1)
O2	7896(1)	-1511(1)	5910(1)	28(1)
C2	7142(1)	-1397(1)	6409(1)	23(1)
N3	7528(1)	-1202(1)	7461(1)	24(1)
O4	6359(1)	-997(1)	8645(1)	31(1)
C4	6368(1)	-1144(1)	7786(1)	24(1)
C5	5111(1)	-1280(1)	6823(1)	24(1)
C6	4266(1)	-498(1)	6578(1)	23(1)
N7	5232(1)	145(1)	6582(1)	22(1)
C8	4713(1)	974(1)	6524(1)	22(1)
C9	4004(1)	1143(1)	7327(1)	23(1)
C10	2775(1)	1591(1)	7047(1)	28(1)
C11	2179(1)	1822(1)	7791(1)	35(1)
C12	2808(2)	1599(1)	8816(1)	37(1)
C13	4013(1)	1141(1)	9097(1)	34(1)
C14	4618(1)	914(1)	8360(1)	28(1)
C15	5943(1)	1551(1)	6719(1)	22(1)

C16	5721(1)	2309(1)	6264(1)	29(1)
C17	6794(2)	2870(1)	6502(1)	36(1)
C18	8103(1)	2685(1)	7193(1)	36(1)
C19	8340(1)	1928(1)	7637(1)	33(1)
C20	7268(1)	1363(1)	7403(1)	27(1)
O21	2896(1)	-269(1)	4777(1)	28(1)
C21	3010(1)	-588(1)	5588(1)	24(1)
O22	2053(1)	-1069(1)	5759(1)	42(1)
C22	819(2)	-1239(1)	4876(1)	56(1)
C23	8920(1)	-968(1)	8067(1)	25(1)
C24	9507(1)	-1262(1)	9063(1)	33(1)
C25	10827(2)	-991(1)	9658(1)	41(1)
C26	11544(1)	-447(1)	9262(1)	39(1)
C27	10964(1)	-172(1)	8254(1)	36(1)
C28	9636(1)	-425(1)	7653(1)	29(1)

Table 3. Bond lengths [Å] and angles [°] for 07022.

O1-C2	1.3561(14)	O1-C5	1.4466(13)
O2-C2	1.1919(14)	C2-N3	1.3984(14)
N3-C4	1.3839(15)	N3-C23	1.4310(15)
O4-C4	1.2028(14)	C4-C5	1.5163(16)
C5-C6	1.5322(16)	C5-H5	1.0000
C6-N7	1.4462(14)	C6-C21	1.5285(15)
C6-H6	1.0000	N7-C8	1.4689(14)
N7-H7N	0.881(14)	C8-C9	1.5193(15)
C8-C15	1.5227(15)	C8-H8	1.0000
C9-C10	1.3890(16)	C9-C14	1.3967(16)
C10-C11	1.3937(17)	C10-H10	0.9500
C11-C12	1.386(2)	C11-H11	0.9500
C12-C13	1.378(2)	C12-H12	0.9500
C13-C14	1.3887(17)	C13-H13	0.9500
C14-H14	0.9500	C15-C16	1.3919(17)
C15-C20	1.3934(16)	C16-C17	1.3855(18)
C16-H16	0.9500	C17-C18	1.384(2)
C17-H17	0.9500	C18-C19	1.3851(19)
C18-H18	0.9500	C19-C20	1.3896(17)
C19-H19	0.9500	C20-H20	0.9500
O21-C21	1.2010(14)	C21-O22	1.3315(14)
O22-C22	1.4513(16)	C22-H22A	0.9800
C22-H22B	0.9800	C22-H22C	0.9800

C23-C24	1.3840(17)	C23-C28	1.3880(17)
C24-C25	1.3893(19)	C24-H24	0.9500
C25-C26	1.377(2)	C25-H25	0.9500
C26-C27	1.386(2)	C26-H26	0.9500
C27-C28	1.3881(18)	C27-H27	0.9500
C28-H28	0.9500		

C2-O1-C5	110.47(8)	O2-C2-O1	123.80(10)
O2-C2-N3	127.56(11)	O1-C2-N3	108.63(9)
C4-N3-C2	111.35(9)	C4-N3-C23	124.58(9)
C2-N3-C23	123.35(9)	O4-C4-N3	127.14(11)
O4-C4-C5	127.40(11)	N3-C4-C5	105.43(9)
O1-C5-C4	104.03(9)	O1-C5-C6	110.26(9)
C4-C5-C6	108.05(9)	O1-C5-H5	111.4
C4-C5-H5	111.4	C6-C5-H5	111.4
N7-C6-C21	115.98(9)	N7-C6-C5	107.58(9)
C21-C6-C5	110.56(9)	N7-C6-H6	107.5
C21-C6-H6	107.5	C5-C6-H6	107.5
C6-N7-C8	117.88(9)	C6-N7-H7N	108.8(9)
C8-N7-H7N	108.7(9)	N7-C8-C9	112.26(9)
N7-C8-C15	109.15(9)	C9-C8-C15	107.74(9)
N7-C8-H8	109.2	C9-C8-H8	109.2
C15-C8-H8	109.2	C10-C9-C14	119.11(11)
C10-C9-C8	119.24(10)	C14-C9-C8	121.46(10)
C9-C10-C11	120.36(12)	C9-C10-H10	119.8
C11-C10-H10	119.8	C12-C11-C10	119.92(12)
C12-C11-H11	120.0	C10-C11-H11	120.0
C13-C12-C11	120.08(11)	C13-C12-H12	120.0
C11-C12-H12	120.0	C12-C13-C14	120.28(12)
C12-C13-H13	119.9	C14-C13-H13	119.9
C13-C14-C9	120.23(12)	C13-C14-H14	119.9
C9-C14-H14	119.9	C16-C15-C20	118.78(11)
C16-C15-C8	119.44(10)	C20-C15-C8	121.61(10)
C17-C16-C15	120.54(12)	C17-C16-H16	119.7
C15-C16-H16	119.7	C18-C17-C16	120.48(12)
C18-C17-H17	119.8	C16-C17-H17	119.8
C17-C18-C19	119.42(12)	C17-C18-H18	120.3
C19-C18-H18	120.3	C18-C19-C20	120.33(12)
C18-C19-H19	119.8	C20-C19-H19	119.8
C19-C20-C15	120.44(11)	C19-C20-H20	119.8
C15-C20-H20	119.8	O21-C21-O22	124.85(11)
O21-C21-C6	125.15(10)	O22-C21-C6	110.00(9)
C21-O22-C22	116.44(10)	O22-C22-H22A	109.5

O22-C22-H22B	109.5	H22A-C22-H22B	109.5
O22-C22-H22C	109.5	H22A-C22-H22C	109.5
H22B-C22-H22C	109.5	C24-C23-C28	121.23(11)
C24-C23-N3	119.79(11)	C28-C23-N3	118.94(10)
C23-C24-C25	118.79(13)	C23-C24-H24	120.6
C25-C24-H24	120.6	C26-C25-C24	120.62(13)
C26-C25-H25	119.7	C24-C25-H25	119.7
C25-C26-C27	120.18(12)	C25-C26-H26	119.9
C27-C26-H26	119.9	C26-C27-C28	120.05(13)
C26-C27-H27	120.0	C28-C27-H27	120.0
C23-C28-C27	119.10(12)	C23-C28-H28	120.5
C27-C28-H28	120.5		

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for 07022. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	27(1)	27(1)	21(1)	-2(1)	8(1)	-1(1)
O2	33(1)	29(1)	25(1)	0(1)	13(1)	2(1)
C2	29(1)	19(1)	21(1)	2(1)	7(1)	1(1)
N3	25(1)	26(1)	19(1)	1(1)	7(1)	1(1)
O4	34(1)	42(1)	20(1)	2(1)	11(1)	0(1)
C4	28(1)	24(1)	21(1)	3(1)	9(1)	0(1)
C5	27(1)	26(1)	20(1)	1(1)	10(1)	-4(1)
C6	23(1)	26(1)	20(1)	-1(1)	9(1)	-3(1)
N7	23(1)	23(1)	22(1)	-2(1)	11(1)	-2(1)
C8	22(1)	25(1)	18(1)	0(1)	6(1)	1(1)
C9	23(1)	24(1)	24(1)	-5(1)	10(1)	-5(1)
C10	25(1)	24(1)	34(1)	-1(1)	11(1)	-3(1)
C11	31(1)	25(1)	55(1)	-7(1)	25(1)	-3(1)
C12	45(1)	32(1)	45(1)	-15(1)	32(1)	-13(1)
C13	39(1)	41(1)	27(1)	-10(1)	16(1)	-14(1)
C14	27(1)	36(1)	23(1)	-4(1)	8(1)	-4(1)
C15	25(1)	25(1)	19(1)	-3(1)	11(1)	-1(1)
C16	31(1)	28(1)	30(1)	2(1)	13(1)	2(1)
C17	41(1)	26(1)	46(1)	3(1)	21(1)	-2(1)
C18	35(1)	34(1)	45(1)	-5(1)	20(1)	-11(1)
C19	26(1)	41(1)	33(1)	-1(1)	10(1)	-6(1)
C20	27(1)	29(1)	26(1)	2(1)	9(1)	-2(1)
O21	28(1)	33(1)	22(1)	1(1)	8(1)	-3(1)

C21	23(1)	28(1)	24(1)	-2(1)	11(1)	-2(1)
O22	32(1)	63(1)	29(1)	6(1)	5(1)	-23(1)
C22	36(1)	86(1)	39(1)	2(1)	2(1)	-31(1)
C23	25(1)	25(1)	23(1)	-2(1)	7(1)	3(1)
C24	33(1)	41(1)	25(1)	3(1)	9(1)	2(1)
C25	36(1)	56(1)	25(1)	0(1)	2(1)	3(1)
C26	29(1)	42(1)	39(1)	-9(1)	2(1)	-2(1)
C27	33(1)	28(1)	43(1)	-2(1)	9(1)	-4(1)
C28	31(1)	24(1)	30(1)	2(1)	7(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 07022.

	x	y	z	U(eq)
H5	4523	-1739	6917	29(3)
H6	3890	-396	7160	24(3)
H7N	5572(14)	66(8)	6072(11)	27(3)
H8	4030	1073	5817	22(3)
H10	2337	1740	6344	30(4)
H11	1343	2132	7596	43(4)
H12	2409	1762	9325	48(5)
H13	4431	980	9798	45(4)
H14	5452	602	8560	32(4)
H16	4828	2442	5787	36(4)
H17	6629	3386	6188	43(4)
H18	8833	3074	7361	49(5)
H19	9240	1795	8104	31(4)
H20	7440	846	7711	31(4)
H22A	162	-1566	5098	68(6)
H22B	1096	-1532	4351	70(6)
H22C	365	-733	4580	80(7)
H24	9016	-1641	9335	36(4)
H25	11239	-1183	10346	54(5)
H26	12440	-258	9679	45(4)
H27	11475	190	7975	43(4)
H28	9224	-230	6967	35(4)

Table 6. Torsion angles [°] for 07022.

C5-O1-C2-O2	179.86(11)	C5-O1-C2-N3	0.67(12)
O2-C2-N3-C4	-177.73(11)	O1-C2-N3-C4	1.43(12)
O2-C2-N3-C23	11.64(18)	O1-C2-N3-C23	-169.21(10)
C2-N3-C4-O4	178.84(12)	C23-N3-C4-O4	-10.66(19)
C2-N3-C4-C5	-2.77(12)	C23-N3-C4-C5	167.73(10)
C2-O1-C5-C4	-2.26(11)	C2-O1-C5-C6	113.38(10)
O4-C4-C5-O1	-178.64(11)	N3-C4-C5-O1	2.98(11)
O4-C4-C5-C6	64.19(15)	N3-C4-C5-C6	-114.20(10)
O1-C5-C6-N7	-62.75(11)	C4-C5-C6-N7	50.33(11)
O1-C5-C6-C21	64.82(11)	C4-C5-C6-C21	177.90(9)
C21-C6-N7-C8	64.74(13)	C5-C6-N7-C8	-170.91(9)
C6-N7-C8-C9	51.28(12)	C6-N7-C8-C15	170.66(9)

N7-C8-C9-C10	-138.45(10)	C15-C8-C9-C10	101.35(12)
N7-C8-C9-C14	46.66(14)	C15-C8-C9-C14	-73.54(13)
C14-C9-C10-C11	1.34(17)	C8-C9-C10-C11	-173.67(11)
C9-C10-C11-C12	-0.56(18)	C10-C11-C12-C13	-0.77(19)
C11-C12-C13-C14	1.29(19)	C12-C13-C14-C9	-0.49(19)
C10-C9-C14-C13	-0.83(17)	C8-C9-C14-C13	174.07(11)
N7-C8-C15-C16	150.66(10)	C9-C8-C15-C16	-87.20(12)
N7-C8-C15-C20	-34.12(13)	C9-C8-C15-C20	88.02(12)
C20-C15-C16-C17	-1.08(17)	C8-C15-C16-C17	174.28(11)
C15-C16-C17-C18	0.17(19)	C16-C17-C18-C19	0.8(2)
C17-C18-C19-C20	-0.9(2)	C18-C19-C20-C15	-0.03(19)
C16-C15-C20-C19	1.01(17)	C8-C15-C20-C19	-174.24(11)
N7-C6-C21-O21	13.49(17)	C5-C6-C21-O21	-109.30(13)
N7-C6-C21-O22	-166.13(10)	C5-C6-C21-O22	71.07(12)
O21-C21-O22-C22	2.8(2)	C6-C21-O22-C22	-177.55(13)
C4-N3-C23-C24	52.30(16)	C2-N3-C23-C24	-138.31(12)
C4-N3-C23-C28	-125.53(12)	C2-N3-C23-C28	43.86(16)
C28-C23-C24-C25	1.36(19)	N3-C23-C24-C25	-176.41(12)
C23-C24-C25-C26	-0.6(2)	C24-C25-C26-C27	-1.1(2)
C25-C26-C27-C28	2.1(2)	C24-C23-C28-C27	-0.35(18)
N3-C23-C28-C27	177.44(11)	C26-C27-C28-C23	-1.40(19)

Table 7. Hydrogen bonds for 07022 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N7-H7N...O21#1	0.881(14)	2.240(15)	3.0568(12)	154.1(12)

Symmetry transformations used to generate equivalent atoms: #1 -x+1,-y,-z+1