Catalytic Intramolecular Conjugate Additions of Aldehyde-Derived Enamines to α,β-Unsaturated Esters

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ABSTRACT: We report a pairing of known catalysts that enables intramolecular conjugate additions of aldehyde-derived enamines to α,β-unsaturated esters. Despite extensive prior exploration of conjugate additions of aldehyde-derived enamines, catalytic conjugate additions to unactivated enoate esters are unprecedented. Achieving enantioselective and diastereoselective six-membered ring formation requires the coordinated action of a chiral pyrrolidine, for nucleophilic activation of the aldehyde via enamine formation, and a hydrogen bond donor, for electrophilic activation of the enoate ester. Proper selection of the hydrogen bond donor is essential for chemoselectivity, which requires minimizing competition from homo-aldol reaction. Utility is demonstrated in a six-step synthesis of (-)-yohimbane from cycloheptene.

Discrimination among competing reaction pathways to favor desired transformations is a central challenge in preparative organic chemistry. Enzymes often exert strict regulation of chemical reactivity because of the highly controlled environment provided to substrates by active sites. Discovering strategies to select among competing reaction pathways via small-molecule catalysts, which cannot envelop substrates, is a driving force for development of new synthetic methods.[1-7]

Prior examples of aldehyde-derived enamines reacting with unactivated α,β-unsaturated esters have involved preformed enamines generated with excess achiral amine.[8] Catalytic addition of aldehydes to unactivated α,β-unsaturated esters, via transient enamine formation, was apparently unknown when we began this work.[9] This reactivity lacuna is surprising because conjugate additions have been explored for over 130 years.[10] Many examples of catalytic conjugate additions of enamine-based nucleophiles to electron-deficient alkenes are known (Figure 1A).[11] The absence of catalytic aldehyde enamine conjugate additions to conventional enoate esters likely stems from the low electrophilicity of these enoate esters, as established by Mayr et al.,[12,13] along with the high electrophilicity of aldehydes, which leads to preference for homo-aldol products.[14] The synthetic value of this unknown transformation arises from the potential utility of the products.[9,15-18]

A few examples of intramolecular conjugate additions of ketone-derived enamines to an enoate ester have been reported. These reactions rely upon use of stoichiometric amine and extended reaction times,[19] or on a carefully chosen bifunctional catalyst.[16,17,20] The diminished electrophilicity of a ketone relative to an aldehyde curtails formation of homo-aldol byproducts in these cases.[13,14] Therefore, achieving chemoselective conjugate addition of a ketone-derived enamine to an enoate ester does not involve the challenges inherent in comparable aldehyde reactions.

We report the identification of an amine-urea catalyst pair that enables efficient and stereoselective six-membered ring formation via intramolecular conjugate addition of an aldehyde-derived enamine to an α,β-unsaturated ester. Many reaction conditions we examined led to substantial homo-aldol product, or no reaction at all. Proper choice of the two catalysts, however, enabled useful control over chemo-, diastereo- and enantioselectivity. The reactivity demonstrated here fills a long-standing void in conjugate additions, extending this reaction mode to the poorest electrophile yet employed with an aldehyde-derived enamine nucleophile.

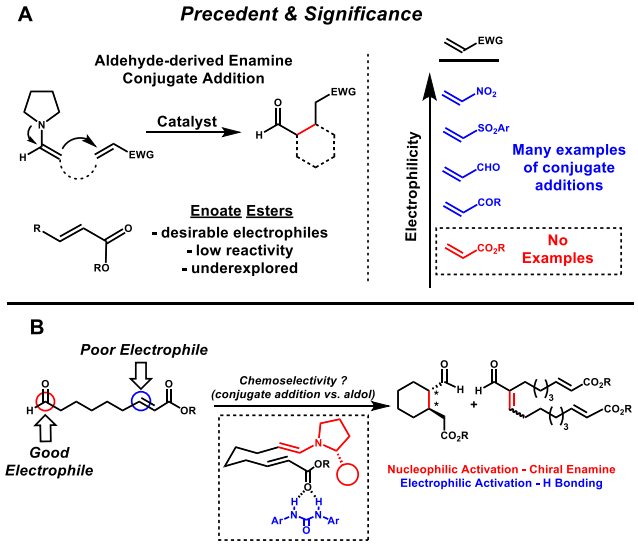

Figure 1. (a) Conjugate addition of aldehyde-derived enamines to electron-deficient olefins is widely practiced but limited by electrophilic reactivity (scale on right adapted from ref. 18). (b) For the desired cyclization, conjugate addition to a weak electrophile (α,β-unsaturated ester) must be favored over the competing homo-aldol pathway reaction, which is achieved with a specific co-catalyst pairing.

Our initial studies focused on the cyclization of aldehyde-enoate substrate **1**, which allowed us to evaluate secondary amines for the ability to catalyze the desired cyclization via transient enamine formation.[21] Pyrrolidine cleanly provided racemic **3**, but only a trace of **3** was detected with the widely used Hayashi-Jørgensen catalyst, **2** (Figure S1).[22,23] Compound **2** and related 2-substituted pyrrolidines have enabled a wide range of enantioselective conjugate additions of aldehydes to electrophiles more reactive than enoate esters.[24,25] However, the increased steric hindrance arising from the bulky substituent adjacent to nitrogen, relative to pyrrolidine itself, apparently inhibits reaction with an enoate ester, a weak electrophile.[12,13]

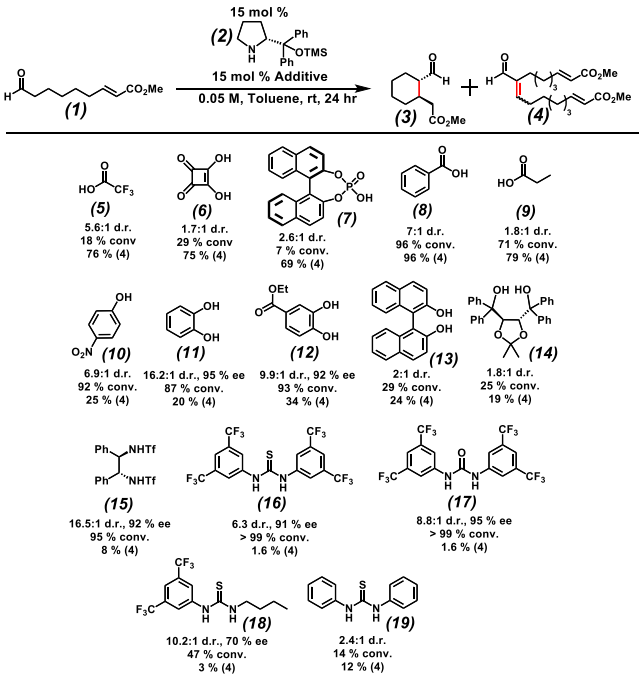

Figure 2. Effect of acidic/hydrogen bond donor additives on reaction pathway. Reactions run on 0.05 mmol scale. Percent conversion of **1** (conv.), d.r. (diastereomeric ratio) of **3**, and percent of crude product that corresponds to the homo-aldol product (**4**), as determined by ^{1}H NMR analysis. Percent enantiomeric excess (ee) determined by chiral HPLC. For calculation of percent conversion, see supporting information.

We hypothesized that the desired conjugate addition would require electrophilic activation of the enoate ester in conjunction with enamine-based (nucleophilic) activation of the aldehyde. Brønsted acid and hydrogen bond donor additives have been employed to enhance carbonyl electrophilicity,[26,27] but use of such of such catalysts in our case could create a chemoselectivity problem. The ideal catalyst should activate the ester in preference to the aldehyde, in order to favor cyclization over the intermolecular homo-aldol pathway. Yamamoto et al. were able to activate aldehydes relative to ketones with exotic Lewis acids,[28] but we are not aware that Brønsted acids or hydrogen bond donors have demonstrated this type of chemoselectivity. We surveyed candidate co-catalysts under a consistent set of conditions (Figure 2).

Brønsted acids were not effective as co-catalysts. The strongest acids we examined, trifluoroacetic acid (**5**), squaric acid (**6**) and BINOL phosphoric acid (**7**), gave low conversions and mostly homo-aldol product. Weaker acids, benzoic acid (**8**) and propionic acid (**9**), gave high conversions, but again mostly the undesired homo-aldol product. Among simple phenolic compounds, which may be considered as hydrogen bond donors rather than Brønsted acids under these conditions, better outcomes were observed. Thus, p-nitrophenol (**10**), catechol (**11**) and ethyl protocatechuate (**12**) supported formation of cyclized product **3** with high diastereo- and enantioselectivity, but in each case a substantial fraction of the starting material was directed along the undesired homo-aldol pathway. BINOL (**13**) and TADDOL (**14**) were poor co-catalysts, each providing relatively low yields of **3**, with little diastereoselectivity and significant homo-aldol byproduct.

Placing our observations in the context of related reports highlights the chemoselectivity challenge inherent in cyclizing aldehyde-enoate ester **1**. Dixon et al. reported enantioselective formation of a six-membered ring via addition of a ketone-derived enamine to an enoate ester with benzoic acid as a co-catalyst.[17] Scheidt et al. used catechol as a co-catalyst for six-membered ring formation in a comparable process.[16] Chemoselectivity was not a major concern in these systems because homo-aldol reactions of ketones are generally unfavorable. Ethyl protocatechuate was an effective co-catalyst for intermolecular conjugate additions of aldehydes to enones,[29] which are more electrophilic than enoate esters.[12,13] 4-Nitrophenol has been used for conjugate additions of enamines derived from **2** to nitro-alkenes,[11i] which are strong electrophiles.[12,13]

We identified three hydrogen bond donor co-catalysts that, in combination with chiral amine **2**, displayed favorable chemo-, enantio-, and diastereoselectivity profiles. Chiral 1,2-bistriflamide (**15**) provided high conversion to **3** with excellent enantio- and diastereoselectivity. Only a modest amount of homo-aldol product (8%) was formed. Compound **15** was reported to catalyze aza-conjugate additions to enoate esters,[30] which suggests that the 1,2-bistriflamide unit may be generally effective for electrophilic activation of this substrate class. Schreiner's thiourea (**16**)[31] and the corresponding urea (**17**) both result in total conversion of **1**, with near-complete selectivity for the cyclization product (98 %).

The electron-deficient aromatic rings in thiourea **16** are critical, because replacing one with an alkyl group (**18**) or replacing both with phenyl rings (**19**) led to much poorer outcomes relative to **16** as co-catalyst. Urea **17** and and thiourea **19** are expected to have very similar pKa values,[32] but they perform very differently as co-catalysts for cyclization of **1**. In contrast, thiourea **16** is considerably more acidic than urea **17**, but they perform similarly as co-catalysts. Thus, pKa is not a principal determinant of enoate ester activation in this reaction. These results suggest that the factors determining the efficacy of catalysis via hydrogen bond donation are complex and deserve further attention. The substantial variation in proportion of homo-aldol vs. intramolecular conjugate addition products observed across the co-catalysts we surveyed raises the possibility that site-selective carbonyl activation might offer a strategy for late-stage functionalization of complex substrates.[33]

We examined a few variants of pyrrolidine **2** (Figure S1). Replacing the trimethylsilyl group with *t*-butyldimethylsilyl led to slight increases in enantioselectivity. Further increases in steric bulk on the pyrrolidine ring substituent, however, caused an erosion in reactivity. The pyrrolidine could not be replaced with an imidazolidinone, which is consistent with earlier studies involving intramolecular conjugate additions of aldehydes.[11d] Trace conversion of starting material **1** was observed in the presence of S-methylbenzylamine, which highlights an important distinction between aldehyde-enoate ester and ketone-enoate ester cyclizations. All known ketone-enoate ester cyclizations have relied on primary amine catalysts,[16,17,19,20] presumably because primary amines are more effective than secondary amines at forming ketone-derived enamines.[21,34]

Toluene and chlorinated solvents were optimal for the cyclization of **1** (Figure S2). Polar solvents, including alcohols, ethers, nitriles, and amides, gave poor overall conversion, which may indicate that Lewis basic groups in the solvent molecules compete with the enoate ester as hydrogen bond acceptors.

Additional studies were carried out to determine whether useful chemoselectivity could be maintained at higher substrate concentrations. The reactions described above were conducted with 0.05 M **1**; Figure 3 summarizes results obtained with 0.5 M **1**. In each case, 15 mol % pyrrolidine **2** and co-catalyst was used. Although competition from the undesired homo-aldol pathway was more apparent with the 10-fold increase in substate concentration, as would be expected, these conditions highlight the superiority of urea co-catalyst **17**, with which the homo-aldol product was formed in only 13% yield. This by-product was formed in slightly higher yield with thiourea **16**, and in much higher yield with bis-triflamide **15** or with catechol (**11**). Retention of selectivity for cyclization at this substrate concentration suggests that urea **17** is highly selective for electrophilic activation of the enoate ester relative to the aldehyde.

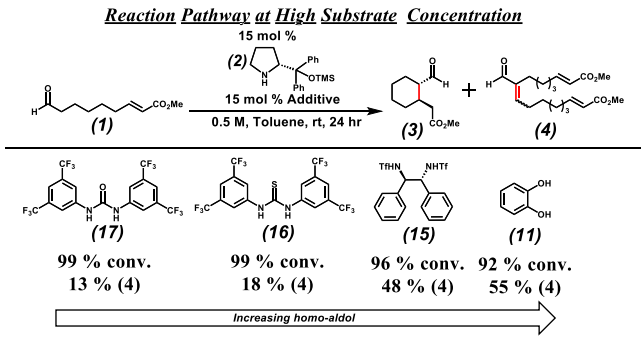

Figure 3. Effect of high substrate concentration on reaction pathway in the presence of lead co-catalysts from Figure 2. Reactions run on 0.05 mmol scale (0.5 M substrate).

We explored substrate scope with catalyst pair **2** + **17** (Figure 4). Methyl (**3**), ethyl (**20**) and benzyl (**21**) ester cyclization products were formed in similar yields, but enantioselectivity diminished as the ester group became bulkier. *Cis* vs. *trans* configurations of the products were assigned via NMR analysis (Figure S18-S53). Absolute configuration was determined by x-ray diffraction for derivatives **3A** and **21A** (Figure 4, S12-S14); other absolute configurations were assigned by analogy.

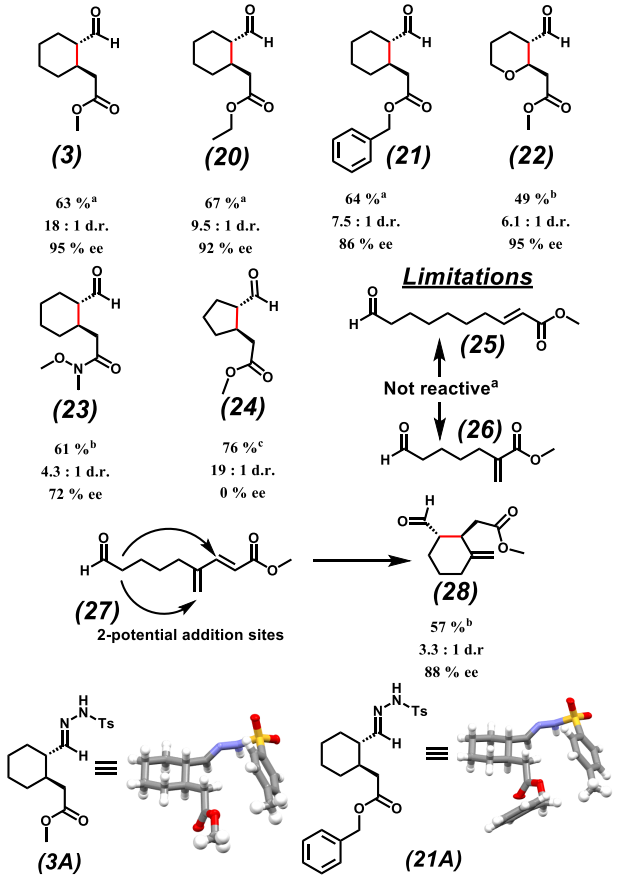

Figure 4. Substrate scope and x-ray structures. Reactions run on 0.5 mmol scale. Yields refer to isolated values. Diastereomeric ratio (d.r.) was determined via ^{1}H NMR analysis of the crude reaction mixture. [a]20 mol % **2**, 20 mol % **17**, 0.025 M toluene, 48 hr, 0° C. [b]30 mol % **2**, 30 mol % **17**, 0.025 M toluene, 72 hr, 0° C. [c]20 mol % **2**, 20 mol % **16**, 0.05 M toluene, 24 hr, rt. Ts = p-toluenesulfonyl. Red indicates bond formed.

Tetrahydropyran product **22** was obtained with high enantioselectivity, although higher catalyst loadings were required to achieve this outcome. We speculate that the Lewis basic oxygen in the substrate may compete with the ester carbonyl for hydrogen bonding to urea **17**. The enoate ester could be replaced with an α,β-unsaturated Weinreb amide (**23**),[35] although the product was formed with only moderate enantioselectivity. When the length of the substrate was reduced, cyclopentyl product **24** was obtained in good yield and diasteroselectivity, but without any enantioselectivity. Compound **24** has been previously used in prostaglandin syntheses.[36,37] The aldehyde-enoate ester substrate (**25**) that might have formed a seven-membered ring did not cyclize under our reaction conditions. Enoate ester **26**, too, was unreactive, which is consistent with Baldwin's ring closure rules.[38] This observation prompted us to evaluate dienoate ester substrate **27**, which underwent regioselective cyclization to form **28**.

Our new method of generating cyclohexyl aldehyde esters enabled a concise total synthesis of (-)-yohimbane from cycloheptene (Figure 5). (-)-Yohimbane, an indole alkaloid of the rauwalfia family, displays antipsychotic and antihypertensive activities.[39] The elegant prior enantioselective syntheses of (-)-yohimbane rely on substrate diastereocontrol,[40] enzymatic resolution,[41] or multiple stereo-defining steps[42] to control the absolute configuration of the final product. Our cyclization simultaneously sets two adjacent C-sp^3 stereocenters, controlling both relative and absolute configurations, which supports a streamlined route.

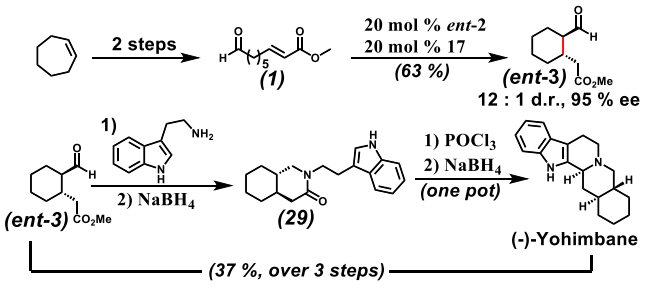

Figure 5. Six-step synthesis of (-)-yohimbane.

Compound **1** could be prepared in gram quantities from cycloheptene via ozonlysis to generate the mono-dimethyl acetal,[43] followed by Horner-Wadsworth-Emmons olefination and acetal hydrolysis. Use of pyrrolidine catalyst *ent*-**2** along with urea co-catalyst **17** produced *ent*-**3**, which was combined with tryptamine in a one-pot reductive amination-cyclization cascade[44] to form lactam **29**. Bischler-Napieralski reaction[45] of **29** generated (-)-yohimbane in 95 % ee.

Our results demonstrate that the reaction pathway followed by an aldehyde-derived enamine can be controlled through careful choice of the electrophile-activating co-catalyst. These findings can be seen as part of an increasing communal interest in the development of catalysts that influence selectivity among alternative reaction pathways.[46] Our work reveals surprising variation among diverse Brønsted acid/hydrogen bond donor co-catalysts in terms of the reactivity channel followed by aldehyde-enoate ester **1** in the presence of the widely used Hayashi-Jørgensen catalyst (**2**; Figure 2). Some co-catalysts favor the intramolecular conjugate addition channel to form cyclohexane derivative **3**, while others favor the intermolecular homo-aldol condensation channel. A third set of co-catalyst candidates does not promote either reaction. The distinctive ability of urea **17** to provide **3** with superior diastereo- and enantioselectivity could not have been predicted. The enantioselective cyclization mode we have identified represents a new frontier in conjugate additions of aldehyde-derived enamines, which have been extremely widely examined with intrinsically reactive electrophiles such as nitro-alkenes but largely unexplored with the more inert enoate esters.

ASSOCIATED CONTENT

Supporting Information. The supporting information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

REFERENCES

1. Brown, D. G.; Bostrom, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **2016**, 59, 4483-4458.
2. Bostrom, J.; Brown, D. G.; Young, R. J.; Keseru, G. M. Expanding the medicinal chemistry synthetic toolbox. *Nature Reviews Drug Discovery* **2018**, 17, 709-727.
3. Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. The importance of synthetic chemistry in the pharmaceutical industry. *Science* **2019**, 363, eaat805.
4. Troshin, K.; Hartwig, J. F. Snap deconvolution: An informatics approach to high-throughput discovery of catalytic reactions. *Science* **2017**, 357, 175-181.
5. McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of an α-Amino C-H Arylation Reaction Using the Strategy of Accelerated Serendipity. *Science* **2011**, 334, 1114-1117.
6. Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*. University Science Books: **2006**.
7. Fleming, I. *Molecular Orbitals and Organic Chemistry Reactions – student edition*. Wiley, **2009**.
8. (a) Norman, M. H.; Heathcock, C. H. Improved Synthesis of N-Benzyl-5-ethyl-1,2,3,4-tetrahydropyridine. *J. Org. Chem.* **1988**, 53, 3371-3373. (b) Ahmad, Z.; Goswami, P.; Venkateswaran, R. V. A Formal Stereocontrolled Synthesis of (±) Isoclovene. *Tetrahedron* **1989**, 45, 6833-6840. (c) Costello, G.; Saxton, J. E. Approaches to the Synthesis of Asidosperma Alkaloids, Part 1, Preliminary Studies in the Vincadifformine Group. *Tetrahedron* **1986**, 42, 6047-6069.
9. For an example of aldehyde-derived enamines adding to activated α,β-unsaturated esters see: Kano, T.; Shirozu, F.; Akakura, M.; Maruoka, K. Powerful Amino Diol Catalyst for Effecting the Direct Asymmetric Conjugate Addition of Aldehydes to Acrylates. *J. Am. Chem. Soc.* **2012**, 134, 16068-16073.
10. Michael, A. On the addition of sodium acetoacetate- and sodium malonic acid esters to the esters of unsaturated acids. *Journal fur Praktische Chemie* **1887**, 35, 349-356.
11. (a) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Gomez, C.; Guillena, G.; Pastor, I. M.; Ramon, D. J. Recent Advances in Asymmetric Organocatalyzed Conjugate Additions to Nitroalkenes. *Molecules* **2017**, 22, 895. (b) Betancort, J. M.; Barbas III, C. F. Catalytic Direct Asymmetric Michael Reactions: Taming Naked Aldehyde Donors, *Org. Lett.* **2001**, 3, 3737-3740. (c) Melchiorre, P.; Jorgensen, K. A. Direct Enantioselective Michael Additions of Aldehydes to Vinyl Ketones Catalyzed by Chiral Amines. *J. Org. Chem.* **2003**, 68, 4151-4157. (d) Hechavarria Fonseca, M. T.; List, B. Catalytic asymmetric intramolecular Michael

reaction of aldehydes. *Angew. Chem. Int. Ed.* **2004**, 43, 3958-3960. (e) Peelen, T. J.; Chi, Y.; Gellman, S. H. Enantioselective Organocatalytic Michael Additions of Aldehydes to Enones with Imidazolidinones: Cocatalyst Effects and Evidence for an Enamine Intermediate. *J. Am. Chem. Soc.* **2005**, 127, 11598-11599. (f) Krause, N., Hoffmann-Rober, A. Recent Advances in Catalytic Enantioselective Michael Additions. *Synthesis* **2001**, 2, 171-196. (g) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. Asymmetric Michael Reaction of Acetaldehyde Catalyzed by Diphenylprolinol Silyl Ether. *Ang. Chem. Int. Ed.* **2008**, 47, 4722-4724. (h) Bournaud, C.; Marchal, E.; Quintard, A.; Sulzer-Mosse, S.; Alexakis, A. Organocatalyst-mediated enantioselective intramolecular Michael addition of aldehydes to vinyl sulfones. *Tetrahedron: Asymmetry* **2010**, 21, 1666-1673. (i) Seebach, D.; Sun, X.; Ebert, M.; Bernd Schweizer, W.; Purkayastha, N.; Beck, A. K.; Duschmale, J.; Wennemers, H. Stoichiometric Reactions of Enamines Derived from Diphenylprolinol Silyl Ethers with Nitro Olefins and Lessons for the Corresponding Organocatalytic Conversions – a Survey. *Helvetica Chimica Acta*. **2013**, 96, 799-852.

12. Allgauer, D. S.; Jangra, H.; Asahara, H.; Li, Z.; Chen, Q.; Zipse, H.; Ofial, A. R.; Mayr, H. Quantification and Theoretical Analysis of the Electrophilicities of Michael Acceptors. *J. Am. Chem. Soc.* **2017**, 139, 13318-13329.
13. Mayr, H. **2015**, Available at: https://www.cup.lmu.de/oc/mayr/ReactScales-Poster.pdf. Accessed March 2, 2020.
14. Appel, R.; Mayr, H. Quantification of the Electrophilic Reactivities of Aldehydes, Imines, and Enones. *J. Am. Chem. Soc.* **2011**, 133, 8240-8251.
15. Gatzenmeier, T.; Kaib, P. S. J.; Lingnau, J. B.; Goddard, R.; List, B. The Catalytic Asymmetric Mukaiyama-Michael Reaction of Silyl Ketene Acetals with α,β-Unsaturated Methyl Esters. *Angew. Chem. Int. Ed.* **2018**, 57, 2464-2468.
16. Younai, A.; Zeng, B.; Meltzer, H. Y.; Scheidt, K. A. Enantioselective Syntheses of Heteroyohimbine Natural Products: A Unified Approach through Cooperative Catalysis. *Angew. Chem. Int. Ed.* **2015**, 54, 6900-6904.
17. Gammack Yamagata, A. D.; Datta, S.; Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. Enantioselective Desymmetrization of Prochiral Cyclohexanones by Organocatalytic Intramolecular Michael Additions to α,β-Unsaturated Esters. *Angew. Chem. Int. Ed.* **2015**, 54, 4899-4903.
18. Leonov, A. I.; Timofeeva, D. S.; Ofial, A. R.; Mayr, H. Metal Enolates – Enamines – Enol Ethers: How Do Enolate Equivalents Differ in Nucleophilic Reactivity? *Synthesis* **2019**, 51, 1157-1170.
19. Hirai, Y.; Terada, T.; Yamazaki, T.; Momose, T. Heterocycles in asymmetric synthesis. Part 1. Construction of the chiral building blocks for enantioselective alkaloid synthesis *via* an asymmetric intramolecular Michael reaction. *J. Chem. Soc., Perkin Trans. 1.* **1992**, 509-516.
20. Kang, J. Y.; Carter, R. G. Primary Amine, Thiourea-Based Dual Catalysis Motif for Synthesis of Stereogenic, All-Carbon Quaternary Center-Containing Cycloalkanones. *Org. Lett.* **2012**, 14, 3178-3181.
21. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.* **2007**, 107, 5471-5569.
22. Marigo, M.; Jorgensen, K. A. Enantioselective Organocatalysis: Reactions and Experimental Procedures; Wiley, 2007.
23. Frazen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T., C.; Kjaersgaard, A.; Jorgensen, K. A. A General Organocatalyst for Direct α-Functionalization of Aldehydes: Stereoselective C-C, C-N, C-F, C-Br, and C-S Bond-Forming Reactions. Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2005**, 127, 18296-18304.
24. Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jorgensen, K. A. The Diarylprolinol Silyl Ethers: Ten Years After. *Angew. Chem. Int. Ed.* **2015**, 54, 13860-13874.
25. Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. Enantioselective Organocatalytic Michael Addition of Aldehydes to Nitroethylene: Efficient Access to γ^2-Amino Acids. *J. Am. Chem. Soc.* **2008**, 130, 5608-5609.
26. Akiyama, T.; Mori, K. Stronger Bronsted Acids: Recent Progress. *Chem. Rev.* **2015**, 115, 9277-9306.
27. (a) Doyle, A. G.; Jacobsen, E. N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. *Chem. Rev.* **2007**, 107, 5713-5743. (b) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis by Chiral Hydrogen-Bond Donors. *Angew. Chem. Int. Ed.* **2006**, 45, 1520-1543.
28. (a) Yamamoto, H.; Futatsugi, K. "Designer Acids": Combined Acid Catalysis for Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2005**, 44, 1924-1942. (b) Saito, S.; Yamamoto, H. Designer Lewis acid catalysts – bulky aluminum reagents for selective organic synthesis. *Chem. Commun.* **1997**, 1585-1592.
29. Chi, Y.; Gellman, S. H. Diphenylprolinol Methyl Ether: A Highly Enantioselective Catalyst for Michael Addition of Aldehydes to Simple Enones. *Org. Lett.* **2005**, 7, 4253-4256.
30. Chung, C. K.; Liu, Z.; Lexa, K. W.; Andreani, T.; Xu, Y.; Ji, Y.; DiRocco, D. A.; Humphrey, G. R.; Ruck, Rebecca, T. Asymmetric Hydrogen Bonding Catalysis for the Synthesis of Dihydroquinazoline-Containing Antiviral, Letermovir. *J. Am. Chem. Soc.* **2017**, 139, 10637-10640.
31. (a) Schreiner, P. R.; Wittkopp, A. H-Bonding Additives Act Like Lewis Acid Catalysts. *Org. Lett.* **2002**, 4, 217-220. (b) Schreiner, P. R. Metal-free organocatalysis through explicit hydrogen bonding interactions. *Chem. Soc. Rev.* **2003**, 32, 289-296. (c) Etter, M.; Panunto, T. W. 1,3-Bis(m-nitrophenyl)urea: An Exceptionally Good Complexing Agent for Proton Acceptors. *J. Am. Chem. Soc.* **1988**, 110, 5896-5897. (d) Curran, D. P.; Kuo, L. H. Altering the Stereochemistry of Allylation Reactions of Cyclic α-Sulfinyl Radicals with Diarylureas. *J. Org. Chem.* **1994**, 59, 3259-3261.
32. Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. (Thio)urea Organocatalyst Equilibrium Acidities in DMSO. *Org. Lett.* **2012**, 14, 1724-1727.
33. Toste, D. F.; Sigman, M. S.; Miller, S. J. Pursuit of Noncovalent Interactions for Strategic Site-Selective Catalysis. *Acc. Chem. Res.* **2017**, 50, 609-615.
34. Erkkila, A.; Majander, I.; Pihko, P. M. Iminium Catalysis, *Chem. Rev.* **2007**, 107, 5416-5470.
35. Nahm, S.; Weinreb. S. M. N-methoxy-n-methylamides as effective acylating agents. *Tetrahedron Letters* **1981**, 22, 3815-3818.
36. Sakai, K.; Inouye, K.; Nakamura, N. Synthesis of (+)-Prostanoic Acid. *Prostaglandins* **1976**, 12, 399-401.
37. Crabbe, P.; Cervantes, A.; Guzman, A. Synthesis of a 9,11-Bis-desoxy-prostaglandin. *Tetrahedron Letters,* **1972**, 12, 1123-1125. (b) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. Total Synthesis of Prostaglandins $F_{2\alpha}$ and E_2 as the Naturally Occurring Forms. *J. Am. Chem. Soc.*, **1970**, 92, 397-398.
38. (a) Baldwin, J. Rules for Ring Closure, *J. Chem. Soc. Chem. Commun*. **1976**, 18, 734-736. (b) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. Rules for ring closure: ring formation by conjugate addition of oxygen nucleophiles. *J. Org. Chem.* **1977**, 42, 3846-3852.

39. Szantay, C.; Blasko, G.; Honty, K.; Dornye, G. *The Alkaloids*; Academic: New York; 1986, Vol. 27.
40. Aube, J.; Ghosh, S.; Tanol, M. Symmetry-Driven Synthesis of Indole Alkaloids: Asymmetric Total Syntheses of (+)-Yohimbine, (-)-Yohimbone, (-)-Yohimbane, and (+)-Alloyohimbane. *J. Am. Chem. Soc.* **1994**, 116, 9009-9018.
41. Ghosh, A. K.; Sarkar, A. Enantioselective Syntheses of (-)-Alloyohimbane and (-)-Yohimbane by an Efficient Enzymatic Desymmetrization Process. *Eur. J. Org. Chem.* **2016**, 6001-6009.
42. Xie, C.; Luo, J.; Zhang, L.; Hong, R. A Chiral Pentenolide-Based Unified Strategy toward Dihydrocorynantheal, Dihydrocorynantheol, Protoemetine, Protoemetinol, and Yohimbane., *Org. Lett.* **2017**, 19, 3592-3595.
43. Claus, R. E.; Schreiber, S. L. Ozonolytic Cleavage of Cyclohexene to Terminally Differentiated Products: Methyl 6-Oxohexanoate, 6,6-Dimethoxyhexanal, Methyl 6,6-Dimethoxyhexanoate. *Org. Synth.* **1986**, 64, 150.
44. (a) Van Tamelen, E. E.; Shamma, M.; Aldrich, P. The Stereospecific Synthesis of dl-Yohimbane. Stereochemistry of Tohimbine. *J. Am. Chem. Soc.* **1956**, 78, 4628-4632. (b) Allin, S. M.; Duffy, L. J.; Bulman Page, P. C.; McKee, V.; McKenzie, M. J. Towards a total synthesis of the manadomanzamine alkaloids: the first asymmetric construction of the pentacyclic indole core. *Tetrahedron Letters* **2007**, 48, 4711-4714. (c) Yang, V.; Hong, B.; Kao, H.; Tu, T.; Chen, C.; Lee, G.; Chou, P. One-Pot Dichotomous Construction of Inside-Azayohimban and Pro-Azayohimban Systems via an Enantioselective Organocatalytic Cascade; Their Use as a Model to Probe the (Aza-)Indole Local Solvent Environment. *Org. Lett.* **2015**, 17, 5816-5819.
45. Bischler, A.; Napieralski, B. A new method for the synthesis of isoquinolines. *Ber. Dtsch. Chem. Ges.* **1893**, 26, 1903-1908.
46. (a) Alford, J. S.; Abascal, N. C.; Shugrue, C. R.; Colvin, S. M.; Romney, R. K.; Miller, S. J. Aspartyl Oxidation Catalysts That Dial in Functional Group Selectivity, along with Regio- and Stereoselectivity. *ACS Cent. Sci.* **2016**, 2, 733-739. (b) Liu, W.; Ren, Z.; Bosse, A. T.; Liao, K.; Goldstein, E. L.; Bacsa, J.; Musaev, D. G.; Stoltz, B. M.; Davies, H. M. L. Catalyst-Controlled Selective Functionalization of Unactivated C-H Bonds in the Presence of Electronically Activated C-H Bonds. *J. Am. Chem. Soc.* **2018**, 140, 12247-12255. (c) Cook, A. K.; Schimler, S. D.; Matzger, A. J.; Sanford, M. S. Catalyst-controlled selectivity in the C-H borylation of methane and ethane. *Science* **2016**, 351, 1421-1424. (d) Hartwig, J. Catalyst-Controlled Site-Selective Bond Activation. *Acc. Chem. Res.* **2017**, 50, 549-555. (e) Jung, S. T.; Lauchli, R.; Arnold, F. H. Cytochrome P450: taming a wild type enzyme. *Current Opinion in Biotechnology* **2011**, 22, 809-817.