

# Catalytic Intramolecular Conjugate Additions of Aldehyde-Derived Enamines to $\alpha,\beta$ -Unsaturated Esters

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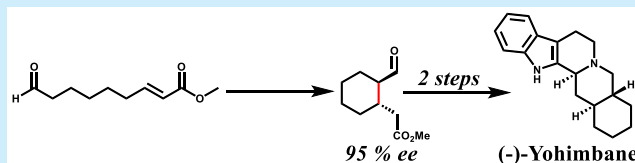


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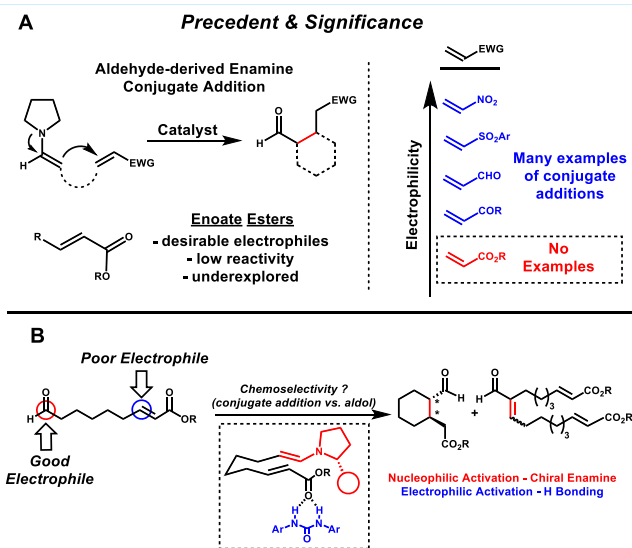
**ABSTRACT:** We report a pairing of known catalysts that enables intramolecular conjugate additions of aldehyde-derived enamines to  $\alpha,\beta$ -unsaturated esters. Despite extensive prior exploration of conjugate additions of aldehyde-derived enamines, catalytic conjugate additions to unactivated 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 homoaldol 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,<sup>1–7</sup> is a driving force for development of new synthetic methods.

Prior examples of aldehyde-derived enamines reacting with unactivated  $\alpha,\beta$ -unsaturated esters have involved preformed enamines generated with excess achiral amine.<sup>8</sup> Catalytic addition of aldehydes to unactivated  $\alpha,\beta$ -unsaturated esters, via transient enamine formation, was apparently unknown when we began this work.<sup>9</sup> This reactivity lacuna is surprising because conjugate additions have been explored for over 130 years.<sup>10</sup> Many examples of catalytic conjugate additions of enamine-based nucleophiles to electron-deficient alkenes are known (Figure 1A).<sup>11</sup> 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.,<sup>12,13</sup> along with the high electrophilicity of aldehydes, which leads to preference for homoaldol products.<sup>14</sup> The synthetic value of this unknown transformation arises from the potential utility of the products.<sup>9,15–18</sup>

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,<sup>19</sup> or on a carefully chosen bifunctional catalyst.<sup>16,17,20</sup> The diminished electrophilicity of a ketone relative to an aldehyde curtails formation of homoaldol byproducts in these cases.<sup>13,14</sup> Therefore, achieving chemo-



**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 ( $\alpha,\beta$ -unsaturated ester) must be favored over the competing homoaldol pathway reaction, which is achieved with a specific cocatalyst pairing.

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selective conjugate addition of a ketone-derived enamine to an enoate ester does not involve the challenges inherent in comparable aldehyde reactions.

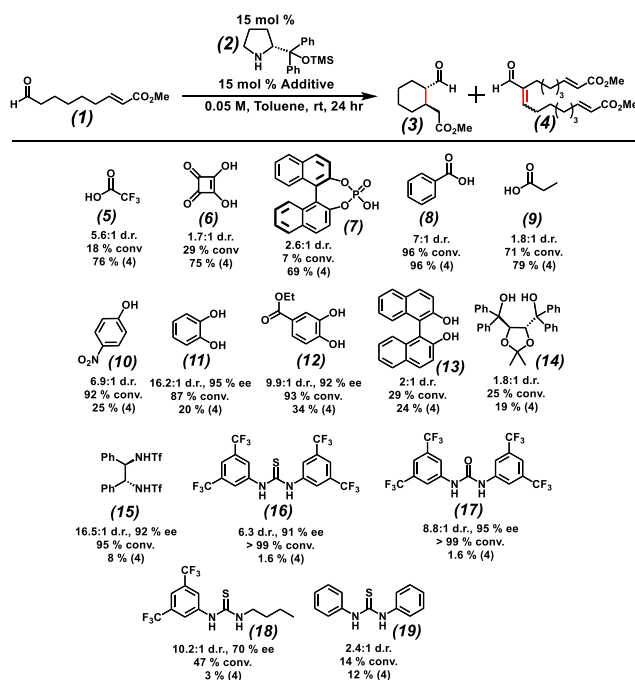
We report the identification of an amine–urea catalyst pair that enables efficient and stereoselective six-membered ring formation via intramolecular conjugate addition of an aldehyde-derived enamine to an  $\alpha,\beta$ -unsaturated ester. Many reaction conditions we examined led to substantial homoaldol 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.

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.<sup>21</sup> Pyrrolidine cleanly provided racemic **3**, but only a trace of **3** was detected with the widely used Hayashi–Jørgensen catalyst, **2** (Figure S1).<sup>22,23</sup> 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.<sup>24,25</sup> 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.<sup>12,13</sup>

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,<sup>26,27</sup> 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 to favor cyclization over the intermolecular homoaldol pathway. Yamamoto et al. were able to activate aldehydes relative to ketones with exotic Lewis acids,<sup>28</sup> but we are not aware that Brønsted acids or hydrogen bond donors have demonstrated this type of chemoselectivity. We surveyed candidate cocatalysts under a consistent set of conditions (Figure 2).

Brønsted acids were not effective as cocatalysts. The strongest acids we examined, trifluoroacetic acid (**5**), squaric acid (**6**), and BINOL phosphoric acid (**7**), gave low conversions and mostly homoaldol product. Weaker acids, benzoic acid (**8**) and propionic acid (**9**), gave high conversions but again mostly the undesired homoaldol 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 protococatechuate (**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 homoaldol pathway. BINOL (**13**) and TADDOL (**14**) were poor cocatalysts, each providing relatively low yields of **3**, with little diastereoselectivity and significant homoaldol 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 cocatalyst.<sup>17</sup> Scheidt et al. used catechol as a cocatalyst for six-



**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 homoaldol product (**4**), as determined by <sup>1</sup>H NMR analysis. Percent enantiomeric excess (ee) determined by chiral HPLC. For calculation of percent conversion, see the Supporting Information.

membered ring formation in a comparable process.<sup>16</sup> Chemo-selectivity was not a major concern in these systems because homoaldol reactions of ketones are generally unfavorable. Ethyl protococatechuate was an effective cocatalyst for intermolecular conjugate additions of aldehydes to enones,<sup>29</sup> which are more electrophilic than enoate esters.<sup>12,13</sup> 4-Nitrophenol has been used for conjugate additions of enamines derived from **2** to nitro-alkenes,<sup>11</sup> which are strong electrophiles.<sup>12,13</sup>

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

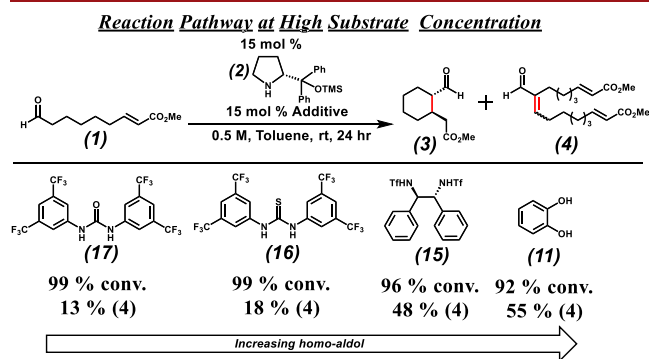
The electron-deficient aromatic rings in thiourea **16** are critical because replacing one with an alkyl group (**18**) or replacing both with phenyl rings (**19**) led to much poorer outcomes relative to **16** as cocatalyst. Urea **17** and thiourea **19** are expected to have very similar *pK<sub>a</sub>* values,<sup>32</sup> but they perform very differently as cocatalysts for cyclization of **1**. In contrast, thiourea **16** is considerably more acidic than urea **17**, but they perform similarly as cocatalysts. Thus, *pK<sub>a</sub>* 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 homoaldol versus intramolecular conjugate addition products observed across the cocatalysts we surveyed raises the possibility that site-selective carbonyl activation might offer a strategy for late-stage functionalization of complex substrates.<sup>33</sup>

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.<sup>11d</sup> 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,<sup>16,17,19,20</sup> presumably because primary amines are more effective than secondary amines at forming ketone-derived enamines.<sup>21,34</sup>

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.

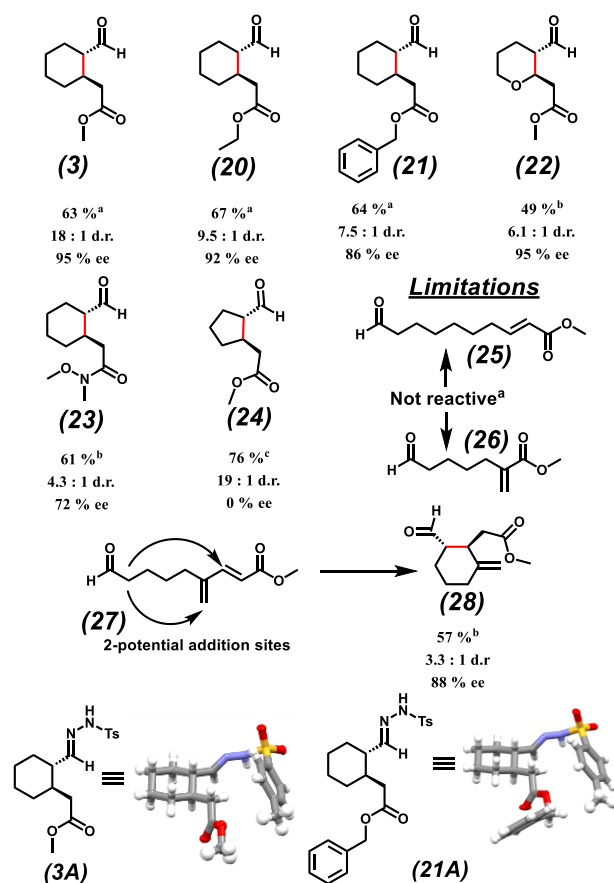
Additional studies were carried out to determine whether useful chemoselectivity could be maintained at higher substrate concentrations. The reactions described above were conducted with 0.05 M **1**; Figure 3 summarizes results obtained with 0.5



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

M **1**. In each case, 15 mol % pyrrolidine **2** and cocatalyst were used. Although competition from the undesired homoaldol pathway was more apparent with the 10-fold increase in substrate concentration, as would be expected, these conditions highlight the superiority of urea cocatalyst **17**, with which the homoaldol product was formed in only 13% yield. This byproduct 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.

We explored substrate scope with catalyst pair **2** + **17** (Figure 4). Methyl (**3**), ethyl (**20**), and benzyl (**21**) ester



**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 <sup>1</sup>H NMR analysis of the crude reaction mixture. (a) 20 mol % **2**, 20 mol % **17**, 0.025 M toluene, 48 h, 0 °C. (b) 30 mol % **2**, 30 mol % **17**, 0.025 M toluene, 72 h, 0 °C. (c) 20 mol % **2**, 20 mol % **16**, 0.05 M toluene, 24 h, rt. Ts = *p*-toluenesulfonyl. Red indicates bond formed.

cyclization products were formed in similar yields, but enantioselectivity diminished as the ester group became bulkier. *Cis* versus *trans* configurations of the products were assigned via NMR analysis (Figures S18–S53). Absolute configuration was determined by X-ray diffraction for derivatives **3A** and **21A** (Figures 4 and S12–S14); other absolute configurations were assigned by analogy.

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  $\alpha,\beta$ -unsaturated Weinreb amide (**23**),<sup>35</sup> 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 diastereoselectivity, but without any enantioselectivity. Compound **24** has been previously used in prostaglandin syntheses.<sup>36,37</sup> 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,<sup>38</sup> which is consistent with Baldwin's ring closure rules.<sup>38</sup> This observation prompted us to evaluate dienolate 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

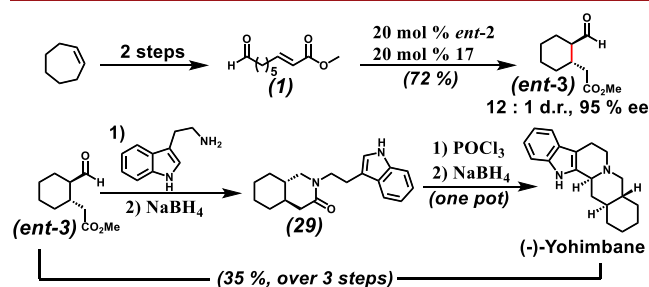


Figure 5. Six-step synthesis of (–)-yohimbane.

the rauwolfia family, displays antipsychotic and antihypertensive activities.<sup>39</sup> The elegant prior enantioselective syntheses of (–)-yohimbane rely on substrate diastereocontrol,<sup>40</sup> enzymatic resolution,<sup>41</sup> or multiple stereodefining steps<sup>42</sup> to control the absolute configuration of the final product. Our cyclization simultaneously sets two adjacent C-sp<sup>3</sup> stereocenters, controlling both relative and absolute configurations, which supports a streamlined route.

Compound 1 could be prepared in gram quantities from cycloheptene via ozonolysis to generate the monodimethyl acetal,<sup>43</sup> followed by Horner-Wadsworth-Emmons olefination and acetal hydrolysis. Use of pyrrolidine catalyst *ent*-2 along with urea cocatalyst 17 produced *ent*-3, which was combined with tryptamine in a one-pot reductive amination-cyclization cascade<sup>44</sup> to form lactam 29. Bischler-Napieralski reaction<sup>45</sup> 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 cocatalyst. These findings can be seen as part of an increasing communal interest in the development of catalysts that influence selectivity among alternative reaction pathways.<sup>46</sup> Our work reveals surprising variation among diverse Brønsted acid/hydrogen bond donor cocatalysts 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 cocatalysts favor the intramolecular conjugate addition channel to form cyclohexane derivative 3, while others favor the intermolecular homoaldol condensation channel. A third set of cocatalyst 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 at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c01666>.

Experimental procedures, optimization studies, HRMS, <sup>1</sup>H and <sup>13</sup>C spectra, crystallographic data, HPLC traces (PDF)

## Accession Codes

CCDC 2004981–2004982 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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## Notes

The authors declare no competing financial interest.

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