Multifunctional Heterocyclic Scaffolds for Hybrid Lewis Acid/Lewis Base Catalysis of Carbon–Carbon Bond Formation

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Abstract: Several new classes of hybrid catalysts have been synthesized by tethering heterocyclic metal (Lewis acid) chelating scaffolds to several different amines capable of facilitating enamine catalysis. Oxazole, thiazole, and imidazole-based chiral precatalysts were prepared in several steps from amino acid starting materials, and these were combined with a variety of metal Lewis acids for potential use as catalysts for various carbon–carbon bond formations. Air- and moisture-tolerant catalysts for enantioselective direct aldol reactions with activated benzaldehyde acceptors were identified, with optimal results obtained with proline-derived oxazole–carboxamide precatalysts combined with Zn(OTf)₂ or lanthanide (III) salts. Control studies support the hypothesis that these act as unimolecular hybrid catalysts for the aldol reaction of propionaldehyde and 4-nitrobenzaldehyde.

Graphical abstract

Hybrid Lewis acid/Lewis base catalysts

cyclic, acyclic; 1°, 2° amines  

heterocycle  
(oxazole, thiazole or imidazole)  

chelating moiety  
(acid, amide, or phenol)  

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Keywords: Hybrid catalyst, Organocatalyst, Lewis acid, Heterocycle, Aldol reaction

1. Introduction

The use of multifunctional catalysts capable of activating multiple reaction partners remains an underutilized strategy in organic synthesis.\(^1\) One such approach involves the use of hybrid catalysts with Lewis acids and Lewis bases in close proximity on the same molecule,\(^1\) \(^2\) \(^3\) which differs from the more common strategy of using separate catalysts, which is termed cooperative, synergistic, or dual catalysis (Fig. 1, top).\(^4\) \(^5\) Instructive examples of hybrid Lewis acid/Lewis base catalysts include type-II aldolases which utilize hydroxyketone substrates,\(^6\) ferrocenylphosphine–gold(I) complexes with tethered amines reported by Ito and Hayashi for asymmetric aldol reactions with isocyanatoacetate substrates,\(^7\) bifunctional phosphine oxide/aluminum(III) catalysts for aldehyde cyanosilylation,\(^8\) and cinchona alkaloid–salicylate ligated In(III) for chiral β-lactam synthesis.\(^9\)

![Diagram of hybrid catalysts](image)

**Fig. 1.** Dual catalysis versus hybrid catalysis.

Small molecule organocatalysis has emerged as an extremely powerful tool in synthetic chemistry,\(^10\) but practical limitations include low turnover frequencies relative to many industrial transition metal catalysts, as well as limited substrate scope in some cases. Additionally, the ability to access alternative diastereoisomeric products by catalyst modification is presently a significant challenge.
that is not unique to organocatalysis, despite recent successes in the area of synergistic organo/transition metal catalysis.\textsuperscript{11}

We believe that hybrid Lewis acid/Lewis base catalysts capable of stabilizing well-defined transition states and assembled using modular, easily modifiable organic building blocks may show improved performance and/or complementary scope relative to current organocatalysts. A reaction of particular interest to us for the preparation of antibiotic and anticancer natural product analogs is the direct aldol reaction, which forms carbon–carbon bonds between ‘donor’ and ‘acceptor’ aldehydes and ketones without the requirement of substrate preactivation. Numerous catalytic asymmetric direct aldol reactions have been reported,\textsuperscript{12; 13} but many of these suffer from sluggish reactions with less activated acceptors, and few catalysts are presently capable of promoting enantioselective \textit{syn}-selective reactions without α-heteroatom containing donors.\textsuperscript{14; 15; 16; 17} To address these challenges, but more generally to investigate underexplored strategies for the catalysis of carbon–carbon bond formations, we have initiated detailed investigations into hybrid Lewis acid/Lewis base catalysts for use in several transformations.

The amino acid proline,\textsuperscript{18} as well as numerous proline derivatives, are well established for the production of \textit{anti}-aldol products. Replacement of the carboxylic acid moiety of proline with suitably positioned chelated Lewis acids offers the opportunity to access alternative product stereochemistries, and could additionally provide improved reactivity over monofunctional catalysts. The use of metal Lewis acids with various amino acid derivatives as bifunctional aldol reaction catalysts has been reported over the years by the groups of Watanabe,\textsuperscript{19} Darbre,\textsuperscript{20} Mlynarski,\textsuperscript{21} Aoki,\textsuperscript{22} Wang,\textsuperscript{23; 24; 25} and Reiser.\textsuperscript{26} However, to our knowledge, no data has been reported on the use of such hybrid aldol reaction catalysts with aldehyde donors that would be particularly useful for the synthesis of chiral polypropionate fragments and building blocks for the synthesis of modified natural products.\textsuperscript{27} This manuscript describes the preparation of several novel heterocyclic precatalysts, as well as their application in direct aldol reactions.
2. Results and discussion

One of the main challenges associated with creating a bifunctional hybrid catalyst is the need to keep the Lewis acid and Lewis base moieties from reacting with each other, while at the same time positioning them close enough in space to facilitate the key bond formation between nucleophile and electrophile. To meet these requirements, we have focused on the preparation of five-membered heterocycles that are capable of complexing Lewis acidic metals, and we have prepared a focused library of bifunctional precatalysts possessing these heterocycles tethered to several amines capable of enamine formation (Fig. 1, bottom).

2.1. Azole–carboxylate precatalysts

Our first series of bifunctional precatalysts are derived from chiral α-amino acids and possess oxazole–carboxylate chelating functionality. The synthesis of our first precatalyst in this category is outlined in Scheme 1.

The synthesis started with a peptide coupling between N-Boc-l-proline and l-threonine methyl ester hydrochloride, which afforded the known dipeptide 3 in moderate yield. The dipeptide was oxidized to ketone 4 with Dess-Martin Periodinane (DMP), then subjected to a cyclization reaction with conditions developed by Wipf (triphenylphosphine, iodine, and triethylamine)28 to generate the protected oxazole 5 in 52% yield. Lithium hydroxide hydrolysis of the

Scheme 1. Oxazole–carboxylates via oxidation-condensation sequence.
methyl ester followed by acid-mediated removal of the Boc group afforded amino acid oxazole 7 as the HCl salt in good yield.

The limited solubility of putative amino acid precatalysts such as 7 in low polarity solvents inspired us to prepare variants with lipophilic solubility handles. For example, the use of 4-hydroxyproline as a starting material permits the convenient incorporation of lipophilic groups that would be expected to have a negligible impact on catalysis. The benzyl ether of N-Boc-l-proline (1b) was coupled with l-serine methyl ester to yield dipeptide 9b in excellent yield. Cyclization of 9b to generate an oxazoline with Deoxo-Fluor™ was followed by in-situ bromination/elimination to form oxazole 10b, according to a protocol reported by Wipf and Williams,29 which we modified slightly to incorporate an aqueous wash between steps. The methyl ester 10b was hydrolyzed to yield acid 11b, which could be coupled with additional building blocks (vide infra), or the Boc group could be removed with HCl to give amino acid 11b. An identical sequence was also used to prepare an intermediate without a solubility handle (11a). Valine-based precatalysts were also prepared in a similar manner, via Boc-protected compound 14 (Scheme 3).

Scheme 2. Pyrrolidine–oxazole–carboxylates via cyclization/oxidation sequence.

Scheme 3. Valine-based oxazole–carboxylates via cyclization/oxidation sequence.
Analogous thiazole-based precatalysts were also synthesized via intermediate thioamides (Scheme 4). Treatment of keto-amide 4 with Lawesson’s reagent\textsuperscript{30} in refluxing THF generated thiazole 15 in moderate yield, which was subjected to the standard hydrolysis/deprotection conditions to yield acid 16 and amino acid 17.

Scheme 4. Thiazole–carboxylates via thioamide formation.

2.2. Azole–carboxamide precatalysts

In order to generate several alternative functionalities capable of coordinating to Lewis acids and holding them in favorable orientations for bifunctional catalysis, we have coupled our N-protected amino acids with a variety of building blocks. A small library of amides was prepared using standard peptide coupling reagents, and select examples generated from oxazoles 6, 11\textsubscript{a}, and 14, and thiazole 16, are given in Table 1. Representative syntheses are given in Schemes 6 and 7. Anilide compounds were the focus of these efforts, since they provide the opportunity to easily modulate the electronics of the coordinating amide. Additionally, amino alcohols were coupled using analogous conditions, and the resulting amido alcohols were used to prepare oxazoline moieties. The resulting precatalysts are the subject of a sister manuscript.\textsuperscript{31}

Table 1. Azole–carboxamide precatalysts\textsuperscript{a}

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Reactions were performed with either EDC, PyBOP, or i-BuOCOCl as coupling agent. See Experimental section for representative examples.

2.3. Imidazole–phenolate precatalysts

In addition to carboxylic acids and carboxamides as chelating groups, we have also prepared a novel class of imidazole–phenolate precatalysts, with a representative example given in Scheme 5. Benzylation of o-hydroxyacetophenone 21 with sodium hydride and benzyl bromide proceeded smoothly to afford benzyl ether 22, followed by α-bromination with NBS under solvent-free conditions. The resulting bromoketone 23 was treated with sodium azide in DMF.
to afford azide 24. A protocol was developed that enabled the azide reduction and isolation of the sensitive amino ketone 25 cleanly as the HCl salt. After several low yielding and messy Staudinger reduction reactions, the azide was cleanly hydrogenated using Pd/C poisoned with diphenylsulfide, according to the report by Sajiki.33 The reaction was performed in acidic methanol to ensure that the resulting amine would immediately be protonated to circumvent intermolecular reactions with the acetophenone. The aminoketone 25 was then coupled with N-Boc-l-phenylalanine to obtain amide 26. Heating with ammonium acetate facilitated a cyclodehydration reaction to yield the desired imidazole 27, which was globally deprotected with hydrogen and Pd/C, followed by HCl, to provide the primary amine precatalyst 28a. The N-methyl phenylalanine-derived precatalyst 29 and the proline-derived precatalyst 30 were synthesized in a similar manner (see Supplementary data for details).

Scheme 5. Imidazole–phenolate precatalysts.

2.4. Screening results

Our interest in the preparation of modified natural products inspired us to explore the catalytic direct aldol reaction, using aldehyde donors as an initial testing ground for our first generation hybrid catalysts. After an initial lack of observed reactivity with less-activated acceptors such as benzaldehyde, we elected to use the direct aldol reaction between propionaldehyde and 4-nitrobenzaldehyde as a
model reaction. Our initial screens involved the combination of each of our precatalysts with at least 13 different metal salts, many of which have some precedent for acting as oxophilic, water-tolerant Lewis acids. For productive enamine catalysis to occur, water must be generated during enamine formation, but is also required to hydrolyze the imine or iminium ion intermediates generated upon carbon–carbon bond formation. Therefore, we took no special precautions to use dry glassware or to exclude air or moisture from reactions, though a commercial source of dry THF was used in the initial reaction screen (Table 2). The detailed screening protocol is provided in the Supplementary data, but in short the precatalysts and metal salts were simply added to reaction vials prior to the addition of substrate solutions, and the reactions were stirred for 24 h prior to a reductive quench with sodium borohydride solution to generate more stable 1,3-diol products. Unless otherwise noted, all precatalysts were used as free bases or zwitterions. Yields and selectivities were determined by chiral HPLC.

Table 2. Representative screening results for direct aldol reaction of propionaldehyde and 4-nitrobenzaldehyde with acid and phenol precatalysts

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*Enantiomeric excess (ee) and yields determined by chiral HPLC with 1,2-dichlorobenzene as internal standard. Reactions were run for 24 h with 0.10 mmol nitrobenzaldehyde (0.1 M final concentration), 0.20 mmol propionaldehyde, and
10 mol % precatalyst and metal salt, unless otherwise noted. NR=no reaction (<1% yield). ND=not determined.

Results with carboxylic acid and phenol-containing precatalysts are given in Table 2. Some of our early amino acid precatalysts, such as 7 (entry 1), and 12a and 17 (not in table), proved to be quite insoluble in organic solvents, even in the presence of metal salts with added base. Therefore, we were not surprised to see a lack of reaction in such cases (e.g., entry 1). A solubility handle was added to these amino acid precatalysts by using hydroxyproline as a starting material; for example, benzyl ether 12b (Scheme 2) was synthesized and subjected to the model reaction. Moderate levels of reactivity and anti enantioselectivity were observed when combined with a number of Lewis acids (entries 3–6). The imidazole–phenol 28b, containing a primary amine as the organocatalytic moiety, gave very good syn selectivity when combined with InCl₃, but low enantioselectivity and only moderate yield (entry 9). The secondary amine analogs 29 and 30 preferably formed the anti products with improved yields and in some cases moderately good enantioselectivity (with Zn(OTf)₂, entry 12). Unfortunately there is a potential background reaction with the imidazole–phenol class of catalysts, as precatalysts such as 28b are able to catalyze somewhat the syn-selective addition of propionaldehyde to 4-nitrobenzaldehyde without the use of metal salts (entry 7). Therefore, this compound class was deprioritized for this reaction.

The most promising results were obtained with the carboxamide-containing precatalysts (Table 3). The combination of these precatalysts with lanthanide Lewis acids frequently generated catalysts with improved reactivities and stereoselectivities, such as with the use of 18a and Eu(OTf)₃ (entry 2: 61% yield, 79% anti selective, 61% ee). There were few clear-cut structure–activity relationships with these catalysts; there were examples of primary amides (e.g., 18g, entries 13–17), secondary amides, and tertiary amides (e.g., 18f, entries 11–12) that provided catalysts with good reactivities and enantioselectivities. However, we observed no thiazole-based catalysts with both good reactivity and enantioselectivity (entries 18–21). There were also not obvious electronic effects at the arene of the carboxamide, though the more electron-rich carboxamide 18e gave a superior yield to the 4-chloro-
substituted 18d with Zn(OTf)₂ (entries 7 vs 9). Of particular note was that Zn(OTf)₂ frequently generated catalysts with high anti enantioselectivities.

**Table 3.** Representative screening results for direct aldol reaction of propionaldehyde and 4-nitrobenzaldehyde with carboxamide precatalysts

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<td>49</td>
<td>28</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>31</td>
<td>20d</td>
<td>Zn(OTf)₂</td>
<td>66</td>
<td>27</td>
<td>34</td>
<td>52</td>
<td>16</td>
</tr>
<tr>
<td>32</td>
<td>20d</td>
<td>InCl₃</td>
<td>84</td>
<td>6</td>
<td>16</td>
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<td>Zn(OTf)₂</td>
<td>59</td>
<td>39</td>
<td>41</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>34</td>
<td>20e</td>
<td>InCl₃</td>
<td>82</td>
<td>12</td>
<td>18</td>
<td>5</td>
<td>31</td>
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</table>

*Enantiomeric excess (ee) and yields determined by chiral HPLC with 1,2-dichlorobenzene as internal standard. Reactions were run for 24 h with 0.10 mmol.
nitrobenzaldehyde (0.1 M final concentration), 0.20 mmol propionaldehyde, and 10 mol % precatalyst and metal salt. ND=not determined.

To differentiate the catalysts further, select examples were tested in reactions with propionaldehyde and the less activated acceptor benzaldehyde. One of the few combinations giving any observable reaction was 18c–Zn(OTf)2 (Table 7). We therefore studied this catalyst in further detail to optimize reaction conditions with the original model reaction. Results with 18c and a variety of metal salts are given in Table 4. Only trace reaction was observed with triflate salts of Mg(II), Sc(III), and Cu(II) (entries 1–3). Interestingly, only trace reaction was observed with ZnBr2 (entry 4), but moderate reactivity and good enantioselectivity was measured with Zn(OTf)2 (entry 5). Conversely, catalysis with InCl3 provided good yield, albeit with low enantioselectivities (entry 7), while In(OTf)3 gave only trace reaction (entry 8). Ga(OTf)3 was the only metal complex providing any level of syn selectivity (61%, entry 6). Lanthanide (III) triflates (entries 9–12) promoted the reaction with moderate yields and moderate to good anti enantioselectivities. Based on the promising results with the initial benzaldehyde reactions and the good anti selectivity and enantioselectivity (entry 5), we continued to study 18c–Zn(OTf)2 in further detail.

Table 4. Detailed metal salt screening with 18c

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal salt</th>
<th>% syn</th>
<th>syn ee</th>
<th>% anti</th>
<th>anti ee</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
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<td>Mg(OTf)2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>4</td>
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<tr>
<td>2</td>
<td>Sc(OTf)3</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
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<td>4</td>
<td>ZnBr2</td>
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<td>Zn(OTf)2</td>
<td>15</td>
<td>42</td>
<td>85</td>
<td>88</td>
<td>40</td>
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<td>6</td>
<td>Ga(OTf)3</td>
<td>61</td>
<td>1</td>
<td>39</td>
<td>54</td>
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<tr>
<td>7</td>
<td>InCl3</td>
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<td>18</td>
<td>55</td>
<td>21</td>
<td>78</td>
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<td>8</td>
<td>In(OTf)3</td>
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<td>ND</td>
<td>ND</td>
<td>3</td>
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<tr>
<td>9</td>
<td>Sm(OTf)3</td>
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<td>16</td>
<td>80</td>
<td>80</td>
<td>37</td>
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<td>10</td>
<td>Eu(OTf)3</td>
<td>37</td>
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<td>63</td>
<td>70</td>
<td>51</td>
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<tr>
<td>11</td>
<td>Gd(OTf)3</td>
<td>19</td>
<td>14</td>
<td>81</td>
<td>86</td>
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Table 5. Solvent screen with 18c–Zn(OTf)$_2$\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>% syn</th>
<th>syn ee</th>
<th>% anti</th>
<th>anti ee</th>
<th>% Yield</th>
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<td>1000:1 THF:H$_2$O</td>
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<td>500:1 THF:H$_2$O</td>
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<td>37</td>
<td>87</td>
<td>84</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>100:1 THF:H$_2$O</td>
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<td>9</td>
<td>55</td>
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<td>35</td>
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<tr>
<td>12</td>
<td>500:1 MeCN:H$_2$O</td>
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<td>78</td>
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<td>81</td>
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\textsuperscript{a}Enantiomeric excess (ee) and yields determined by chiral HPLC with 1,2-dichlorobenzene as internal standard. Reactions were run for 24 h with 0.10 mmol nitrobenzaldehyde (0.1 M final concentration), 0.20 mmol propionaldehyde, and 10 mol % precatalyst and metal salt, unless otherwise noted. ND=not determined.
Table 6. Control reactions for 18c–Zn(OTf)$_2$-catalyzed direct aldol reaction$^{a}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precatalyst(s) (10 mol %)</th>
<th>Metal salt (10 mol %)</th>
<th>% syn</th>
<th>% syn ee</th>
<th>% anti</th>
<th>% anti ee</th>
<th>% Yield</th>
</tr>
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<td>Zn(OTf)$_2$</td>
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<td>80</td>
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<td>6</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>NR</td>
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<td>18c–HCl</td>
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<td>Zn(OTf)$_2$</td>
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<td>74</td>
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<tr>
<td>7</td>
<td>(±)-2-Phenyl-pyrrolidine</td>
<td>Zn(OTf)$_2$</td>
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<td>39</td>
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<td>N-Acetyl-18c</td>
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<td>N-Acetyl-18c</td>
<td>Zn(OTf)$_2$</td>
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<td>86</td>
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$^{a}$Enantiomeric excess (ee) and yields determined by chiral HPLC with 1,2-dichlorobenzene as internal standard. Reactions were run for 24 h at rt with 0.20 mmol propionaldehyde (0.1 M final concentration), 0.10 mmol 4-nitrobenzaldehyde, and 10 mol % precatalyst(s) and metal salt, unless otherwise noted. ND=not determined. NR=no reaction.

Table 7. Exploration of substrate scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Donor</th>
<th>Acceptor</th>
<th>Product</th>
<th>% syn</th>
<th>% syn ee</th>
<th>% anti</th>
<th>% anti ee</th>
<th>% Yield</th>
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<td>32a</td>
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<td>80</td>
<td>76</td>
<td>54</td>
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<tr>
<td>2</td>
<td>31a</td>
<td>32b</td>
<td>33ab</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>NR</td>
</tr>
<tr>
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<td>31a</td>
<td>32c</td>
<td>33ac</td>
<td>—</td>
<td>—</td>
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<td>32a</td>
<td>33ba</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<td>NR</td>
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</table>

Tetrahedron, Vol 72, No. 27-28 (July 7, 2016); pg. 3905-3916. DOI. This article is © Elsevier and permission has been granted for this version to appear in e-Publications@Marquette. Elsevier does not grant permission for this article to be further copied/distributed or hosted elsewhere without the express permission from Elsevier.
Next, an investigation of solvent effects was carried out (Table 5). The model reaction was sluggish in benzene, but very good anti enantioselectivity (91% ee) was observed (entry 1). In prior aldol studies, we had observed improved reactivities with added water, but in this case increasing amounts of water with THF as the organic solvent did nothing to improve reaction yields or enantioselectivities (entries 4–9). In fact, sharply diminished anti enantioselectivities were observed with higher concentrations of water, potentially due to a reversible reaction. In contrast, the use of water as cosolvent with acetonitrile gave improved yields and anti enantioselectivity; we selected 9:1 MeCN:H$_2$O (entry 14) as our solvent of choice for these reactions, despite the slightly higher enantioselectivities observed with the less polar solvents.

At this stage, it was important to determine if 18c–Zn(OTf)$_2$ is actually acting as a hybrid catalyst to promote the model aldol reaction. To address this question, we carried out a series of control reactions (Table 6). A slight reaction (6% yield) was observed with only 18c (entry 2) and no reaction was observed with only Zn(OTf)$_2$ (entry 3). Little to no reaction was observed with the HCl salt of 18c, either in the absence (entry 4) or presence (entry 5) of Zn(OTf)$_2$. To explore the possibility of a dual catalyst mechanism, whereby 18c activates the donor via enamine formation for attack on the acceptor activated by a separate molecule of Zn(OTf)$_2$, we examined the use of several precatalyst analogs that lacked either the metal chelating functionality or the amine moiety capable of activating the donor. First, the use of (±)-2-phenyl-pyrrolidine catalyzed the reaction to a

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significant extent (30% yield, entry 6), indicating that simple amines can catalyze the model reaction, but this catalysis was attenuated by Zn(OTf)$_2$ (11% yield, entry 7), likely due to self-quenching. A precatalyst without an amine, N-acetyl-18c, was unable to promote the reaction with or without Zn(OTf)$_2$ (entries 8–9). The addition of (+)-2-phenyl-pyrrolidine to a mixture of N-acetyl-18c, presumably still with the ability to complex Zn(OTf)$_2$, and Zn(OTf)$_2$ (all in 10 mol %), gave results very similar to that of (+)-2-phenyl-pyrrolidine alone (entry 10), in both yield and lack of enantioselectivity. This sequence of experiments was repeated with N-methyl-18c, which could possess the ability to act as a chiral base in the reaction (e.g., for enolate formation). However, no reaction was observed with N-methyl-18c (entries 11–12), and the addition of (+)-2-phenyl-pyrrolidine to a mixture of N-methyl-18c and Zn(OTf)$_2$ again provided some reaction, though interestingly in this case some enantioselectivity was observed for formation of the syn isomer (entry 13). Clearly, the combination of 18c and Zn(OTf)$_2$ is synergistic (entry 1), in particular with the elevated yields and significant enantioselectivity observed for the model reaction. The results of Table 5 are consistent with a unimolecular hybrid catalysis mechanism, whereby the Lewis acid and Lewis base are present in the same molecule (Fig. 1). To benchmark the performance of 18c–Zn(OTf)$_2$, and to confirm our HPLC peak assignments, we compared it to l-proline, tested under the same conditions (entry 14). 18c–Zn(OTf)$_2$ performs very similarly to generate the anti product selectively with good, but not excellent, enantioselectivity (76% ee under these conditions).

To determine the potential utility of our catalyst system, alternative aldol reactions were investigated (Table 7). Unfortunately, little practical substrate scope was observed with our optimal conditions. No reaction was observed between propionaldehyde and the less activated acceptors 4-chlorobenzaldehyde (entry 2) and benzaldehyde (entry 3), even at 70 °C. The use of isobutyraldehyde (31b) as donor also failed with all substrates (entries 4–6). Pleasingly, cyclohexanone gave reactions with all 3 acceptors, albeit in low yield. Moderately good anti enantioselectivity (73% ee) was observed with 4-nitrobenzaldehyde as acceptor (entry 7).
2.5. Structural studies

In order for hybrid catalysis to be feasible, it is critical that the Lewis acid and Lewis base moieties do not poison each other. Our catalysts have been designed with this objective in mind, but structural studies could potentially confirm this. To shed light on the specific interactions between the precatalysts and Lewis acids, we have initiated NMR, MS, and X-ray studies of a variety of systems. Preliminary NMR studies of Zn(II) containing catalysts demonstrate that complexation is indeed occurring, but the highly broad signals have thus far precluded characterization of discrete complexes. Mass spectrometry with electrospray ionization of 18c mixed with Zn(OTf)₂ shows signals corresponding to two precatalyst molecules bound to zinc (see Supplementary data). Though it is possible that such 2:1 complexation observed in the mass spectrometer is not reflective of the major species present under reaction conditions, at this stage we cannot rule out the presence of higher order complexes with precatalysts such as 18c that may involve the reversible coordination of the amine nitrogen to zinc.

Thus far, we have obtained one crystal structure to indicate that our general catalyst design with a central five-membered heterocycle can facilitate the formation of metal complexes without self-quenching of the Lewis acid and Lewis base sites. A single crystal was obtained by mixing 12a and NiI₂ in 1:1 MeCN:benzene (Fig. 2). Though this catalyst gave only trace reaction in the model reaction, it does illustrate that the amine and Lewis acid moieties can be situated close together without self-quenching. Two independent octahedral complexes, each with a 2:1 precatalyst to metal ratio, were present in the unit cell. It is clear that the pyrrolidine nitrogens in this structure are uncomplexed to metals, and thus would be available for activation of a donor reactant. Efforts are ongoing to obtain crystal structures of active aldol catalysts.
3. Conclusion

21 different amino acid-derived precatalysts have been synthesized, with each example containing an amine moiety capable of organocatalysis appended to a functionalized heterocycle designed to complex a Lewis acidic metal in an appropriate orientation for carbon–carbon bond formation between ‘donor’ and ‘acceptor’ reactants. The functionalized heterocycles synthesized include examples of oxazole– and thiazole–carboxylates, imidazole–phenols, and oxazole– and thiazole–carboxamides. Many different putative hybrid catalysts were generated by mixing these catalysts with a variety of Lewis acids, and the catalysts were screened initially in the aldol reaction between propionaldehyde and 4-nitrobenzaldehyde. The carboxamide-based precatalysts gave the best combination of reactivity and enantioselectivity when used with certain metal salts, including zinc triflate and lanthanide (II) salts. The optimal catalysts were also selective for the anti stereoisomer, with enantiomeric excess of up to 91% observed. One of the optimal catalysts, 18c–Zn(OTf)₂, was studied with a series of controls to support the hypothesis that it acts as a true hybrid catalyst to promote the desired aldol reaction.
Despite these proof of concept results, our first-generation hybrid catalysts at this stage offer no obvious benefits over simpler organocatalysts for direct aldol reactions. Though the catalysts we have identified are tolerant of air and moisture and are highly robust (preliminary results show prolonged catalyst activity well beyond 24 h), the substrate scope is very limited, and they suffer the same disadvantage of organocatalysts, namely sluggish reactions and/or high catalyst loading. The relatively low catalyst activity is also consistent with some previously reported hybrid catalysts for the direct aldol reaction.24 We believe that alternative geometries for hybrid systems may lead to more reactive catalysts, and computational and synthetic efforts are underway to explore next-generation hybrid systems with well-defined ligand/metal geometries for the aldol and other carbon–carbon bond forming reactions.

4. Experimental section

4.1. General information

All reagents and solvents were purchased from commercial vendors and used as received. NMR spectra were recorded on Varian 300 MHz or 400 MHz spectrometers as indicated. Proton and carbon chemical shifts are reported in parts per million (ppm; δ) relative to tetramethylsilane, CDCl₃ solvent, or DMSO-d₆ (¹H δ 0, ¹³C δ 77.16, or ¹³C δ 39.5, respectively). NMR data are reported as follows: chemical shifts, multiplicity (obs=obscured, app=apparent, br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, comp=complex overlapping signals); coupling constant(s) in Hz; integration. Unless otherwise indicated, NMR data were collected at 25 °C. Flash chromatography was performed using Biotage SNAP cartridges filled with 40–60 μm silica gel, or C18 reverse phase columns (Biotage® SNAP Ultra C18 or Isco Redisep® Gold C18Aq) on Biotage Isolera systems, with photodiode array UV detectors. Analytical thin layer chromatography (TLC) was performed on Agela Technologies 0.25 mm glass plates with 0.25 mm silica gel. Visualization was accomplished with UV light (254 nm) and aqueous potassium permanganate (KMnO₄) stain followed by heating, unless otherwise noted. Tandem liquid chromatography/mass spectrometry (LC-MS) was performed on a Shimadzu LCMS-2020 with autosampler,
photodiode array detector, and single-quadrupole MS with ESI and APCI dual ionization, using a Peak Scientific nitrogen generator. Unless otherwise noted, a standard LC-MS method was used to analyze reactions and reaction products: Phenomenex Gemini C18 column (100×4.6 mm, 3 μm particle size, 110 Å pore size); column temperature 40 °C; 5 μL of sample in MeOH at a nominal concentration of 1 mg/mL was injected, and peaks were eluted with a gradient of 25–95% MeOH/H₂O (both with 0.1% formic acid) over 5 min, then 95% MeOH/H₂O for 2 min. Purity was measured by UV absorbance at 210 or 254 nm. High-resolution mass spectra were obtained at the University of Wisconsin–Milwaukee Mass Spectrometry Laboratory with a Shimadzu LCMS-IT-TOF with ESI and APCI ionization. Gas chromatography/mass spectrometry (GC–MS) was performed with Agilent Technologies 6850 GC with 5973 MS detector, and Agilent HP-5S or Phenomenex Zebron ZB-5MSi Guardian columns (30 m, 0.25 mm ID, 0.25 μm film thickness). IR spectra were obtained as a thin film on NaCl or KBr plates using a Thermo Scientific Nicolet iS5 spectrometer. Optical rotations were measured with a Perkin Elmer 341 polarimeter at λ=589 nm, with a 10 mL cell with 10 cm path length. Specific rotations are reported as follows: [α]D °C (c=g/100 mL, solvent).

4.2. Synthesis of precatalysts

4.2.1. tert-Butyl (S)-2-(((2S,3R)-3-hydroxy-1-methoxy-1-oxobutan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (3)

\[ \text{N-Boc-l-Proline 1a (1.02 g, 4.65 mmol), l-threonine methyl ester HCl salt 2 (0.788 g, 4.65 mmol), HOBt (0.356 g, 2.32 mmol) and DIPEA (2.83 mL, 16.3 mmol) were dissolved in DCM (40 mL) at room temperature. After all solids had gone into solution, EDC-HCl (1.07 g, 5.58 mmol) was added and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with DCM (100 mL), washed with water (50 mL), saturated NaHCO₃ (50 mL), brine (50 mL), and dried over sodium sulfate. The combined organics were concentrated and purified by flash chromatography (SiO₂, 75%–85% EtOAc/hexanes) to give the title compound as a colorless oil (887 mg, 58%). This compound has been previously reported and characterized (CAS# 80897-23-0).} \]

\[ ^1H \text{ NMR (300 MHz, DMSO-d₆)} \]
\[ \delta = 0.86 - 0.1.11 \text{ (m, 3H)}, 1.23 - 1.4.6 \text{ (m, 9H)}, 1.90 - 1.59 \text{ (m, 3H)}, \\
1.93 - 2.26 \text{ (m, 1H)}, 3.04 - 3.42 \text{ (m, 3H)}, 3.62 \text{ (t, } J = 2.1 \text{ Hz, 3 H)}, 3.80 - 4.18 \text{ (m, 1H)}, 4.19 - 4.37 \text{ (m, 2H)}, 4.82 - 5.02 \text{ (m, 1H)}, 7.80 \text{ (d, } J = 8.5 \text{ Hz, 1H)}. \\
\]

4.2.2. *Methyl (S)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-5-methylloxazol-4-carboxylate (5)*

Alcohol 3 (887 mg, 2.69 mmol) was dissolved in DCM (25 mL). Dess–Martin periodinane (1.36 g, 3.22 mmol) was added. The reaction was stirred at room temperature for 2 h, after which time the reaction was concentrated and pushed through a silica plug eluting with 7:3 EtOAc:hexanes. The eluent was concentrated to yield 1.21 g of the crude oil 4, which was carried onto the next step without further purification.

Triphenylphosphine (1.63 g, 6.20 mmol) and iodine (1.45 g, 5.71 mmol) were sealed in a flask under N\textsubscript{2} and dissolved with dry THF (25 mL), then cooled to \(-78^\circ\text{C}\). Triethylamine (1.50 mL, 5.71 mmol) was added via syringe, followed by the dropwise addition of crude 4 (1.21 g) in THF (15 mL) via syringe. After addition, the reaction was stirred at \(-78^\circ\text{C}\) for 3 h, then warmed to room temperature and diluted with water (100 mL) and extracted with DCM (2×75 mL). The combined organics were washed with water (75 mL), sodium thiosulfate solution in water (75 mL), and brine (75 mL), then dried over sodium sulfate and concentrated. The crude oil was purified by chromatography (SiO\textsubscript{2}, 12\%–100\% EtOAc/hexanes) to give the title compound as a colorless oil (590 mg, 52\%). This compound has been previously reported and characterized (CAS# 182360-15-2). \[^1\text{H} \text{NMR (400 MHz, CDCl}_3\text{)} \delta = 1.27 - 1.49 \text{ (m, 9H)}, 1.85 - 1.98 \text{ (m, 1H)}, 1.99 - 2.17 \text{ (m, 2H)}, 2.2 - 2.38 \text{ (m, 1H)}, 2.60 \text{ (s, 3H)}, 3.36 - 3.67 \text{ (m, 2H)}, 3.8 - 3.97 \text{ (m, 3H)}, 4.81 - 4.99 \text{ (m, 1H)}. \]

4.2.3. *(S)-2-(4-Carboxy-5-methylloxazol-2-yl)pyrrolidin-1-ium chloride (7)*

Oxazole 5 (593 mg, 1.90 mmol) was dissolved in THF (15 mL) and water (15 mL), followed by the addition of LiOH (80.0 mg, 1.90 mmol). The reaction was stirred at room temperature for 2 h, after which time the pH was adjusted to 2 with concentrated aqueous
HCl, and the mixture was extracted with DCM (3×50 mL). The combined organics were washed with water (50 mL) and brine (50 mL), then dried over sodium sulfate and concentrated to yield a viscous oil. The oil was dissolved in DCM (30 mL), excess 4N HCl in dioxane was added, and the reaction was stirred for 16 h, yielding a white precipitate. The precipitate was collected by filtration, washed with DCM, and dried under high vacuum to give the title compound as a white solid (379 mg, 86%). \([\alpha]_{D}^{25} -16\) (1.1, MeOH); IR (thin film): 2954, 2755, 2669, 2538, 1724, 1409, 1165, 1107, 1019, 786 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta=1.88-2.11\) (m, 2H), 2.11–2.26 (m, 1H), 2.27–2.41 (m, 1H), 2.56 (s, 3H), 3.25 (t, \(J=7.3\) Hz, 2H), 4.79 (t, \(J=7.8\) Hz, 1H), 9.67 (s, 1H), 10.62 (s, 1H); \(^13\)C NMR (75 MHz, DMSO) \(\delta=11.9, 23.4, 28.4, 45.1, 53.8, 127.8, 156.6, 156.9, 162.6\); HRMS (ESI\(^+\)) calcd for C\(_9\)H\(_{12}\)N\(_2\)O\(_3\) [M+H] 197.0921, found 197.0925.

4.2.4. tert-Butyl (2S)-2-[(3-hydroxy-1-methoxy-1-oxopropan-2-yl)carbamoyl]pyrrolidine-1-carboxylate (9a)

\(N\)-Boc-l-proline 1a (4.00 g, 18.6 mmol), l-serine methyl ester 8 (3.18 g, 20.4 mmol) and HOBt (4.27 g, 27.9 mmol) were added to a 500 mL round bottom flask with stir bar and dissolved in DCM (150 mL). DIPEA (7.95 mL, 46.5 mmol) was then added by syringe, followed by EDC-HCl (5.34 g, 27.9 mmol). The reaction was stirred at room temperature for 48 h, then the reaction was transferred to a separatory funnel and washed with water (~125 mL), 1M HCl (~125 mL), then saturated sodium bicarbonate (~125 mL). The organic portion was dried with sodium sulfate, filtered, and concentrated to a white foam. The crude compound was dissolved in DCM (~10 mL) and purified by flash chromatography (100 g SiO\(_2\) cartridge; 0–10\% MeOH/DCM gradient) to yield the title compound (5.08 g, 86\%) as a white foam. This compound has been previously reported and characterized (CAS# 955401-52-2). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta=1.45\) (s, 9 H), 1.68 (s, 1 H), 1.89 (br), 2.06 (br), 2.18 (br), 3.47 (br), 3.80 (s, 3 H), 3.89 (br), 4.03 (br), 4.18 (br), 4.62 (br m, 1 H), 7.06 (br).
4.2.5. Methyl 2-[(2S)-1-[(tert-butoxy)carbonyl]pyrrolidin-2-yl]-1,3-oxazole-4-carboxylate (10a)

Dipeptide 9a (3.42 g, 10.8 mmol) was added to a 250 mL flask with stir bar and sealed under nitrogen, then DCM (120 mL) was added, and the solution was cooled to −20 °C. Deoxo-Fluor (2.12 mL, 11.9 mmol) was added via syringe, and the reactions was stirred for 45 min at −20 °C. The reaction was then quenched with saturated aqueous sodium bicarbonate (~30 mL). The organic portion was dried with sodium sulfate, filtered, and concentrated and dried under high vacuum. The crude material was redissolved in DCM (120 mL) and cooled to 0 °C in an ice bath. Bromotrichloromethane (3.94 mL, 40.0 mmol) was added via syringe, followed by DBU (5.16 mL, 40.0 mmol), which was added dropwise over ~5 min. The reaction was removed from the ice bath and allowed to warm to room temperature while stirring overnight. Water (100 mL) was added to the solution, then the mixture was extracted with EtOAc (×3) in a separatory funnel. The combined organics were dried with sodium sulfate, filtered, and concentrated to a dark brown oil. The crude was purified by flash chromatography (100 g SiO2 cartridge; 0~100% EtOAc/hexanes gradient) to yield the title compound (2.51 g, 78%) as a white foam. This compound has been previously reported and characterized (CAS# 955401-52-2). 1H NMR (300 MHz, CDCl3) δ=1.22−1.46 (comp, 9 H), 1.86−2.01 (m, 1 H), 2.03−2.20 (comp, 2 H), 2.24−2.45 (m, 1 H), 3.44−3.68 (comp, 2 H), 3.84−3.98 (comp, 3 H), 4.89−5.07 (comp, 1 H), 8.18 (s, 1 H).

4.2.6. 2-[(2S)-1-[(tert-Butoxy)carbonyl]pyrrolidin-2-yl]-1,3-oxazole-4-carboxylic acid (11a)

Ester 10a (2.48 g, 8.37 mmol) was added to a 50 mL flask with stir bar along with THF (25 mL) and water (8 mL). LiOH (261 mg, 17.6 mmol) was added and the flask was stirred for 24 h, after which time TLC analysis (10% MeOH/DCM) indicated that the reaction was complete. The reaction was diluted with DCM (~75 mL) and water (~75 mL), then the pH was adjusted to 4 with 2 M aq HCl. The layers were separated and the aqueous phase was re-extracted with DCM (2×50 mL). The combined organics were then dried with sodium sulfate, filtered, and concentrated to yield the title compound (1.23 g,
94%) as an off-white foam. This compound has been previously reported and characterized (CAS# 1511857-57-0). \( ^1H \) NMR (300 MHz, CD\(_3\)OD) \( \delta = 1.27 \) (rotamer 1); 1.44 (rotamer 2) (9 H), 1.90–2.16 (comp, 3 H), 2.37 (m, 1 H), 3.49 (m, 1 H), 3.59 (m, 1 H), 4.94 (m, 2H), 8.47 (s, 1 H). IR (thin film) 3435, 2978, 2537, 1685, 1585, 1406, 1250, 1611, 1113, 982 cm\(^{-1}\).

4.2.7. tert-Butyl (2S,4R)-4-(benzyloxy)-2-[(3-hydroxy-1-methoxy-1-oxopropan-2-yl)carbamoyl] pyrrolidine-1-carboxylate (9b)

Benzylloxyproline 1b (5.20 g, 16.2 mmol), l-serine methyl ester 8 (2.77 g, 17.8 mmol) and HOBt (3.72 g, 24.3 mmol) were added to flask with stir bar and dissolved in DCM (150 mL). DIPEA (6.93 mL, 40.5 mmol) was then added by syringe, followed by EDC-HCl (4.65 g, 24.3 mmol). The reaction was stirred at room temperature for 48 h, then the reaction was washed with water (~125 mL), 1M HCl (~125 mL), then saturated sodium bicarbonate (~125 mL). The organic portion was dried with sodium sulfate, filtered, and concentrated to a white foam. The crude compound was dissolved in DCM (~10 mL) and purified by flash chromatography (100 g SiO\(_2\) cartridge; 0–10% MeOH/DCM gradient) to yield the title compound (6.45 g, 94%) as a white foam. \([\alpha]_D^{20} +75\) (0.010, DCM); IR (thin film): 3421.0, 2976.9, 1746.3, 1668.8, 1525.8, 1392.9, 1206.3, 1160.6, 1068.7, 909.5 cm\(^{-1}\); \(^1H\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) ppm 1.47 (s, 9 H) 2.25 (s, 1 H) 2.29 (d, \( J = 5.9 \) Hz, 1 H) 3.24–3.49 (m, 1 H) 3.57 (br, 1 H) 3.67 (br, 1 H) 3.78 (s, 2 H) 3.85 (br, 2 H) 4.12 (br, 2 H) 4.18–4.28 (m, 1 H) 4.32 (t, \( J = 7.4 \) Hz, 1 H) 4.45–4.57 (m, 2 H) 4.62 (br, 1 H) 6.95–7.11 (m, 1 H) 7.21–7.40 (m, 5 H); \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \( \delta = 21.3, 28.53, 35.1, 52.9, 55.6, 59.6, 62.3, 70.6, 71.3, 81.16, 127.83, 127.92, 128.1, 128.6, 128.7, 137.8, 155.4, 171.0, 171.4, 172.1; HRMS (ESI\(^+\)) calcd for C\(_{21}\)H\(_{30}\)N\(_2\)O\(_7\) [M+H] 423.2125, found 423.2120.
4.2.8. Methyl 2-[(2S,4R)-4-(benzyloxy)-1-[(tert-butoxy)carbonyl]pyrrolidin-2-yl]-1,3-oxazole-4-carboxylate (10b)

Dipeptide 9b (3.13 g, 7.41 mmol) was added to a 250 mL flask with stir bar and sealed under nitrogen, then DCM (120 mL) was added, and the solution was cooled to −20 °C. Deoxo-Fluor (1.50 mL, 8.18 mmol) was added via syringe, and the reaction was stirred for 45 min at −20 °C. The reaction was then quenched with saturated aqueous sodium bicarbonate (~30 mL). The organic portion was dried with sodium sulfate, filtered, and concentrated and dried under high vacuum. The crude material was dissolved in DCM (120 mL) and cooled to 0 °C in an ice bath. Bromotrichloromethane (3.94 mL, 40.0 mmol) was added via syringe, followed by DBU (5.16 mL, 40.0 mmol), which was added dropwise over ~5 min. The reaction was removed from the ice bath and allowed to warm to room temperature while stirring overnight. Water (100 mL) was added to the solution, then the mixture was extracted with EtOAc (×3). The combined organics were dried with sodium sulfate, filtered, and concentrated to a dark brown oil. The crude was purified by flash chromatography (100 g SiO2 cartridge; 0–100% EtOAc/hexanes gradient) to yield the title compound (1.37 g, 46%) as a colorless oil. [α]D25 −81 (0.029, DCM); IR (thin film): 2976.5, 1744.3, 1697.7, 1583.7, 1393.2, 1366.4, 1160.8, 1109.9, 1001.9 cm−1; 1H NMR (400 MHz, CDCl3) δ=1.21−1.35 (m, 6 H), 1.40−1.48 (m, 4 H), 2.22−2.39 (m, 1 H), 2.50 (br, 1 H), 3.69 (dd, J=11.5, 4.5 Hz, 1 H), 3.88−3.95 (m, 3 H), 4.20−4.32 (m, 1 H), 4.47−4.61 (m, 2 H), 5.03−5.17 (m, 1 H), 7.28−7.41 (m, 3 H), 8.07−8.20 (m, 1 H); 13C NMR (75 MHz, CDCl3) δ=28.4, 28.6, 38.8, 53.9, 71.3, 76.0, 80.6, 127.9, 128.1, 128.8, 143.6; HRMS (ESI+) calcd for C21H26N2O6 [M+H] 403.1860, found 423.1864.

4.2.9. 2-[(2S,4R)-4-(Benzyloxy)-1-[(tert-butoxy)carbonyl]pyrrolidin-2-yl]-1,3-oxazole-4-carboxylic acid (11b)

Ester 10b (1.68 g, 4.18 mmol) was added to a 50 mL flask with stir bar along with THF (25 mL) and water (8 mL). LiOH (210 mg, 8.77 mmol) was added and the flask was stirred for 24 h, after which
time TLC analysis (10% MeOH/DCM) indicated that the reaction was complete. The reaction was diluted with DCM (~75 mL) and water (~75 mL), then the pH was adjusted to 4 with 2 M aq HCl. The layers were separated and the aqueous phase was re-extracted with DCM (2×50 mL). The combined organics were then dried with sodium sulfate, filtered, and concentrated to yield the title compound (1.61 g, 90%) as an off-white foam. This compound was moved forward without further characterization.

4.2.10. 2-[(2S,4R)-4-(Benzyloxy)pyrrolidin-2-yl]-1,3-oxazole-4-carboxylic acid (12b)

Carboxylic acid 11b (0.723 g, 1.85 mmol) was added to a 50 mL flask with stir bar and dissolved in DCM (~5 mL). 4M HCl in dioxane (4.62 mL, 18.5 mmol) was added and the flask was stirred for 24 h. The resulting slurry was filtered through paper and rinsed with hexanes. The white solid was moved to a 25 mL flask, dissolved in water (~5 mL), and 30% aqueous ammonium hydroxide (1 mL) was added and stirred for 5 min 2M HCl was then added until the pH was neutral. The solution was then extracted with DCM (3×10 mL), and the combined organics were concentrated to yield the title compound (0.41 g, 76%) as a colorless oil. [a]D25 +77 (0.023, DCM); IR (thin film): 2931.1, 1583.0, 1495.6, 1453.9, 1384.9, 1249.3, 1215.4, 1093.7, 1027.4, 907.9 cm−1; 1H NMR (300 MHz, CD3OD) δ=2.56 (ddd, J=14.2, 10.4, 4.4 Hz, 1H), 2.81 (dd, J=14.1, 6.7 Hz, 1H), 3.55–3.69 (m, 2H), 4.52–4.57 (m, 1H), 4.57–4.69 (m, 2H), 5.15 (dd, J=10.9, 7.0 Hz, 1H) 7.21–7.49 (m, 5H), 8.64 (s, 1H); 13C NMR (75 MHz, CD3OD) δ=35.2, 51.3, 54.0, 71.0 76.8, 127.8, 127.9, 128.4, 134.16, 137.6, 159.4, 162.3; HRMS (ESI+) calcd for C15H16N2O4 [M+H] 289.1183, found 289.1186.

4.2.11. Methyl 2-[(1S)-1-[(tert-butoxy)carbonyl]amino]-2-methylpropyl]-1,3-oxazole-4-carboxylate (13)

Dipeptide 12c (6.50 g, 20.5 mmol) was added to a 500 mL flask with stir bar and sealed under nitrogen, then DCM (200 mL) was added, and the solution was cooled to −20 °C. Deoxo-Fluor (4.14 mL, 22.5 mmol) was added via syringe, and the reactions was stirred for 45 min at −20 °C. The reaction was then quenched with saturated
aqueous sodium bicarbonate (∼70 mL). The organic portion was dried with sodium sulfate, filtered, concentrated, and dried under high vacuum. The crude material was redissolved in DCM (200 mL) and cooled to 0 °C in an ice bath. Bromotrichloromethane (7.44 mL, 75.5 mmol) was added via syringe, followed by DBU (9.75 mL, 75.5 mmol), which was added dropwise over ∼5 min. The reaction was removed from the ice bath and allowed to warm to room temperature while stirring overnight. Water (200 mL) was added to the solution, then the mixture was extracted with EtOAc (×3). The combined organics were dried with sodium sulfate, filtered, and concentrated to a dark brown oil. The crude was purified by flash chromatography (100 g SiO$_2$ cartridge; 0–100% EtOAc/hexanes gradient) to yield the title compound (6.09 g, 79%) as a white solid. This compound has been previously reported and characterized (CAS# 158068-97-4). $^1$H NMR (300 MHz, CDCl$_3$) δ=0.87−0.98 (m, 6 H), 1.44 (s, 9 H), 2.10−2.29 (m, 1 H), 3.92 (s, 3 H), 4.74−4.88 (m, 1 H), 5.28 (d, J=7.2 Hz, 1 H), 8.19 (s, 1 H).

4.2.12. 2-[(1S)-1-{{[(tert-Butoxy)carbonyl](methyl)amino}-2-methylpropyl]-1,3-oxazole-4-carboxylic acid (14)

Ester 13 (1.90 g, 6.13 mmol) was added to a 250 mL flask with stir bar along with THF (60 mL) and water (5.6 mL). LiOH (306 mg, 12.3 mmol) was added and the flask was stirred for 24 h, after which time TLC analysis (10% MeOH/DCM) indicated that the reaction was complete. The reaction was diluted with DCM (∼75 mL) and water (∼50 mL), then the pH was adjusted to 4 with 2 M aq HCl. The layers were separated and the aqueous phase was re-extracted with DCM (2×50 mL). The combined organics were then dried with sodium sulfate, filtered, and concentrated to yield the title compound (1.76 g, 97%) as a pale yellow solid. The compound was advanced without further purification. This compound has been previously reported and characterized (CAS# 220717-54-4). $^1$H NMR (300 MHz, CDCl$_3$) δ=0.94 (s, 6 H), 1.42 (s, 9 H), 1.86 (s, 1 H), 2.21 (s, 1 H), 3.76 (s, 1 H), 4.82 (br, 1 H), 5.92 (br, 1 H), 8.29 (s, 1 H).
4.3. Representative procedure A (for valine-based secondary and tertiary amides) (Scheme 6)

4.3.1. tert-Butyl N-[(1S)-2-methyl-1-{4-[(4-methylphenyl)carbamoyl]-1,3-oxazol-2yl}propyl] carbamate (14a)

Carboxylic acid 14 (0.505 g, 1.76 mmol) was dissolved in DCE (8 mL), and 4-methylaniline (0.191 g, 1.76 mmol) and PyBOP (1.10 g, 2.11 mmol) were added to the solution. DIPEA (0.763 mL, 4.40 mmol) was added and the reaction was stirred for 3 h. The solution was diluted with DCM (~20 mL). The reaction solution was washed with 2M HCl (25 mL), then half-saturated aqueous sodium bicarbonate (25 mL). The organic layer was then dried with sodium sulfate and concentrated. The crude was purified by flash chromatography (50 g SiO2 cartridge; 0–100% EtOAc/hexanes gradient) to yield the title compound as a colorless oil (0.510 g, 78%). [
\[a\]D25 +77 (0.094, DCM); IR (thin film): 3322.9, 2969.9, 1676.5, 1600.8, 1520.6, 1456.3, 1391.8, 1239.9, 1163.1, 1099.5 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3)
\(\delta = 0.97 (d, J=8.5 \text{ Hz}, 3 \text{ H}), 0.95 (d, J=8.2 \text{ Hz}, 3 \text{ H}), 1.47 (s, 9 \text{ H}), 2.11–2.28 (m, 1 \text{ H}), 2.34 (s, 3 \text{ H}), 3.82–3.89 (m, 1 \text{ H}), 4.75–4.86 (m, 2 \text{ H}), 5.16, (d, J=8.8 \text{ Hz}, 1 \text{ H}), 7.17 (d, J=8.2 \text{ Hz}, 2 \text{ H}), 7.42 (ddd, J=8.4, 7.1, 1.1 \text{ Hz}, 1 \text{ H}), 7.54–7.60 (m, 2 \text{ H}), 7.66–7.74 (rotamer 1, dt J=8.4, 1.1 \text{ Hz}, 0.5 \text{ H}), 8.03 (rotamer 2, dt, J=8.4, 1.1 Hz, 0.5 \text{ H}), 8.22 (s, 1 \text{ H}), 8.61 (s, 1 \text{ H}); \(^{13}\)C NMR (75 MHz, CDCl3) \(\delta = 18.3, 18.9, 21.2, 28.6, 32.9, 40.4, 54.6, 79.8, 108.9, 120.1, 120.5, 125.1, 128.6, 129.8, 134.4, 135.0, 136.5, 141.6, 158.3; HRMS (ESI\(^+\)) calcd for C\(_{20}\)H\(_{27}\)N\(_3\)O\(_4\) [M+H] 374.2074, found 374.2074.

4.3.2. 2-[[1(S)-1-Amino-2-methylpropyl]-N-(4-methylphenyl)-1,3-oxazole-4-carboxamide (20a)

Carbamate 14a (0.72 g, 1.85 mmol) was added to a 50 mL flask with stir bar and dissolved in DCM (5 mL). 4M HCl in dioxane (4.62 mL, 18.5 mmol) was added and the flask was stirred for 24 h. The resulting slurry was filtered through paper and rinsed with hexanes. The white solid was moved to a 25 mL flask, dissolved in water (∼5 mL), and 30% aqueous ammonium hydroxide (1 mL) was added and stirred for 5 min 2M HCl was then added until the pH was neutral. The solution was then extracted with DCM (3×10 mL). The combined organics were concentrated to yield the title compound as an off-white solid (0.41 g, 76%). mp 140–144 °C. [a] D25 +134 (0.013, DCM); IR (thin film): 2958.9, 1657.9, 1598.4, 1520.4, 1466.1, 1318.2, 1090.1, 914.6, 815.5 cm−1; 1H NMR (300 MHz, CDCl3) δ=0.97 (dd, J=6.7, 4.10 Hz, 6 H), 1.72 (s, 2 H), 2.06–2.23 (m, 1 H), 2.33 (s, 3 H), 3.59–3.80 (m, 1 H), 7.17 (d, J=5.9 Hz, 1 H), 7.17 (d, J=7.9 Hz, 2 H), 7.54–7.61 (m, 2 H), 8.22 (s, 1 H), 8.66 (br, 1 H); 13C NMR (75 MHz, CDCl3) δ=18.0, 19.2, 21.1, 33.8, 56.1, 120.0, 129.8, 134.4, 135.1, 136.4, 141.5, 158.6, 167.2; HRMS (ESI+) calcd for C15H19N3O2 [M+H] 274.1550, found 274.1546.

4.4. Representative procedure B (for primary amides) (Scheme 7)

4.4.1. Methyl 2-[(1S)-1-[[[(tert-butoxy)carbonyl]amino]-2-methylpropyl]-1,3-oxazole-4-carboxylate (14b)

7N Ammonia in methanol (6.0 mL, 42.2 mmol) was added to DCM (60 mL). Ester 14 (0.40 g, 1.40 mmol) was added to the ammonia solution and stirred for 16 h, after which time LC-MS analysis indicated that the reaction was complete. The reaction solution was then washed with water (3×25 mL), dried with sodium sulfate, and concentrated. The crude oil was purified by flash chromatography (50 g SiO2 cartridge; 0–10% MeOH/DCM gradient) to yield the title compound (0.48 g, 86%) as a colorless oil. This compound was moved forward without further characterization.
Scheme 7. Synthesis of carboxamide precatalyst 20e.

4.4.2. 2-[(1S)-1-Amino-2-methylpropyl]-1,3-oxazole-4-carboxamide (20e)

Carbamate 14b (0.33 g, 1.15 mmol) was added to a 25 mL flask with stir bar and dissolved in DCM (5 mL). 4M HCl in dioxane (1.44 mL, 5.77 mmol) was added and the reaction was stirred for 24 h. The solvent was evaporated by blowing nitrogen gas through the flask, then the crude solid was dissolved in water (~5 mL), and 30% aqueous ammonium hydroxide (0.20 mL) was added and stirred for 5 min 2M HCl was then added until the pH was neutral. The mixture was then extracted with DCM (3×10 mL). The combined organics were concentrated to yield the title compound as an off-white solid (0.21 g, 97%). mp 240–245 °C; [a]$_D^{25}$ −18 (0.012, DCM); IR (thin film): 3101.5, 2959.6, 1654.4, 1616.1, 1411.5, 1317.1, 1109.2, 987.9, 921.5, 864.9 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ=0.95 (dd, $J$=6.9, 4.25 Hz, 6 H), 1.63 (s, 3 H), 2.04–2.21 (m, 1 H), 3.87 (d, $J$=5.9 Hz, 1 H), 5.62 (br, 1 H), 6.82 (br, 1 H), 8.17 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ=18.0, 19.2, 33.7, 56.0, 135.6, 141.6, 162.8, 167.3; HRMS (ESI$^+$) calcd for C$_8$H$_{13}$N$_3$O$_2$ [M+H] 184.1081, found 184.1086.

4.5. Representative procedure C (for proline-based secondary and tertiary amides) (Scheme 8)

4.5.1. tert-Butyl (S)-2-(4-[(p-tolylcarbamoyl)oxazol-2-yl]pyrrolidine-1-carboxylate (11c)

Acid 11a (600 mg, 2.13 mmol) was added to a 20 mL reaction vial, followed by HOBt (586 mg, 3.83 mmol) 4-methylaniline (273 mg, 2.55 mmol), DCM (15 mL), and DIEA (1.09 mL, 6.37 mmol). EDC-HCl (733.4 mg, 3.83 mmol) was then added to the vial and the mixture was stirred at room temperature for 16 h. The reaction was diluted with DCM (30 mL) and washed with 0.1 N HCl (50 mL), saturated sodium bicarbonate (50 mL), and brine (30 mL). The organic layer was
then dried over sodium sulfate and concentrated, and the crude material was purified by chromatography (SiO$_2$, 0–60% EtOAc/hexanes) to give the title compound as a white solid (789 mg, 83%). mp=125–130 °C; R$_f$ (50% EtOAc/hexanes) 0.60; [a]$_0^{25}$ –62 (1.0, DCM); IR (thin film): 3360, 2975, 1686, 1599, 1512, 1364, 1101, 876, 666 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$=1.30 (s, 6H), 1.46 (s, 3H), 1.88–2.02 (m, 1H), 2.04–2.18 (m, 2H), 2.34 (s, 4H), 3.22–3.8 (m, 2H), 4.85–5.07 (m, 1H), 7.18 (d, $J$=7.8 Hz, 2H), 7.57 (d, $J$=8.2 Hz, 2H), 8.19 (s, 1H),8.62 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$=20.9, 23.6, 28.2, 28.4, 32.4, 46.4, 54.7, 80.1, 119.8, 129.5, 134.2, 134.8, 136.4, 140.9, 141.3, 158.2, 165.4; HRMS (ESI$^+$) calcd for C$_{20}$H$_{25}$N$_3$O$_4$ [M+Na] 394.1737, found 394.1732.

**Scheme 8.** Synthesis of carboxamide precatalyst 18c.

4.5.2. **(S)-2-(Pyrrolidin-2-yl)-N-(p-tolyl)oxazole-4-carboxamide (18c)**

Carbamate 11c (555 mg, 1.50 mmol) was added to a 50 mL round bottom flask, followed by DCM (20 mL). 4 M HCl in dioxane (9.30 mL) was added, and the reaction was stirred for 3 h. The reaction was diluted with DCM (50 mL) and washed with satd aq NaHCO$_3$ (300 mL). The phases were separated, and the aqueous phase was extracted with DCM (3×50 mL). The combined organics were dried over Na$_2$SO$_4$, concentrated to a crude oil, and purified by flash chromatography (SiO$_2$, 0–20% MeOH/DCM) to give the deprotected amine as a yellow solid (260 mg, 64%). mp=65–70 °C; R$_f$ (10% MeOH/DCM) 0.29; [a]$_0^{20}$ –15 (1.0, MeOH); IR (thin film): 3360, 2974, 1686, 1662, 1512, 1101, 816 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$=1.83–2.01 (m, 2H), 2.09 (ddt, $J$=12.3, 7.7, 6.2 Hz, 1H), 2.19–2.32 (m, 2H), 2.34 (s, 3H), 3.07 (ddd, $J$=10.2, 7.5, 6.2 Hz, 1H), 3.19 (ddd, $J$=10.0, 7.2, 6.0 Hz, 1H), 4.40 (dd, $J$=8.0, 5.9 Hz, 1H), 7.17 (d, $J$=8.3 Hz, 2H), 7.57 (d, $J$=8.4 Hz, 2H), 8.21 (s, 1H), 8.64 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$=21.2, 25.6, 31.2, 47.2, 55.6, 120.1, 129.8,
4.6. Representative procedure D (synthesis of imidazole–phenols from azido-ketone 24)

4.6.1. 1-(2-(Benzyloxy)phenyl)-2-bromoethan-1-one (22)

O-hydroxyacetophenone (5.00 g, 36.7 mmol) 21 was added to an oven-dried flask with a magnetic stir bar and sealed under nitrogen. Anhydrous DMF (15 mL) was added via syringe followed by sodium hydride (60% dispersion in paraffin oil, 1.62 g, 40.4 mmol). The mixture was stirred at room temperature under nitrogen for 15 min before benzyl bromide (5.05 mL, 40.4 mmol) was added dropwise via syringe. The reaction was left to stir under nitrogen for 16 h. The reaction mixture was added to TBME (300 mL) and washed with saturated ammonium chloride (2×75 mL), followed by water (150 mL) and brine (150 mL). The organic layer was then dried over sodium sulfate and concentrated to yield a pale yellow oil. The oil was purified by flash chromatography (SiO₂, 5% TBME in hexanes) to afford the title compound as a colorless oil (7.41 g, 89%). This compound has been previously reported and characterized (CAS# 31165-67-0). ¹H NMR (300 MHz, CDCl₃) δ=2.62 (s, 3H), 5.17 (s, 2H), 6.91–7.84 (m, 9H).

4.6.2. 1-[2-(Benzyloxy)phenyl]-2-bromoethan-1-one (23)

Ketone 22 (7.40 g, 32.7 mmol) was placed in a 25 mL flask followed by PTSA (622 mg, 3.27 mmol) and NBS (6.40 g, 35.9 mmol) and the resulting slurry was stirred at room temperature for 16 h. The reaction mixture was diluted with MTBE (500 mL) and washed with water (2×400 mL) and brine (400 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated to yield a yellow oil. The oil was purified by flash chromatography (SiO₂, 5% EtOAc in hexanes), and the resulting yellow oil was recrystallized from hot ethanol to afford the title compound as an off-white solid (8.18 g, 82%). This compound has been previously reported and characterized (CAS# 56443-24-4). ¹H NMR (300 MHz, CDCl₃) δ 4.54 (s, 2H), 5.19 (s, 2H), 6.93–7.14 (m, 2H), 7.31–7.57 (m, 6H), 7.75–7.9 (m, 1H).
4.6.3. 2-(2-(Benzyloxy)phenyl)-2-oxoethan-1-aminium chloride (24)

Bromoketone 23 (7.40 g, 24.25 mmol) was added to a 100 mL round bottom flask with a magnetic stir bar. Anhydrous DMF (40 mL) was added via syringe followed by sodium azide (3.15 g, 48.5 mmol). The flask was fitted with a septum and flushed with nitrogen. The reaction was stirred at room temperature for 5 h, after which time the mixture was diluted with EtOAc (350 mL) and washed with water (3×150 mL) and brine (150 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated to afford an orange oil. The orange oil was dissolved with a 50:50 mixture of DCM and hexanes and purified by flash chromatography (SiO$_2$, 5–25% EtOAc in hexanes) to give title compound as a pale yellow oil (3.93 g, 60%). $R_f$ (10% EtOAc in hexanes) 0.20; IR (thin film): 2101, 1678, 1596, 1483, 1449, 1290, 1234, 1197, 1163, 1007, 911, 757 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ=4.44 (s, 2H), 5.16 (s, 2H), 7–7.15 (m, 2H), 7.3–7.46 (m, 4H), 7.46–7.58 (m, 1H), 7.93 (dd, $J$=8.0, 1.9 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ=59.7, 71.2, 113.0, 121.6, 125.1, 128.0, 128.9, 129.1, 131.4, 135.2, 135.7, 158.7, 194.6; HRMS (ESI$^+$) calcd for C$_{15}$H$_{13}$N$_3$O$_2$ [M+H] 290.0900, found 290.0905.

4.6.4. (S)-2-(2-(1-Amino-2-phenylethyl)-1H-imidazol-4-yl)phenol (28b)

Azide 24 (62.3 mg, 0.233 mmol) was dissolved in MeOH (5 mL) in a 20 mL vial. Concentrated aqueous HCl (37%–12N) (39 μL, 0.47 mmol) was then added, followed by diphenyl sulfide (0.39 μL, 0.0019 mmol). The flask was flushed with nitrogen, then 10% Pd/C (12.5 mg) was added. The flask was sealed with a septum and a balloon of hydrogen was placed on the flask. 1 balloon was allowed to bubble through the solution to displace the nitrogen, then the balloon was refilled and the reaction was stirred under hydrogen for 3 h. The mixture was passed through a cake of Celite to remove the Pd/C catalyst and concentrated to afford an off-white solid. This crude product was used directly in the next step without further purification.

The crude aminoketone 25 was dissolved in DCM (5 mL) in a 20 mL vial, of Boc-protected amino acid (0.233 mmol), and HOBT
(53.5 mg, 0.350 mmol) were added. DIEA (79 μL, 0.466 mmol) was added via syringe. EDC-HCl (67.0 mg, 0.350 mmol) was then added and the flask was stirred at room temperature overnight. The reaction with DCM (10 mL) and washed with 0.25 N HCl (25 mL), saturated sodium bicarbonate (10 mL), and brine (10 mL). The organic layer was then dried over sodium sulfate and concentrated to yield a yellow oil. The crude oil was dissolved in DCM and passed through a 5” Pasteur pipet packed with silica gel, then eluted with EtOAc. The organic phase was then concentrated to give the crude amide 26 as a colorless oil, which was used directly in the next step.

The crude amide 26 was dissolved in xylenes (5 mL) in a 20 mL vial. Ammonium acetate (449 mg, 5.83 mmol) was added and the vial was fitted with a drying tube. The reaction was heated at 135 °C for 16 h, after which time TLC showed complete consumption of the starting material. The reaction was concentrated, taken up in EtOAc, and passed through a 5” Pasteur pipet packed with silica gel, eluting with EtOAc. The resulting solution was concentrated to give the crude imidazole 27 as a brown oil, which was used directly in the next step.

The crude oil 27 (2.00 g) was dissolved in MeOH (20 mL) in a 50 mL round bottom Schlenk flask. The flask was purged with N2×3, then 10% Pd/C (24.8 mg) was added. The flask was then fitted with a hydrogen balloon via a 3 way valve and it was evacuated and purged with hydrogen ×5. The reaction was stirred under hydrogen for 16 h, then the mixture was passed through a pad of Celite and concentrated to afford a yellow oil. The crude oil was is dissolved in DCM (20 mL) and transferred to a 20 mL vial, and 4M HCl in dioxane (291 μL, 1.16 mmol) was added and the reaction was stirred for 16 h. The reaction was quenched by adding saturated NaHCO3 solution (10 mL), then the phases were separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organics were dried over Na2SO4 and concentrated to give a brown oil, which was purified by flash chromatography (SiO2, 10–20% MeOH/DCM) to give the title compound 28b (65 mg, 48%) over 4 steps. Rf (10% MeOH in DCM) 0.29; [α]D20 −52 (1.0, CH2Cl2); IR (thin film): 3407, 1641, 1251, 1113, 751 cm−1; 1H NMR (300 MHz, CDCl3) δ=1.70 (s, 2H), 2.91 (dd, J=13.7, 8.7 Hz, 1H), 3.38 (dd, J=13.7, 4.5 Hz, 1H), 4.37 (dd, J=8.6, 4.5 Hz, 1H), 6.84 (td, J=7.5, 1.3 Hz, 1H), 6.99 (dd, J=8.2, 1.3 Hz, 1H), 7.09–7.37 (m, 7H), 7.46 (dd, J=7.7, 1.7 Hz, 1H), 9.68 (s, 1H);
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta=$43.8, 51.3, 109.9, 117.4, 117.4, 119.3, 124.8, 127.1, 128.4, 128.9, 129.6, 137.5, 140.7, 149.2, 156.0; HRMS (ESI$^+$) calcd for C$_{17}$H$_{17}$N$_3$O [M+H] 280.1444, found 280.1440.

4.7. Crystallographic data

CCDC 1463770 contains the supplementary crystallographic data for Fig. 2 in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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References and notes


Supplementary data

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Supplementary Material

Multifunctional heterocyclic scaffolds for hybrid Lewis acid/Lewis base catalysis of carbon–carbon bond formation

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1. Author contributions

Dennis Wiedenhoeft: Assisted with catalyst design; designed experiments; designed, investigated, and optimized precatalyst synthetic routes; synthesized and characterized precatalysts and aldol products; developed HPLC methods; screened reactions; analyzed data; wrote supporting information; supervised research; grew single crystals for x-ray analysis.

Adam Benoit: Assisted with catalyst design; designed, investigated, and optimized precatalyst syntheses; characterized products; developed HPLC methods; screened reactions; analyzed data; designed experiments; wrote supporting information; edited the manuscript; supervised research.

Yibiao Wu: Synthesized and characterized precatalysts and aldol products; screened reactions.

Jacob Porter: Synthesized and characterized precatalysts; performed NMR and MS studies.

Elisia Meyle: Synthesized and characterized precatalysts.

Teresa Yeung: Synthesized precatalyst intermediates.

Raechel Huff: Synthesized precatalyst intermediates.
Sergey Lindeman: Determined x-ray structure.

Chris Dockendorff: Designed catalysts; designed synthetic routes; analyzed data; designed experiments; wrote and edited the manuscript and supporting information; supervised research.

2. General reaction screening protocol

Stock solutions of **precatalyst** (0.02 M), **benzaldehyde acceptor** (0.40 M), and **aldehyde or ketone donor** (0.80 M) were prepared. All precatalysts were used as free bases (or zwitterions) by neutralizing HCl salts with aqueous ammonium hydroxide and extracting with DCM prior to use.

1) **Metal salts** (0.01 mmol) were weighed into separate 1.5 mL HPLC vials.

2) If solid additives were included, they were added to the vials at this time.

3) **Precatalyst** solutions (500 µL of 0.02 M stock solution, 0.01 mmol) were added to each vial.

4) If additive solutions were included, they were added to the vials next.

5) **Aldehyde acceptor** solution (250 µL of 0.40 M solution, 0.1 mmol), was added to each vial.

6) **Aldehyde or ketone donor** (250 µL of 0.80 M solution, 0.2 mmol) was added to each vial.

After addition of all reagents, the vials were capped (PTFE septa) and placed in a cardboard vial box attached to a vortex shaker. Vials were shaken for 24 hours on the lowest speed to avoid leakage from the vials. 9 mL glass test tubes were labeled to correspond to each of the reaction vials and sodium borohydride (~75 mg, 2 mmol, 20 eq.) was added to each tube and cooled on ice. 4:1 DCM:MeOH (1 mL) was added, then the reaction solutions were pipetted dropwise (over ~30 s) to the test tubes. The tubes were removed the ice bath and warmed to room temperature over thirty minutes, with periodic mixing. Saturated aqueous ammonium chloride solution (1 mL) was then added via pipet dropwise (~ 1 min.) to each tube to quench the reduction reaction, followed by 1 M aqueous HCl (1 mL) added via pipet dropwise (~1 min.) to further neutralize the solutions and to help dissolve solid precipitates. DCM (~1 mL) was added to each tube to resolve the phases. The organic phases were separated to fresh 9 mL tubes, then the remaining solutions were extracted with additional DCM (2 x 2 mL). The combined organic solutions were concentrated via Speedvac (initially at 400 torr with low heating, then 25 torr). A stock solution
of LC-MS grade isopropanol with 5 mg/mL of o-dichlorobenzene as an internal standard was made. Each crude sample was dissolved in 1 mL of this stock solution and filtered through a 0.22 micron nylon syringe filter into a 1.5 mL HPLC vial. The samples were analyzed by HPLC using 5 uL injections and 13:87 IPA:hexane isocratic method (1 mL/min.) for 20 min., with a Phenomenex Lux 5 µm Cellulose-2 column (250 x 4.6 mm) and UV detection at λ = 254 nm. Representative retention times: 3.3 min: o-dichlorobenzene; 9.3 min: benzyl alcohol; 10.7 min., syn enantiomer 1; 12.0 min., syn enantiomer 2; 14.5 min., anti enantiomer 1; 15.6 min., anti enantiomer 2.

3. Synthetic protocols for the preparation of precatalysts 29 and 30

(S)-2-(2-(pyrrolidin-2-yl)-1H-imidazol-4-yl)phenol (29b)

The compound was made following Representative Procedure D (see main manuscript) using N-Boc-L-proline as starting material: beige solid, Rf (10% MeOH in DCM) 0.21; [a]D^20 -123 (1.0, CH2Cl2); IR (thin film): 2870, 1578, 1476, 1398, 1252, 756 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ = 1.7–1.9 (m, 2H), 1.98–2.32 (m, 2H), 2.83–3.15 (m, 2H), 4.41 (dd, J = 8.0, 5.5 Hz, 1H), 6.73–6.87 (m, 1H), 6.88–7.01 (m, 1H), 7.06–7.17 (m, 1H), 7.19 (d, J = 0.5 Hz, 1H), 7.35–7.5 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ = 25.9, 28.7, 32.1, 47.0, 55.8, 109.8, 117.4, 119.2, 124.7, 124.7, 128.3, 141.0, 149.3, 156.0; HRMS (ESI⁺) calculated for C₁₃H₁₅N₃O [M+H] 230.1288, found 230.1281.

(S)-2-(2-(1-(methylamino)-2-phenylethyl)-1H-imidazol-4-yl)phenol (30)

The compound was made following Representative Procedure D (see main manuscript) using N-methyl-N-Boc-L-phenylalanine as starting material: yellow solid, Rf (10% MeOH in DCM) 0.42; [a]D^20 -7 (1.0, CH₂Cl₂); IR (thin film): 3118, 1585, 1479, 1412, 1244, 1126, 735 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 2.33 (t, J = 1.5 Hz, 3H), 2.97 (dd, J = 13.9, 8.4 Hz, 1H), 3.23 (dd, J = 13.9, 4.8 Hz, 1H), 3.88–4.22 (m, 1H), 6.84 (td, J = 7.5, 1.7 Hz, 1H), 6.99 (dd, J = 8.4, 1.8
Hz, 1H), 7.14 (d, J = 7.1 Hz, 3H), 7.2–7.38 (m, 5H), 7.46 (dd, J = 7.9, 1.8 Hz, 1H), 9.53 (s, 1H); 
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta = 34.8, 41.5, 60.1, 110.0, 117.3, 117.5, 119.2, 124.7, 127.2, 128.4, \\
129.0, 129.4, 137.3, 140.9, 148.2, 156.1;\) HRMS (ESI\(^{+}\)) calculated for C\(_{18}\)H\(_{19}\)N\(_3\)O [M+H] 
294.1601, found 294.1605.

**4. MS study of 18c–Zn(OTf)\(_2\)**

Zn(OTf)\(_2\) (2.0 mg, 0.006 mmol) and 18c (0.006 mmol) were added to a 4.0 mL vial then 
dissolved in CH\(_3\)CN (1.0 mL). The solids were dissolved and the mixtures sat for 1 h before 
being analyzed by mass spectrometry. Samples were made by adding an aliquot of ligand-metal 
mixture to LC-MS grade methanol (approximately 1 mL). The samples were directly injected 
into the mass spectrometer (Shimadzu 2020 single quadrupole) using methanol as the mobile 
phase. The mass range analyzed was 100-1300 m/z and the interface voltage was set to 4.5 kV. 
Dual ESI and APCI ionization modes were used (positive mode).

**18c + Zn(OTf)\(_2\)**

![Image](image.png)
5. NMR spectra