J|A|C|S COMMUNICATIONS

Published on Web 07/24/2009

Hydrogen-Bonding Asymmetric Metal Catalysis with α-Amino Acids: A Simple and Tunable Approach to High Enantioinduction

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Asymmetric transition-metal catalysis has become a major area of research in synthetic chemistry.[1] One challenge in this field, however, is how to identify the correct chiral ligand for high enantioselectivity. The subtle nature of asymmetric catalysis can make it difficult to predict the optimal ligand to use in a particular reaction.[2] This presents a significant issue, since the ligands found to lead to high enantioselectivity are often themselves complex and typically require a multistep synthesis prior to screening and tuning. Both others and ourselves have been actively pursuing alternatives to chiral ligands in asymmetric catalysis (e.g., chiral counteranions,[3] Bronsted acids,[4,5] chiral environments[6]), though these can again require synthesizing chiral scaffolds for high enantioselectivity. An alternative would be to employ naturally occurring sources of chirality in metal catalysis without structural modification, such as α-amino acid derivatives. The latter are inexpensive and commercially available in a variety of forms. The difficulty is how to associate such units to catalysts in a manner that can lead to high enantioinduction without, as is often the case, ultimately moving beyond the natural chiral pool to tune their selectivity.[7,8]

In considering this issue, one possibility would be to change how amino acids are used in metal catalysis. There exist a range of metal-catalyzed reactions with substrates that can interact with Bronsted acids. As such, we postulated that coupling metal catalysis with the ability of amino acids to hydrogen bond could provide an easy route for inducing both enantioselectivity (via the amino acid) and the tunability often required to obtain high selectivity (by changes to the metal catalyst) (Figure 1). Bronsted acid catalysts have recently attracted significant attention,[5] including in metal catalysis,[4] though these latter typically employ chiral phosphoric acid scaffolds. In contrast, we describe herein how simple amino acid hydrogen bonding can provide a method for introducing chirality into metal catalysis. In addition, the modularity of this system makes tuning it for high enantioselectivity a straightforward process. This includes the potential for designing substrate-specific chiral catalysts.

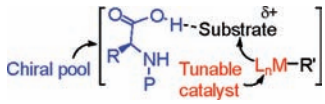
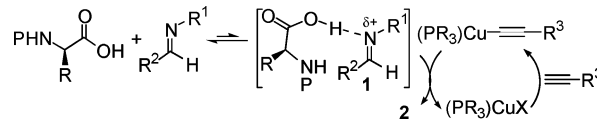
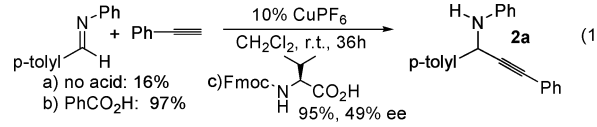


Figure 1. Hydrogen-bonding amino acids in metal catalysis.

The reaction we examined is the copper-catalyzed coupling of alkyne and imine. This has been found to form propargylamines in good enantioselectivity with synthetic ligands (e.g., Py-BOX derivatives).[9] Our previous research has shown that imines can be activated toward metal-catalyzed coupling reactions by in situ generation of *N*-acyliminium salts.[10] As such, it seemed viable that this reaction might proceed more rapidly upon hydrogen bonding to the imine to create the electrophile **1** (Scheme 1).[11] This effect is illustrated in eq 1. While $CuPF_6$ catalyst alone leads to **2a** in low yield, the addition of a mild Bronsted acid (10% $PhCO_2H$) results in near-quantitative **2a** formation. In view of the catalytic influence of carboxylic acids, the amino acid Fmoc-valine was examined. As hoped, a similar acceleration was observed, and **2a** was formed in 49% ee.

Scheme 1. Proposed Mechanism for Imine/Alkyne Coupling





The above demonstrates that an amino acid can catalyze the coupling of imines and alkynes, albeit with only moderate selectivity. However, it is straightforward to exploit the advantage of this system: its tunability. Changing the commercial amino acid is trivial and can significantly influence the enantioselectivity. For example, histidine and asparagine led to <25% ee, while several other derivatives increased the selectivity relative to valine. A single day of screening allowed *N*-Boc-proline to be identified as the optimal amino acid for the reaction (61% ee).

In addition to the amino acid, the copper catalyst can also be tuned, as a route for modulating the selectivity beyond that provided by available amino acid derivatives. A variety of ligands were found to influence the enantioselectivity (Table 1), likely by changing the steric bulk of the copper catalyst for reaction with **1**. Overall, the use of P(*o*-tolyl)$_3$ with *N*-Boc-proline leads to **2a** in high yield and 96% ee (entry 11) (Figure 2).

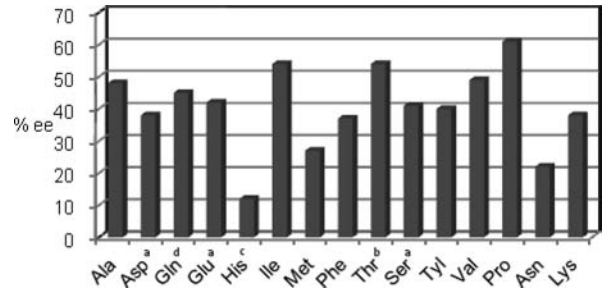


Figure 2. *N*-Boc-protected amino acid influence on enantioselectivity. Superscripts a, b, c, and d indicate *O*-benzyl, *O*-*t*-Bu, *N*-tosyl, and *N*-xan, respectively.

Preliminary studies were consistent with α-amino acid/imine association during catalysis. ^{1}H NMR analysis of *N*-Boc-proline with (*p*-tolyl)HC═N(Bn) showed a significant downfield shift in the $-CO_2H$ resonance (from 11.58 to 14.66 ppm), as anticipated for hydrogen bonding. Titration studies provided a K_{assoc} of 14 M^{-1}. Consistent with this weak, equilibrium association to form **1** during catalysis, kinetic

10.1021/ja904185b CCC: $40.75

Table 1. Ligands in $CuPF_6$/*N*-Boc−Proline-Catalyzed Coupling (eq 1)

entry	L (10 mol %)	yield (%)	% ee[a]
1	−	94	61
2	PPh_3	95	71
3	PBu_3	78	80
4	$P(OPh)_3$	89	81
5	$P(O(2,4,6\text{-}(t\text{-}Bu)_3C_6H_2))_3$	88	73
6	$P(cyclohexyl)_3$	92	81
7	$P(1\text{-napthyl})_3$	96	85
8	$P(t\text{-}Bu)_2(2\text{-}N\text{-phenyllpyrrole})$	52	65
9	$P(t\text{-}Bu)_2(o\text{-biphenyl})$	48	80
10	$P(o\text{-tolyl})_3$ (20%)	96	93
11	$P(o\text{-tolyl})_3$	89	96[b]

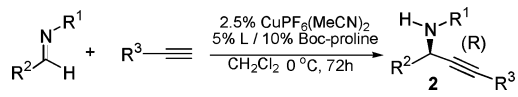
[a] Determined using a Chiral Pak AD-H column. [b] Conditions: 2.5% $CuPF_6$/5% L, 0 °C, 3 days.

experiments showed the rate to have a first-order dependence on the *N*-Boc-proline concentration (from 3 to 50 mol %) and to be independent of the $CuPF_6$ concentration (10 mol %).[12] Notably, no change in % ee was observed over this range. Alternatively, the addition of base (20% NEt_3) completely inhibited catalysis, presumably by blocking this Bronsted acid activation.

From a synthetic perspective, this combined amino acid/copper catalyst provides a simple system for synthesizing a range of propargylamines with high enantioselectivity. This includes coupling with various *N*- and *C*-aryl imines (**2b**−**h**) as well as vinyl, alkyl, and functionalized alkynes, each forming **2** in high yield and up to 99% ee (Table 2). The accelerating influence of the amino acid also allowed the use of substrates previously considered incompatible with coupling. For example, despite considerable efforts,[9] electron-rich *N*-alkylimines have been reported as unreactive toward alkynylation, likely because of their reduced electrophilicity. In contrast, *N*-Boc proline activates these toward coupling, forming *N*-protected **2n** in 93% ee.

Perhaps the most significant advantage of this approach is its flexibility. Asymmetric catalysis is notorious for its substrate specificity,

Table 2. Diversity of Asymmetric Imine Alkynylation[a]



2	R^1	R^2	R^3	L	%	% ee (O.R.)[b]
2b	Ph	Ph	Ph	$P(o\text{-tolyl})_3$	89	96 (+)
2c	Ph		Ph	$P(o\text{-tolyl})_3$	65	93 (+)
2d		*p*-tolyl	Ph	$P(o\text{-tolyl})_3$	85	94 (+)[c]
2e	Ph		Ph	$P(o\text{-tolyl})_3$	89	95 (+)
2f		*p*-tolyl	Ph	$P(o\text{-tolyl})_3$	87	95 (+)
2g	Ph		Ph	$P(o\text{-tolyl})_3$	82	93 (+)
2h		*p*-tolyl	Ph	$P(o\text{-tolyl})_3$	83	93 (+)
2i	Ph	*p*-tolyl		$P(o\text{-tolyl})_3$	79	99 (+)
2j	Ph	*p*-tolyl			78	89 (+)[c]
2k			Ph		92	91 (+)
2l	Ph	*p*-tolyl	$SiMe_3$	"	84	90 (+)[c]
2m	Ph	*p*-tolyl		"	81	92 (+)
2n		*p*-tolyl	Ph	"	92	93 (+)
2o		Ph	Ph	"	89	92 (+)

[a] See the Supporting Information for conditions. [b] O.R. = optical rotation.[13] [c] Room temperature.

with even seemingly small changes leading to loss in enantioselectivity and the potential need to redesign the chiral ligand. An example is with 1-hexyne (**2j**), which led to product in 80% ee, consistent with reports of low selectivity with alkyl alkynes.[9] However, because the availability of amino acids and phosphines, it was straightforward to identify the correct ligand for this system (i.e., PCy_3). This modularity can also allow the expansion of this reaction to new classes of imines, such as *C*-alkylimines, which in this case provided **2k** in 91% ee with $P(1\text{-napthyl})_3$ as the ligand. As far as we are aware, this represents the most general and easily tunable catalytic system for the synthesis of optically active propargylamines.

In conclusion, these results suggest what is to our knowledge a new approach for incorporating chirality into metal catalysis, namely, the use of hydrogen-bonding amino acid derivatives with metal catalysts. In contrast to complex chiral ligands, these catalysts are accessible and commercially available, and their modularity can be used to create a large number of different catalysts by using different members of the available pools of amino acids and phosphines, with screening often limited only by the rate of HPLC analysis. This provides a facile approach for tuning chiral catalysts for high enantioselectivity, even for specific substrates. Experiments directed toward determining the applicability of this approach to other catalytic reactions are currently underway.

Acknowledgment. The authors thank the NSERC (Canada) Discovery and AGENO programs for support of this research.

Supporting Information Available: Synthesis and characterization of **2** and kinetic/titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) This effect has recently been postulated with synthetic phosphate counteranions and protonated *C*-ester-substituted imines.[4a].
(12) While amino acid/copper secondary coordination is possible, the catalysis is zeroth-order in [$CuPF_6$], also suggesting separate roles for Cu and the amino acid in the reaction (see the Supporting Information). Notably, other H-bonding acids can also lead to enantioselectivity, though at lower ee's [(*S*)-mandelic acid, 19% ee; L-2-pyrrolidone-5-carboxylic acid, 0% ee].
(13) See the Supporting Information for configuration assignment (for **2b** and **2g**, see ref 9c).

JA904185B