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Copper-Catalyzed Asymmetric Propargylation of Cyclic Aldimines

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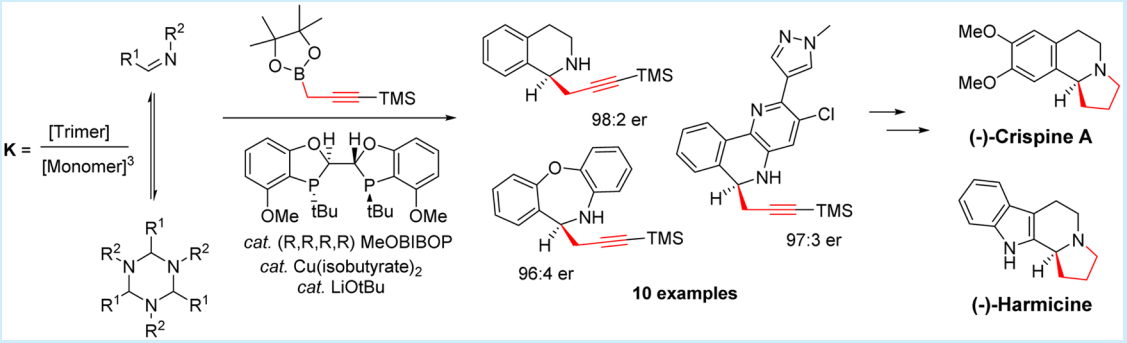
Supporting Information



ABSTRACT: The copper-catalyzed asymmetric propargylation of cyclic aldimines is reported. The influence of the imine trimer to inhibit the reaction was identified, and equilibrium constants between the monomer and trimer were determined for general classes of imines. Asymmetric propargylation of a diverse series of *N*-alkyl and *N*-aryl aldimines was achieved with good to high asymmetric induction. The utility was demonstrated by a titanium catalyzed hydroamination and reduction to generate the chiral indolizidines (−)-crispine A and (−)-harmicine.

Asymmetric additions to carbonyl and imine species can be regarded as seminal advances necessary for the sustainable synthesis of bioactive natural products and pharmaceuticals.[1] Stereoselective propargylations are strategically advantageous reactions because they enable the concomitant formation of a chiral center and installation of a synthetically versatile alkyne functional group.[2] Recently, significant advances in catalytic asymmetric propargylations have been achieved for the addition to aldehydes,[2,3] ketones[2,4] and protected imines.[5] The latter studies used hydrazones,[3d] phosphinoyl imines,[6] or sulfonyl imines,[7] because these functional groups share attributes necessary for an effective catalytic cycle. The imine protecting group stabilizes the imine by preventing oligomerization,[8] provides chemoselectivity between the electrophile and reagents,[9] and activates the substrate for the addition.[10] However, unprotected *N*-alkyl and *N*-aryl imines encompass a plethora of structural diversity, and only limited examples for the asymmetric allylation and stoichiometric propargylation are reported.[2,11] Recognizing this potential utility, we report the copper-catalyzed asymmetric propargylation of cyclic aldimines.

We introduced the propargyl borolane **2**[12] to effect propargylations through B/Zn[13] and B/Cu[3b,4b] exchange processes that demonstrated a suppressed background reaction between the reagent and carbonyl electrophile over typical allyl or allenyl borolane reagents. The background reaction[9b] between the parent dihydroisoquinoline **1a** was more pronounced and proceeded at ambient temperature with high selectivity for the allenyl product **4a** (Figure 1). The selectivity was reversed to strongly favor the propargylation pathway by the addition of catalytic diethyl zinc and lowering the reaction temperature to allow the catalytic reaction to effectively compete with the background process. Furthermore, the boron−metal exchange mechanism generates an *N*-boropinacol complex, thereby protecting the amine from metal coordination until liberation

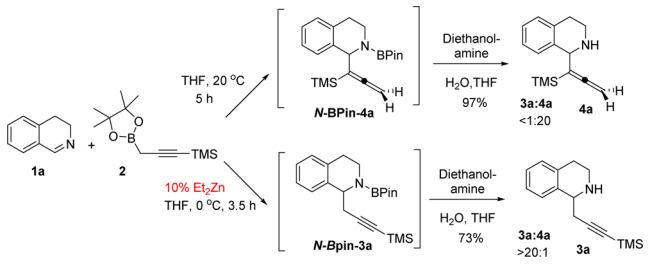


Figure 1. Catalyst influence on the site selectivity for the addition of propargyl borolane **2** to imine **1a**. Site selectivity determined by HPLC and isolated yield for the major isomer.

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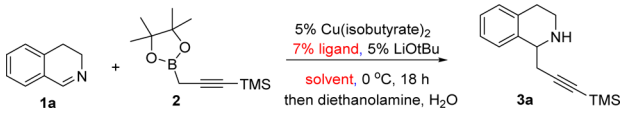
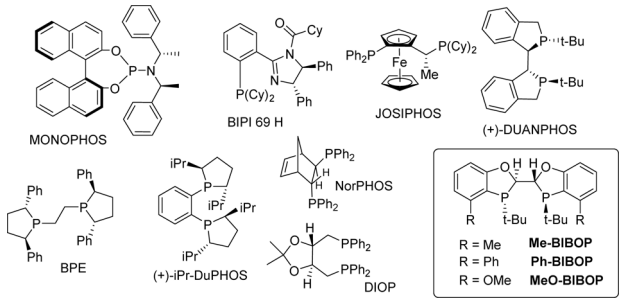
by an aqueous workup. Utilization of this boron−metal exchange strategy allowed entry into the copper catalyzed process wherein diverse classes of chiral ligands can be screened for asymmetric induction (Table 1). Several ligands, JOSIPHOS, BPE, and

Table 1. Initial Optimization for the Asymmetric Propargylation of Aldimines[a]



entry	ligand	solvent	conv (%)[b]	[er][c]
1	BINAP	THF	75	68:32
2	DIOP	THF	80	64:36
3	BIPI 69 H	THF	79	56:44
4	JOSIPHOS	THF	84	85:15
5	BPE	THF	77	85:15
6	*i*Pr-DuPHOS	THF	67	63:37
7	DUANPHOS	THF	75	74:26
8	NorPHOS	THF	72	51:49
9	MONOPHOS	THF	82	84:16
10	Me-BIBOP	THF	76	63:37
11	Ph-BIBOP	THF	77	85:15
12	MeO-BIBOP	THF	95[d]	95:5
13	MeO-BIBOP	toluene	72[e]	96:4
14[f]	MeO-BIBOP	toluene	>95[g]	98:2

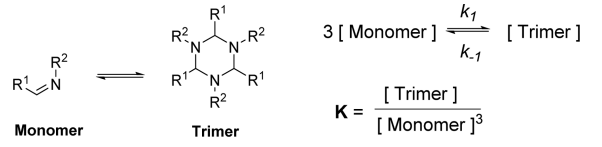
[a]Catalyst preformed in THF and subjected to the substrate under the indicated conditions. [b]Relative conversion by HPLC at 205 nm. [c]Absolute enantiomeric ratio determined by chiral HPLC. [d]78:22 **3a** to **4a** and 75% yield for **3a**. [e]68:32 **3a** to **4a** and 45% yield for **3a**. [f]9 mol % Cu catalyst utilized and reaction conducted for 36 h at −15 °C. [g]84:16 **3a** to **4a** and 84% yield for **3a**.



MONOPHOS, provided moderate enantiomeric ratios, but the MeOBIBOP ligand furnished a high 95:5 er. Changing the solvent to toluene and lowering the reaction temperature to −15 °C improved chemoselectivity over the background reaction and increased the er to 98:2 (entry 14).

One challenge with *N*-aliphatic aldimines was the propensity to trimerize.[8] In previous reports, inconsistencies were apparent in the nature of the equilibrium and within the characterization complicating methodologies associated with their use. NMR analysis of the classical Δ^1-piperidine[8a,c,e] revealed a rapid concentration dependent equilibrium between the monomer and trimer. Systematic variation of the concentration (Table 2) allowed the solution equilibrium constants[8e,14] for representative imine classes to be determined. Δ^1-Piperidine demonstrated a strong preference for the trimer, while the dihydroisoquinoline, *β*-alkalidene, and *N*-aryl imines strongly favored the monomer. Surprisingly, 3,4-dihydro-*β*-carboline **1d** showed a moderate equilibrium with the trimer. In addition to the solution behavior of imines, some imines are known to crystallize as the trimer,

Table 2. Monomer−Trimer Solution Equilibrium Constants for Respective Classes of Aldimines[a]



imine	K (M^{-2}) [Log K] DMSO-d_6	C_6D_6	$CDCl_3$
Δ^1 Piperidine	2.4 x 10^5 [5.4]	2.3 x 10^6 [6.4][b]	7600 [3.9]
1a	< 0.01	< 0.01	< 0.01
1d	36 [1.6]	-[c]	-[c]
1e	< 1	< 1	< 1
1f	< 0.01	< 0.01	< 0.02

[a]Concentrations determined by ^{1}H NMR spectroscopy with an internal standard at 18−20 °C. Less than represents limit of detection. Average of two values for $K > 1$ at different concentrations. [b]Average for four measurements with 6 h to 3 d of solution aging. [c]Not determined due to limited solubility.

such as Δ^1-piperidine.[8a,c] Dihydroisoquinoline **1a** was isolated as an oil, which slowly crystallized as the trimer (Figure 2), whereas

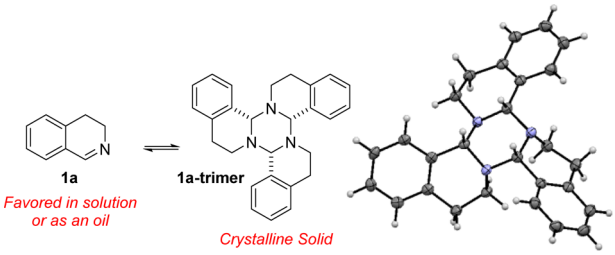


Figure 2. Crystallization driven trimerization of imine **1a**. ORTEP diagram for a single crystal X-ray of crystalline trimer of **1a**.

in solution or as a melted oil, this compound displays a strong equilibrium preference toward the monomer. This property of the parent imine demonstrated a profound influence on the optimized copper-catalyzed conditions. While the asymmetric reaction proceeded smoothly by subjecting the imine oil or solution to the catalyst solution, no reaction was observed if the crystalline trimer was charged to the catalyst. Trace conversion was also observed with Δ^1-piperidine, which has a strong preference for the trimer in solution, to further support the inhibitory effect of the trimer on the catalyst. Therefore, the substrate scope focused on imine classes that demonstrated an equilibrium favoring the imine monomer.

The copper catalyzed asymmetric propargylation utilizing the MeOBIBOP ligand demonstrated a broad substrate scope for both *N*-aliphatic and *N*-aryl aldimines (Table 3). Dihydroisoquinolines (**1a−c**), dibenzo-oxazepines (**1f** and **1g**), *β*-alkalidene imine (**1e**), and phenathridine systems (**1h−1j**) were tolerated to provide reasonable to high asymmetric

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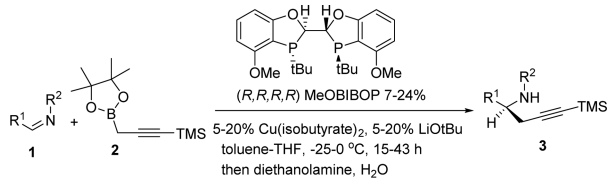
Table 3. Substrate Scope for the Asymmetric Propargylation of Aldimines[a]



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entry	imine	product	yield (%)[b]	er[c]
1[f,j]	1a	3a	84	98:2
2[d,i]	1b	3b	86	97:3
3[d,k]	1c	3c	52	96:4
4[g,h]	1d	3d	68	95:5
5[f,h]	1e	3e	97	83:17
6[e,j]	1f	3f	86	96:4
7[e,j]	1g	3g	91	94:6
8[e,j]	1h	3h	99	93:7
9[e,j]	1i	3i	99	85:15
10[e,j]	1j	3j	87	97:3

[a]See Supporting Information for reaction and isolation conditions for every example. [b]Isolated yields. [c]Enantiomeric ratio determined by chiral HPLC with reference to racemic standards. Absolute stereochemistry assigned by analogy to the determined configuration of **3b** and **3d**. [d]5 mol % catalyst with 7 mol % ligand. [e]7 mol % catalyst with 9 mol % ligand. [f]9 mol % catalyst with 11 mol % ligand. [g]20 mol % catalyst with 28 mol % ligand. [h]0 °C. [i]−10 °C. [j]−15 °C. [k]−25 °C.

induction. These diverse structures also allowed the incorporation of valuable heterocycles such as a quinoline (**1g**), pyrazoloquinoline (**1i**), and benzonapthyridine (**1j**) into the substrates. Due to the diverse scope, the reaction conditions were optimized for each substrate with most systems proceeding with good conversion and high selectivity with 5−9 mol % catalyst loadings and at −25 to 0 °C. The 3,4-dihydro-β-carboline (**1d**) proved to be a challenging substrate for the methodology, requiring a 20% catalyst loading to achieve high conversion. This poor reactivity may be due to the unprotected indole *N*-H or its equilibrium with the trimer in contrast to the other substrates (Table 2). Overall, a broad diversity of aldimine scaffolds was tolerated, including several complex heterocyclic systems.[15]

The asymmetric propargylation provides ideal substrates for an intramolecular reductive hydroamination to generate indolizidine alkaloids.[16] However, related attempts with catalytic silver led to oxidative products with loss of the chiral center.[17] Therefore, titanium based systems were examined with the TMS-deprotected alkynes **5a**, **5b**, and **5d**. While the Ackermann et al. system ($TiCl_4$ and $tBuNH_2$)[18] furnished poor yields, the Schafer et al. catalyst[19] provided high yields and complete stereointegrity after reduction (Figure 3). The reductive hydroamination sequence with the dimethoxy (**5b**) and indole (**5d**) substrates allowed rapid access to both (−)-crispine A[20] and (−)-harmicine.[21]

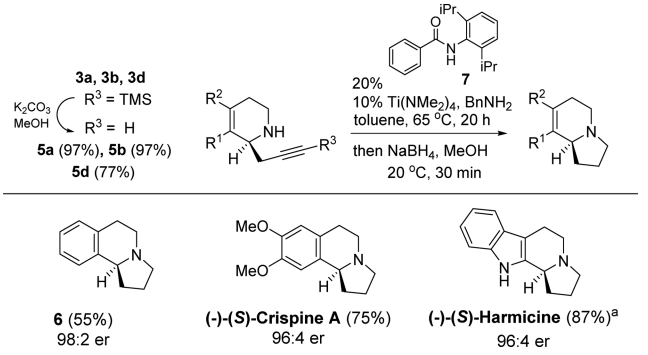

Figure 3. Reductive hydroamination toward indolizidine alkaloids. Enantiomeric ratios determined by chiral HPLC. [a]20% Titanium catalyst with 40% ligand **7** employed.

In conclusion, the copper catalyzed asymmetric propargylation of *N*-aliphatic and *N*-aryl aldimines was developed. The reactions generally proceeded in high yield with synthetically useful enantiomeric ratios and excellent selectivity for the propargylation pathway. The imine substrate demonstrated a propensity for dynamic trimerization, an equilibrium that was dependent on the imine structure, solvent, and state of matter. Tabulating this property allowed predictable substrate selection and reproducibility for the methodology while simultaneously rectifying the inconsistency in the literature as to the nature of these trimerization equilibria. The structural breadth of the aldimine substrates combined with the installation of the synthetically versatile alkyne boosts the potential impact of this propargylation chemistry, which will facilitate the continued development of novel medicines and materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03253.

Complete optimization studies, experimental procedures, characterization data, equilibrium constants determination, X-ray data, copies of chiral HPLC chromatograms, ^1H and ^{13}C NMR spectra for all products (PDF, PDF, PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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