Asymmetric Catalysis

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Enantio- and Diastereoselective Synthesis of Homopropargyl Amines by Copper-Catalyzed Coupling of Imines, 1,3-Enynes, and Diborons

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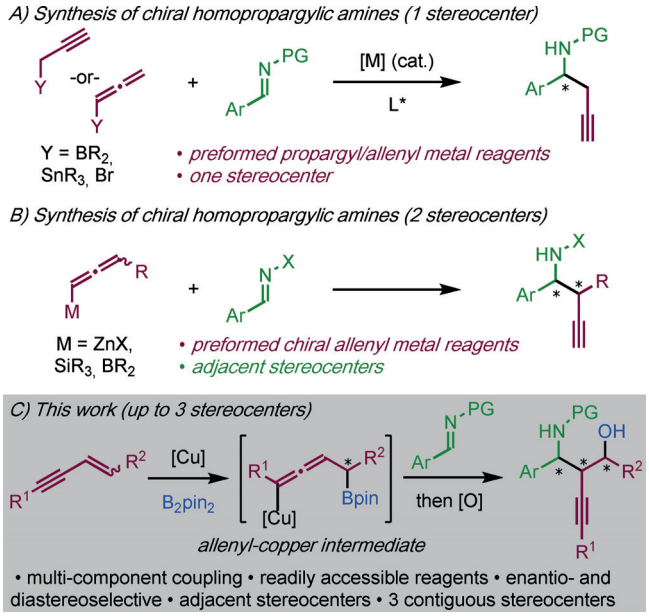
Abstract: *An efficient, enantio- and diastereoselective, copper-catalyzed coupling of imines, 1,3-enynes, and diborons is reported. The process shows broad substrate scope and delivers complex, chiral homopropargyl amines; useful building blocks on the way to biologically-relevant compounds. In particular, functionalized homopropargyl amines bearing up to three contiguous stereocenters can be prepared in a single step.*

Chiral homopropargyl amines are used in the synthesis of many natural products, and biologically and medicinally important molecules.[1–3] Most methods for homopropargyl amine synthesis involve the union of imines and propargylic or allenic substrates. These methods deliver racemic homopropargylic amines[4] and asymmetric variants selectively generate products with a stereocenter adjacent to the amino group (Scheme 1 A). In general, these methods use a transition metal catalyst and chiral ligand, or imines bearing a chiral auxiliary.[5] Constructing homopropargyl amines with more than one stereocenter, particularly if the stereocenters are adjacent, is a more challenging process (Scheme 1 B), few procedures address this goal and these require difficult-to-access reagents and/or chiral auxiliaries.[6] Thus, a general preparation of chiral homopropargylic amines, bearing multiple stereocenters, from readily-accessible substrates, remains an important challenge.

Copper-catalyzed borylative transformations are a powerful method for uniting unsaturated hydrocarbons and electrophiles.[7] Importantly, these methods produce densely functionalized, chiral molecules from simple, achiral substrates, and use cheap and non-toxic transition metal catalysts. We and others have described efficient routes to amines through the multicomponent coupling of imines with hydrocarbon pro-nucleophiles and boron reagents.[8–10] Krische pioneered the use of enynes as hydrocarbon pro-nucleophiles in transition metal-catalyzed transformations,[11–13] however, in both reductive and borylative coupling, the asymmetric union of imines and enynes remains an unmet challenge.[14]



Scheme 1. Enantioselective transition metal-catalyzed nucleophilic addition to imines for the synthesis of homopropargyl amines. PG = protecting group; X = PG or chiral auxiliary; Pin = pinacolato.

We envisaged a new approach to homopropargyl amines involving the copper-catalyzed enantio- and diastereoselective multicomponent coupling of imines, enynes, and diboron reagents (Scheme 1 C). Furthermore, through routine oxidation of the carbon–boron bond, biologically relevant 1,3-amino alcohols would be accessible.[15] Herein, we disclose an efficient method for obtaining functionalized chiral homopropargyl amines, bearing up to three stereocenters and various synthetic handles (amino, boron, alkynyl), using an inexpensive, non-toxic, and readily-available copper catalyst, and a commercial phosphine ligand.

We explored the copper-catalyzed coupling of imine **1a**, 1,3-enyne **2a** and bis(pinacolato)diboron (B_2pin_2). Using CuCl and (*S*,*S*)-Ph-BPE (**L1**), the desired product **3a′** (PG = PMP) was obtained in 70% yield and the major diastereoisomer was found to have an *ee* of 53% (Table 1, entry 1). After screening reaction conditions with imine **1a**, we turned our attention to *N*-phosphinoylimine **1b**. With this imine, the enantioselectivity and diastereoselectivity of the reaction increased (89% *ee*, > 95:5 dr), however, only 37% yield of the desired product was obtained (entry 2). By screening the copper salt, base, and solvent, we found that the use of CuOAc, KOMe, and THF was optimal; **3a** was obtained in high yield, with excellent diastereoselectivity and enantioselectivity (entry 3).[16] X-ray crystallographic analysis of **3d** revealed the relative and absolute stereochemistry of the

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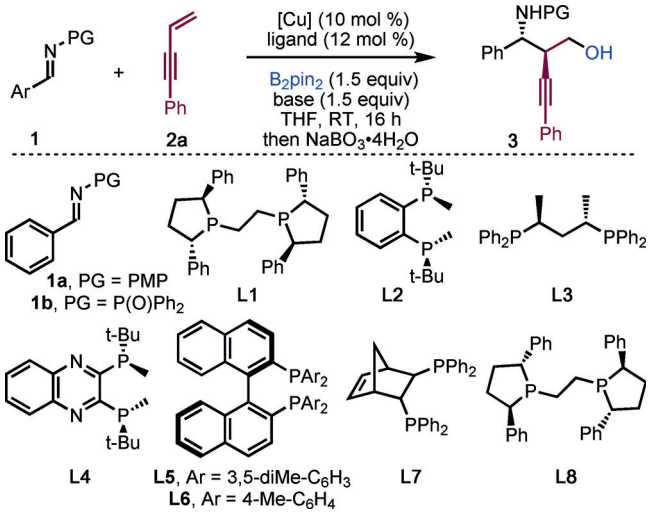
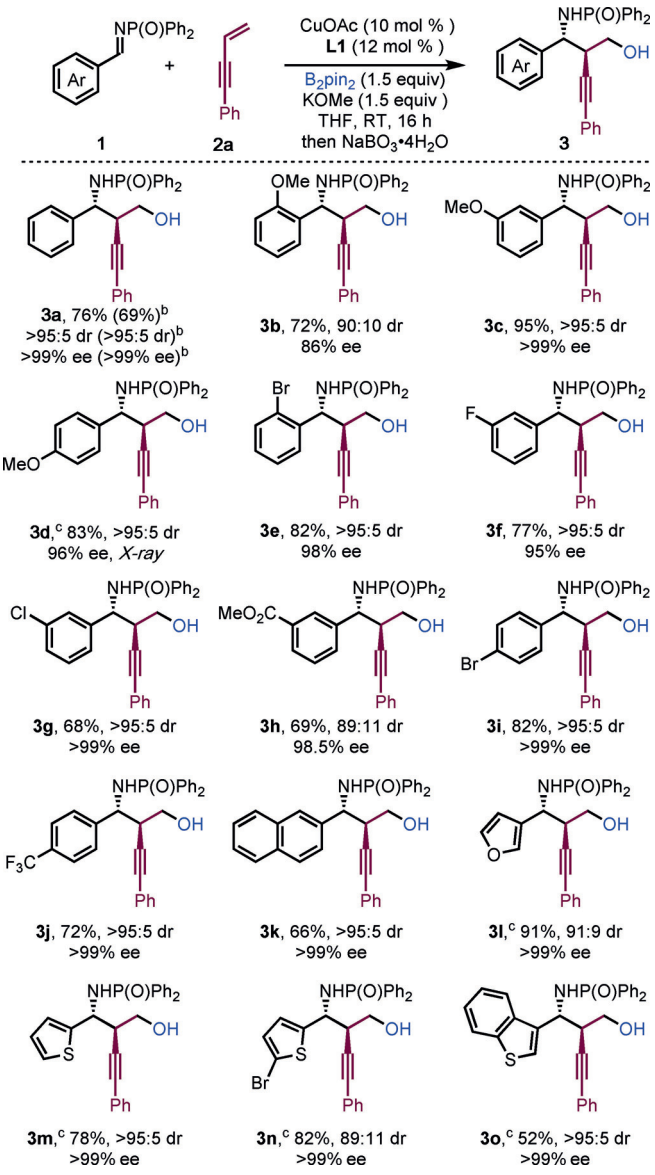
Table 1: Screening of reaction conditions[a]



Entry	Imine	Ligand	Cu^{I}/base	dr	**3** Yield/*ee*[b] [%]
1	**1a**	**L1**	CuCl/NaO*t*Bu	87:13	70/53[c]
2	**1b**	**L1**	CuOAc/NaO*t*Bu	>95:5	37/89
3	**1b**	**L1**	CuOAc/KOMe	>95:5	92/99
4	**1b**	**L2**	CuOAc/KOMe	–	–
5	**1b**	**L3**	CuOAc/KOMe	–	–
6	**1b**	**L4**	CuOAc/KOMe	–	–
7	**1b**	**L5**	CuOAc/KOMe	>95:5	56/34
8	**1b**	**L6**	CuOAc/KOMe	–	–
9	**1b**	**L7**	CuOAc/KOMe	88:12	37/16
10	**1b**	**L8**	CuOAc/KOMe	>95:5	88/96[d]
11	**1b**	**L1**	CuOAc/KOMe	90:10	56/92[e]

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), B_2pin_2 (0.3 mmol), base (0.3 mmol), Cu^{I} (10 mol%), ligand (12 mol%) in THF (2.0 mL) at RT for 16 h under nitrogen. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude product mixtures. NMR yields are given. [b] The *ee* values were determined by chiral HPLC after oxidation. [c] The *ee* values were measured by chiral HPLC analysis of the boron-containing product. [d] The enantiomer of **3a** was formed. [e] B_2neo_2 (0.3 mmol) was used. THF = tetrahydrofuran. PMP = 4-methoxyphenyl; Neo = neopentyl glycolato.

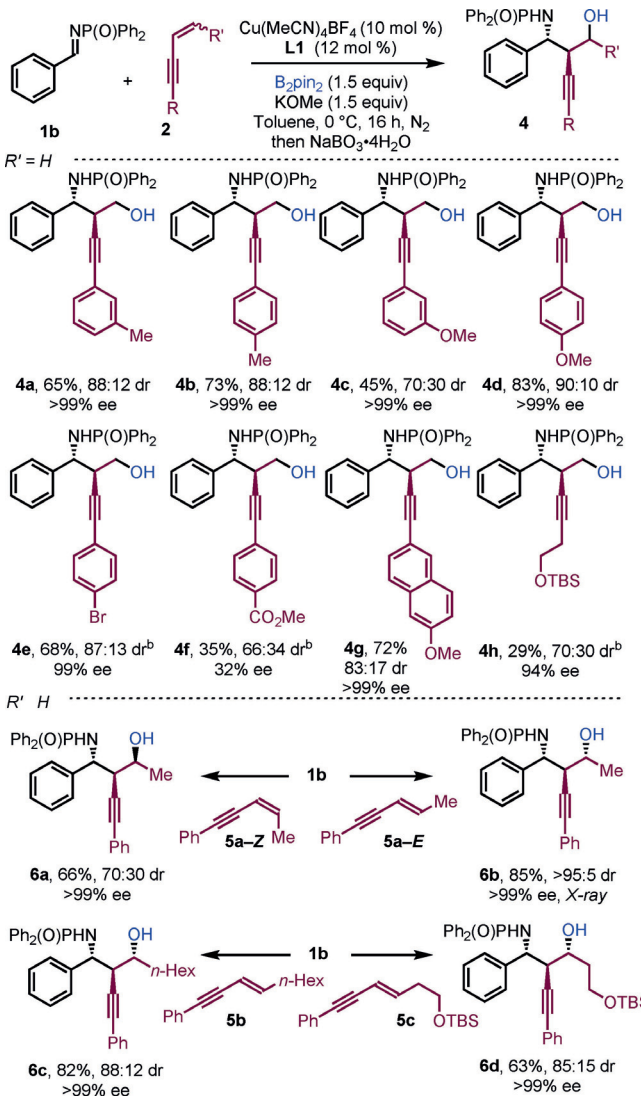


Scheme 2. Scope with respect to the imine. [a] Reaction conditions: See Table 1. Yields of isolated products are given. [b] Values in parentheses indicate the result of a 1 g scale reaction. [c] 0 °C in MTBE. MTBE = methyl-*t*-butyl ether.

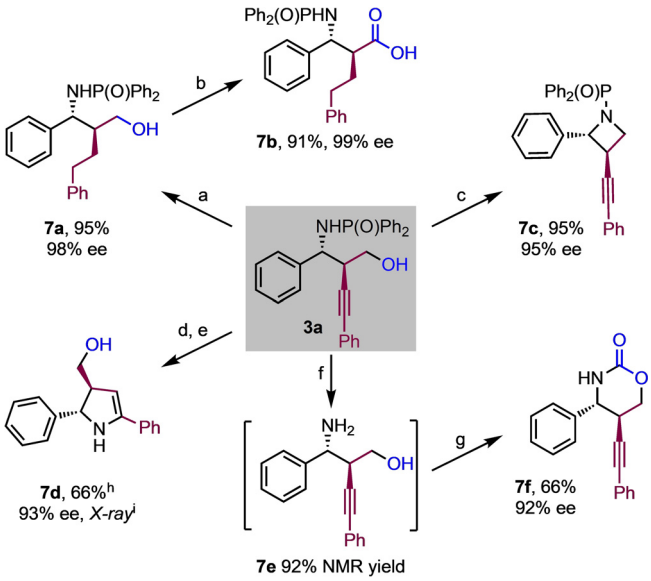
product.[16] Other diboron reagents are applicable in the reaction; the use of bis(neopentyl glycolato)diboron (B_2neo_2) gave **3a** in moderate yield but with high diastereo- and enantiocontrol (entry 11).

The reaction tolerated electron-donating and electron-withdrawing substituents on the aryl ring of the aldimine; the desired products were obtained in high yield and with excellent enantio- and diastereoselectivity (Scheme 2). For example, electron-rich aldimines were well tolerated in the reaction and only a slight decrease in enantioselectivity was observed when an *ortho*-methoxy substituent was used (**3b**). Similarly, imines bearing electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-positions (**3e–3j**), including halogen (**3e–3g**, **3i**), ester (**3h**), and trifluoromethyl (**3j**) substituents, also performed well. The reaction also proceeded efficiently when heteroaryl-aldimines were used (**3l–3o**). The reaction could be executed on a gram scale without significant detriment to the yield or selectivity (**3a**). Attempts to use an aliphatic aldimine in the process were unsuccessful (See Supporting Information).

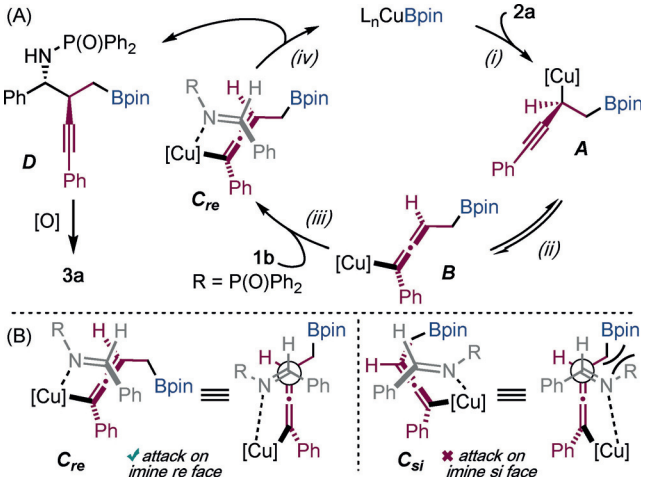
Aryl-substituted 1,3-enynes bearing electron-donating groups delivered the corresponding products in good to excellent yield and with high enantioselectivities (Scheme 3, **4a–4d**). Mixed results were obtained when using electron-deficient enynes; for example, whereas the bromo-substituted product **4e** was prepared in good yield, with high selectivity, an ester substituent severely affected the efficiency of the coupling (**4f**). The use of an alkyl substituted enyne gave **4h** in low yield but with high enantiocontrol. Substitution at the terminal position of the alkene was investigated: *E*-enynes gave products **6b–6d** in good to high yield, with good diastereoselectivity and excellent enantioselectivity. The structure of **6b** was confirmed by X-ray crystallography.[16] The use of *Z*-enyne **5a**-*Z* gave alternative diastereoisomeric product **6a**. Thus, the process delivers amino alcohols bearing three contiguous stereocenters with essentially complete enantiocontrol.



Scheme 3. Scope with respect to 1,3-enyne. [a] Reaction conditions: **1b** (0.2 mmol), **2** (0.3 mmol), B_2pin_2 (0.3 mmol), KOMe (0.3 mmol), $Cu(MeCN)_4BF_4$ (10 mol%), (*S*,*S*)-Ph-BPE **L1** (12 mol%) in toluene (2.0 mL) at 0°C for 16 h under nitrogen. Yields of isolated products. [b] THF at RT with CuOAc.



Scheme 4. Manipulation of product **3a**. [a] Pd/C (10 mol%), H_2 (1 atm), MeOH, 40°C, 24 h. [b] $RuCl_3$ (5 mol%), $NaIO_4$ (1.5 equiv), CCl_4:MeCN:H_2O = 1:1:1.2, 3 h, RT. [c] TsCl (1.5 equiv), NaH (6 equiv), THF, 40°C, 8 h. [d] From borylated/non-oxidized form of **3a**: Ph_3PAuCl (10 mol%), AgOTf (10 mol%), DCE, 8 h, 80°C. [e] $NaBO_3·4H_2O$ (5 equiv), THF:H_2O = 1:1, 6 h, RT. [f] 4 N HCl, MeOH, RT, 3 h, RT. [g] Triphosgene (1.0 equiv), Et_3N (2 equiv), THF, 3 h, 0°C. [h] 4:1 Mixture of tautomers. [i] X-ray of minor tautomer of **7d**.



Scheme 5. Proposed catalytic cycle for the enantioselective coupling.

Amine **3a** was readily hydrogenated, to give the branched chain alkane **7a**, and the β-amino acid derivative **7b** was accessed by oxidation of **7a** (Scheme 4). Biologically- and medicinally-relevant *N*-containing heterocycles were also prepared, for example, azetidine **7c**, or 2,3-dihydropyrrole **7d** through π-activation of the alkyne bond using a Au–Ag catalyst system.[17] The phosphinoyl group could be removed to reveal the free amine **7e**,[9a] which was subjected to urethanation to give oxazinone **7f**.

Regioselective borocupration provides intermediate **A** (1),[12a,13a] which is proposed to undergo propargyl-to-allenyl isomerization to **B** (2) (Scheme 5A).[12d] We propose that intermediate **B** is the major allenyl–copper isomer in the reaction.[12d] Coupling of the allenyl–copper intermediate **B** with imine **1b** ($\mathbf{C}_{re}$, 3) gives chiral homopropargylic amine **D** and closes the catalytic cycle (4).[12b–d] Scheme 5B provides an explanation for the *anti*-diastereoselectivity observed in the reaction. Coupling (3) between allenyl intermediate **B** and imine **1b** can occur from attack at either the *re* face ($\mathbf{C}_{re}$) or the *si* face ($\mathbf{C}_{si}$) of the imine. However, reaction at the *si* face ($\mathbf{C}_{si}$) incurs unfavorable interactions between the *N*-phosphinoyl group and the -CH_2Bpin group and is disfavored.

In conclusion, a highly enantio- and diastereoselective coupling of imines, 1,3-enynes, and diborons using an inexpensive copper catalyst and a commercial ligand, delivers chiral homopropargyl amines with up to three contiguous stereocenters. The products provide access to important targets, including β-amino acids and *N*-heterocycles.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · borylative coupling · copper · 1,3-enynes · homopropargyl amines

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