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

Srimanta Manna, Quentin Dherbassy, Gregory J. P. Perry, and David J. Procter*

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 en route 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. Most methods for homopropargyl amine synthesis involve the union of imines and propargylic or allenic substrates. These methods deliver racemic homopropargyl amines and asymmetric variants selectively generate products with a stereocenter adjacent to the amino group (Scheme 1A). In general, these methods use a transition metal catalyst and chiral ligand, or imines bearing a chiral auxiliary. Constructing homopropargyl amines with more than one stereocenter, particularly if these stereocenters are adjacent, is a more challenging process. Despite some progress (Scheme 1B), few procedures address this goal and these require difficult-to-access reagents and/or chiral auxiliaries. Thus, a general preparation of chiral homopropargyl 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. 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. Krische pioneered the use of enynes as hydrocarbon pro-nucleophiles in transition metal-catalyzed transformations, however, in both reductive and borylative coupling, the asymmetric union of imines and enynes remains an unmet challenge.

We envisaged a new approach to homopropargyl amines involving the copper-catalyzed enantio- and diastereoselective multicomponent coupling of imines, enynes and diborons (Scheme 1C). In addition, through routine oxidation of the carbon-boron bond, biologically relevant 1,3-amino alcohols would be accessible. 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 (B2pin2). Using CuCl and (S,S)-Ph-BPE, the desired product 3a∗ (PG = PMP) was obtained in 70% yield and the major diastereoisomer was found to have an ee of 53% (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).[10] X-ray crystallographic

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.
analysis of 3d revealed the relative and absolute stereochemistry of the product.\(^{[1]6}\) Other diboron reagents are applicable in the reaction; the use of bis(neopentyl glycolato)diboron (B\(^{3}neo\)) gave 3a in moderate yield but with high diastereo- and enantiocontrol (entry 11).

Table 1. Screening of Reaction Conditions\(^{[4]}\)

| entry | imine | ligand | Cu(I)/base | dr | 3 yield/ee (%) |
|-------|-------|--------|------------|----|---------------|
| 1     | 1a    | L1     | CuCl(NaO)Bu | 87:13 | 70/53\(^{3}\) |
| 2     | 1b    | L1     | CuOAc(NaO)Bu | >95:5 | >95:5 dr | 99% ee (99% ee) |
| 3     | 1b    | L1     | CuOAcKO Me | >95:5 | >95:5 dr | 99% ee (99% ee) |
| 4     | 1b    | L2     | CuOAcKO Me | - | - |
| 5     | 1b    | L3     | CuOAcKO Me | - | - |
| 6     | 1b    | L4     | CuOAcKO Me | - | - |
| 7     | 1b    | L5     | CuOAcKO Me | >95:5 | 56/34 |
| 8     | 1b    | L6     | CuOAcKO Me | - | - |
| 9     | 1b    | L7     | CuOAcKO Me | 88:12 | 37/16 |
| 10    | 1b    | L8     | CuOAcKO Me | >95:5 | 88/96\(^{2}\) |
| 11    | 1b    | L1     | CuOAcKO Me | 90:10 | 56/92\(^{2}\) |

[a] Reaction conditions: 1 (0.2 mmol), 2a (0.3 mmol), B\(^{3}neo\) (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 H NMR analysis of the crude product mixture. NMR yields are given. [b] ee values were determined by chiral HPLC after oxidation. [c] ee values were determined by chiral HPLC analysis of the boron-containing product. [d] The enantiomer of 3a was formed. [e] B\(^{3}neo\) (0.3 mmol) was used. THF = tetrahydrofuran. PMP = 4-methoxyphenyl. Neo = neopentyl glycolato.

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 (3i-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).

Scheme 2. Scope with respect to the imine. [a] Reaction conditions: See Table 1. Isolated yields 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.
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Scheme 3. Scope with respect to 1,3-enyne. [a] Reaction conditions: 1a (0.2 mmol), 2 (0.3 mmol), B_{2}P(O)Ph (0.3 mmol), Cu(MeCN)_{2}BF_{4} (10 mol %), L1 (12 mol %). [b] THF at RT with CuOAc. [c] [b] THF at RT with CuOAc. [d] THF at RT with CuOAc. [e] THF at RT with CuOAc. [f] THF at RT with CuOAc. [g] 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_{2} (6 mol %), NaOAc, (1.5 equiv), CCl_{4}, MeCN, H_{2}O: 1:1:1:2, 3 h, RT. [c] TsCl (1.5 equiv), NaH (6 equiv), THF, 40 °C, 8 h. [d] From borylated/non-oxidised form of 3a: Ph_{2}PAuCl (10 mol %), AgOTf (10 mol %), DCE, 8 h, 80 °C; [e] NaBO_{2}•H_{2}O (5 equiv), THF, H_{2}O: 1:1, 6 h, RT. [f] 4N HCl, MeOH, RT, 3 h, RT. [g] Triphosgene (1.0 equiv), Et₂N (2 equiv), THF, 5 h, 0 °C. [h] 4:1 Mixture of tautomers, [i] X-ray of minor tautomer of 7d.

Aryl-substituted 1,3-enynes bearing electron-donating groups delivered the corresponding products in good to excellent yield and with high enantioselectivities (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. 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.
A highly enantio- and diastereoselective coupling of imines, 1,3-enynes, and diborons uses an inexpensive copper catalyst and a commercial ligand and 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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Keywords: homopropargyl amines • copper • borylative coupling 1,3-enynes • asymmetric catalysis

Scheme 5. Proposed catalytic cycle for the enantioselective coupling.

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The enantio- and diastereoselective, copper-catalyzed three-component coupling of imines, 1,3-enynes, and diborons delivers complex, chiral homopropargyl amines; useful building blocks en route to biologically- and medicinally-relevant compounds. In particular, functionalized homopropargyl amines bearing up to three contiguous stereocenters can be prepared in a single step.