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Direct Catalytic Asymmetric Alkynylation of Ketoimines

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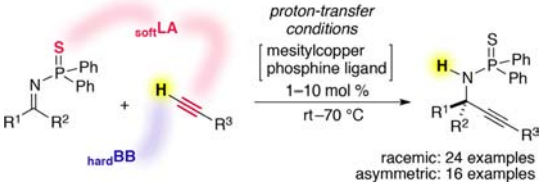
ABSTRACT



An efficient protocol for direct catalytic alkynylation of ketoimines is described. The simultaneous activation of a soft Lewis basic terminal alkyne and a ketoimine bearing a thiophosphinoyl group by soft Lewis acid Cu(I) is crucial for high conversion. The reaction can be rendered asymmetric with a chiral bisphosphine ligand (*S,S*)-Ph-BPE.

Construction of a tetrasubstituted stereogenic center is still a subject of intensive research in organic chemistry.[1] Approaches that incorporate the atom-economical proton-transfer reaction are highly desirable.[2] A generally adopted method to access α-tetrasubstituted amines **1** is a catalytic asymmetric C−N bond-forming reaction (Scheme 1a).[3] The alternative way to access **1** is by a catalytic asymmetric addition of carbon nucleophiles to ketoimines **2**.[4] The latter would be more favorable because the stereogenic center is produced with concomitant formation of carbon frameworks (Scheme 1b). However, the scope of a catalytic asymmetric addition of carbon pronucleophiles to ketoimines **2** that proceeds with perfect atom economy is severely limited, presumably because of a highly congested transition state. Enantioselective additions under proton-transfer conditions have been sporadically reported using HCN,[5] allylic cyanides,[6] and nitromethane.[7,8] Herein we report the first example of a direct catalytic asymmetric addition of terminal alkynes to ketoimines under proton-transfer conditions.[9] The simultaneous activation of pronucleophiles and electrophiles, terminal alkynes and ketoimines, is key to achieving this unprecedented reaction.

The direct catalytic addition of terminal alkynes to ketoimines is in its infancy and has suffered from low yield

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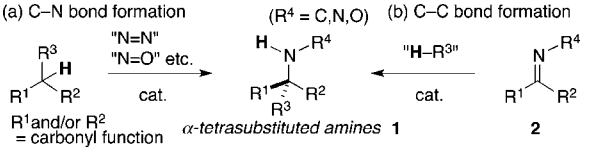
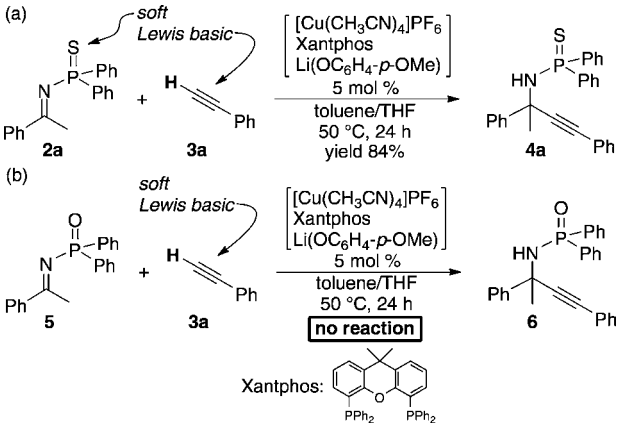
Scheme 1. Enantioselective Access to α-Tetrasubstituted Amines **1** via (a) C−N Bond Formation and (b) C−C Bond Formation



and low catalytic efficiency, even in the racemic manifestation. Due to steric constraints and electronic factors, the susceptibility of ketoimines toward nucleophilic attack is significantly lower compared with the corresponding aldimines.[10] Ketoimines derived from cyclic ketones exhibit generally higher electrophilicity, and the direct catalytic addition to them has been partly addressed by the use of Ir/Mg,[11] Cu(I),[12] and Au catalysis.[13] Quite recently, Larsen et al. disclosed a high-yielding protocol for the direct addition of a terminal alkyne to in situ generated ketoimines derived from acyclic ketones using Cu/Ti bimetallic catalysis.[14,15] Despite the successful broadening of substrate generality, the requirements for high temperature and a substoichiometric amount of $Ti(OEt)_4$ (50 mol %) may be the subject of further improvement.[14]

We hypothesized that simultaneous activation of terminal alkynes and ketoimines compensates for the intrinsic low reactivity of this specific reaction, allowing for the efficient production of the desired propargyl amines bearing a tetrasubstituted carbon (Scheme 2). Catalytic generation of the active nucleophile, Cu-alkynylide, can be achieved by using a soft Lewis acid/hard Brønsted base

Scheme 2. Direct Alkynylation of Ketoimine Based on Simultaneous Activation of Terminal Alkyne and Ketoimine



cooperative catalytic system.[16,17] To render the simultaneous activation in close proximity, soft Lewis basic functionality was installed on the ketoimine. The thiophosphinoyl group[18] emerged as a suitable soft Lewis basic functionality, and the direct addition of phenylacetylene **3a** to ketoimine **2a** proceeded smoothly at 50 °C with 5 mol % of the soft Lewis acid/hard Brønsted base cooperative catalyst comprising $[Cu(CH_3CN)_4]PF_6$, Xantphos, and Li-(OC_6H_4-*p*-OMe) (Scheme 2a).[16b,19] The analogous phosphinoyl-type ketoimine[20] substrate **5** lacking soft Lewis basic functionality failed to afford the corresponding alkynylation product, indicating that the activation of ketoimine **2a** through the interaction between sulfur and copper is crucial to promote the reaction (Scheme 2b). The catalytic system was simplified to mesitylcopper/Xantphos.[21] Cu-phenylacetylide **7** was formed with the liberation of mesitylene in the

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Scheme 3. Direct Alkynylation of Ketoimine Based on the Simultaneous Activation of Terminal Alkyne and Ketoimine

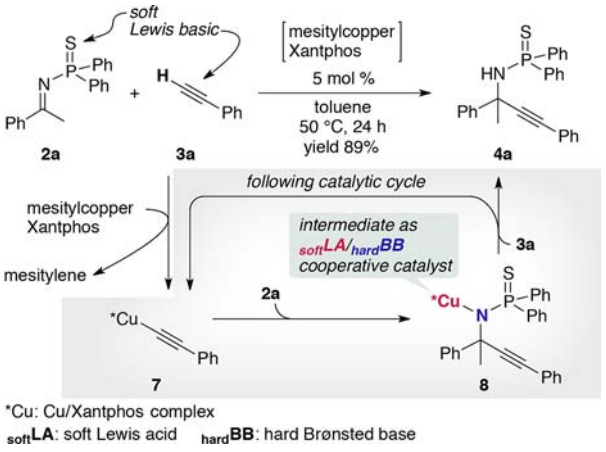
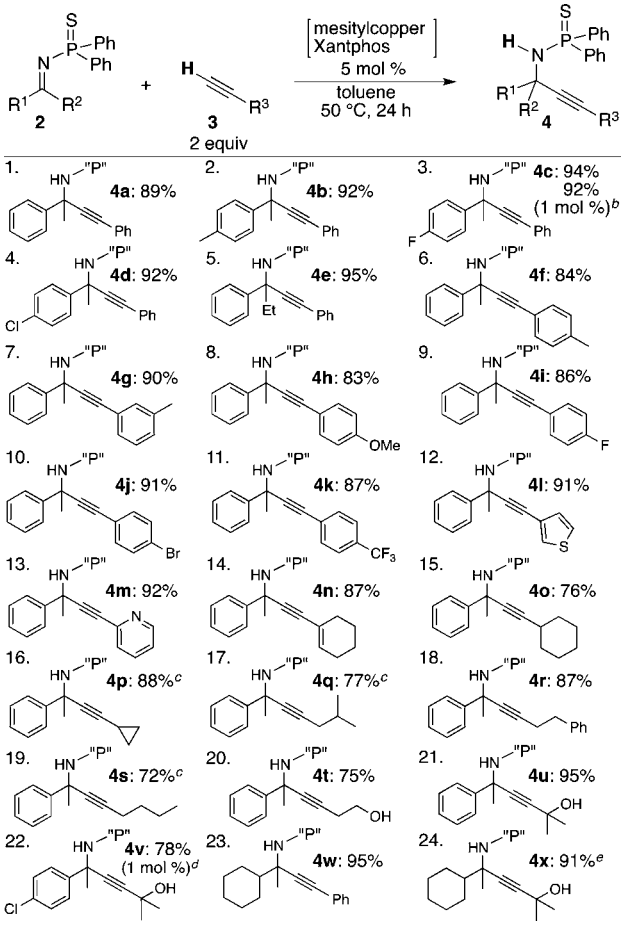
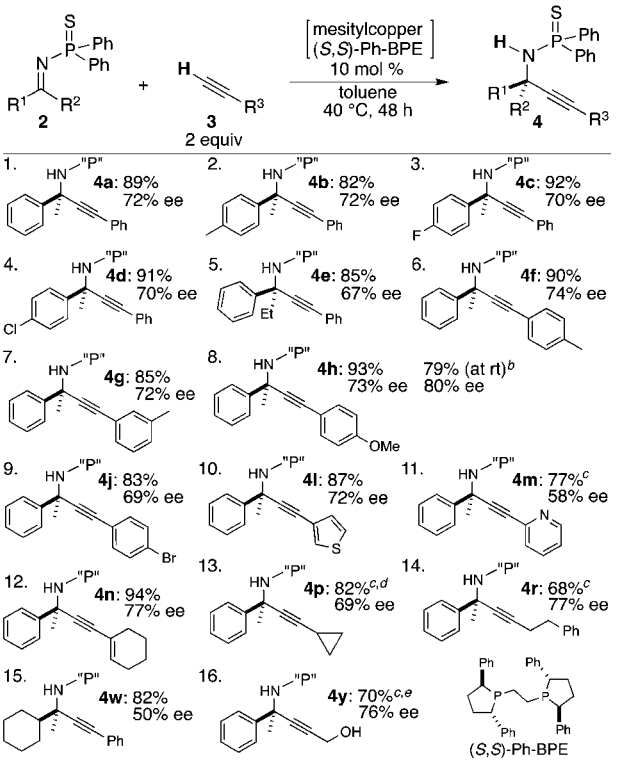


Table 1. Direct Catalytic Alkynylation of Ketoimines[a]



[a] **2**, 0.1 mmol; **3**, 0.2 mmol. "P" stands for diphenylthiophosphinoyl group. [b] Reaction was run at 60 °C for 48 h. [c] 5 equiv (0.5 mmol) of alkyne were used. [d] Reaction was run at 70 °C for 48 h. 1.0 g of ketoimine was used. [e] Reaction was run with dried MS4A (50 mg) in toluene/THF = 1/1 for 48 h.

Table 2. Direct Catalytic Asymmetric Alkynylation of Ketoimines[a]



[a] **2**, 0.1 mmol; **3**, 0.2 mmol. "P" stands for diphenylthiophosphinoyl group. [b] Reaction time was 72 h. [c] Reaction temperature was 50 °C. [d] 5 equiv of alkyne were used. [e] *O*-THP protected propargyl alcohol was used. Acidic treatment (10 mol % of NH_2SO_3H, THF/H_2O = 1/1, at rt, 1 h) afforded **4y**. THP = tetrahydro-2*H*-pyran-2-yl.

initial cycle, and the reaction intermediate Cu-amido complex **8** functioned as a soft Lewis acid/hard Brønsted base cooperative catalyst to drive the following catalytic cycle (Scheme 3).[22]

These reaction conditions showed broad substrate generality (Table 1). High conversion was observed with a 5 mol % catalyst loading irrespective of the electronic nature of the aromatic group or steric factors of the alkyl group adjacent to the ketoimine carbon (entries 1–5). The reaction could be run with as little as a 1 mol % catalyst loading at a marginally higher temperature with a longer reaction time (entry 3). Substituted phenylacetylenes served as suitable substrates in this direct alkynylation, affording the corresponding propargylamine in high yield (entries 6–11). No detrimental effect was observed in the reaction employing terminal alkynes bearing soft Lewis basic thienyl or pyridyl functionality (entries 12, 13). Terminal alkynes bearing branched or linear alkyl substituents could be used

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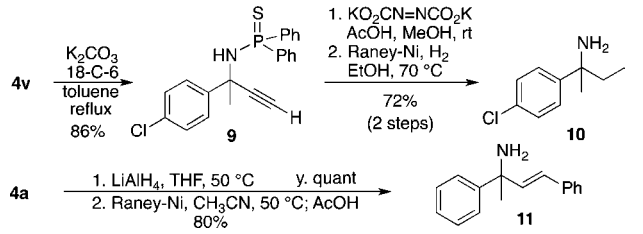
Scheme 4. Transformation of the Alkynylation Product



(entries 14−22). In particular, the successful adaptation of alkynes bearing a free hydroxyl group highlighted the utility of this alkynylation protocol (entries 20−22). The reaction using 2-methylbut-3-yn-2-ol is worth noting because it is an acetylene equivalent, and basic treatment of the product generated a synthetically versatile terminal alkyne (entries 21, 22, vide infra). The reaction could scaled to proceed using 1 g of ketoimine. A ketoimine derived from aliphatic ketone was sufficiently stable under the reaction conditions, and the corresponding alkynylation products **4w** and **4x** were produced (entries 23, 24).

The disclosed efficient protocol for direct alkynylation of ketoimines was rendered asymmetric with the use of (*S*,*S*)-Ph-BPE as a chiral bisphosphine ligand (Table 2). With a range of substrates studied in a racemic system, direct catalytic asymmetric alkynylation proceeded with 10 mol % of a mesitylcopper/(*S*,*S*)-Ph-BPE precatalyst, affording the propargylamines **4** with 50−80% ee.

A screening of chiral ligands showed (*S*,*S*)-Ph-BPE to outperform the other chiral phosphine ligands.[23] Although there is still room for improvement in enantioselectivity, to the best of our knowledge, this is the first example of a direct catalytic asymmetric alkynylation of acyclic ketoimines derived from simple ketones, displaying the utility of a simultaneous activation strategy in asymmetric proton-transfer catalysis.[24]

Subjection of **4v** to K_2CO_3/18-crown-6 in refluxing toluene led to the loss of the acetone unit to afford terminal alkyne **9** in 86% yield (Scheme 4).[25] Diimide reduction of **9** afforded the corresponding saturated product, and subsequent treatment with Raney-Ni under a hydrogen atmosphere cleaved the N−P bond to give free amine **10**.[18b] The reduction of **4a** with $LiAlH_4$ converted the alkyne part to an *E*-configured double bond in quantative yield. Raney-Ni reduction in acetonitrile at 50 °C followed by acidic treatment produced allylic amine **11** in 80% yield.[26]

In conclusion, an efficient protocol for the direct catalytic alkynylation of ketoimines was disclosed. The simultaneous activation of both pronucleophiles and electrophiles, terminal alkynes and ketoimines, is key to achieving high conversion. Despite the moderate enantioselectivity, the present catalysis was implemented to render the reaction asymmetric. Improvements in the enantioselectivity and application of the protocol to the enantioselective synthesis of biologically active compounds are currently underway.

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Supporting Information Available. Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) See Supporting Information.

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The authors declare no competing financial interest.