Enantioselective Catalysis

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A Robust, Efficient, and Highly Enantioselective Method for Synthesis of Homopropargyl Amines**

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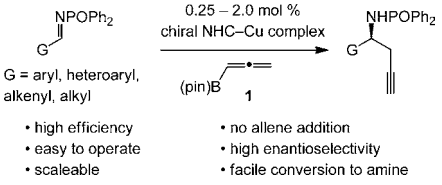
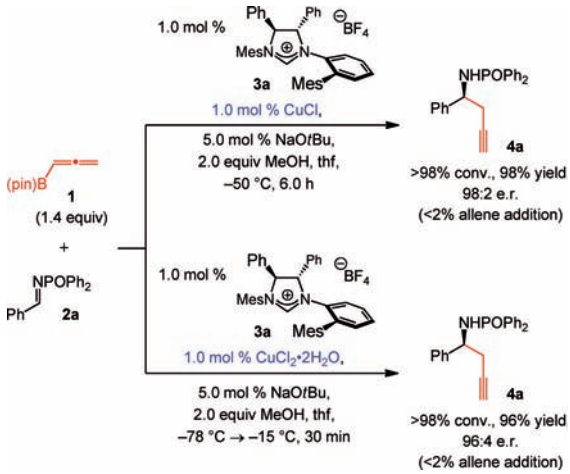
Catalytic protocols that generate α-branched amines efficiently and enantioselectively facilitate the preparation of many important biologically active molecules.[1] Among such entities are homopropargyl amines, used in the total synthesis of a number of natural products.[2] Several investigations have adopted the chiral auxiliary strategy; the desired products are obtained in high diastereoselectivity as trimethylsilyl-substituted alkynes.[3] In contrast, the corresponding catalytic protocols are scarce. The first relevant report included three examples of reactions of allenyl stannanes with a glyoxylate-derived tosylimine,[4] affording homopropargyl sulfonamides in 34–96% yield and 55:45–93:7 enantiomeric ratio (e.r.).[5] A notable recent advance entails enantioselective additions of a readily available allenylboron to tosylimines catalyzed by a Ag-phosphine catalyst to furnish a wider range of products and higher enantioselectivity (87:13 to more than 98:2 e.r.). Nonetheless, reactions of substrates that do not bear an aryl substituent proved to be less efficient, those of enolizable alkyl-substituted tosylimines were not reported and, as with the aforementioned initial development, removal of the tosyl unit requires strong reducing conditions.[6–8]

Herein, we present a broadly applicable and efficient catalytic method for enantioselective synthesis of homopropargyl amides (Scheme 1); acid hydrolysis generates the parent amines. Transformations are performed with 0.25–2.0 mol% of a chiral N-heterocyclic carbene (NHC) complex of copper, derived from a readily available chiral imidazolinium salt and CuCl or the more robust $CuCl_2 \cdot 2H_2O$, both of which are commercially available. Aryl-, heteroaryl-, alkenyl-, as well as alkyl-substituted *N*-phosphinoyl imines can serve as substrates. Additions proceed to completion in seven hours or less, delivering homopropargyl amides in 65% to more than 98% yield and 92:8 to more than 98:2 e.r. The Cu-catalyzed process is amenable to gram-scale operations, and can be performed in a common fume hood without the need for strictly anhydrous and/or oxygen-free conditions.



Scheme 1. A practical and broadly applicable, efficient, and highly enantioselective method for synthesis of homopropargyl amines.

We began by probing the capacity of chiral C_1-symmetric imidazolinium salt[9] **3a** (Scheme 2), effective for reactions of



Scheme 2. NHC–Cu-catalyzed propargyl addition can be performed with CuCl or the air-stable $CuCl_2 \cdot 2H_2O$ with exceptional efficiency and high enantioselectivity. Mes = 2,4,6-$(Me)_3C_6H_2$.

allylborons with *N*-phosphinoyl imines,[10] in serving as the catalyst precursor. In the presence of the NHC–Cu complex prepared in situ with CuCl and NaO*t*Bu, more than 98% conversion is achieved within six hours, and the desired amine **4a** is formed in 98% yield and 98:2 e.r (Scheme 2, top). None of the allene addition product is formed (less than 2%, as judged by 400 MHz ^{1}H NMR analysis). When $CuCl_2 \cdot 2H_2O$, more stable to air and moisture than CuCl, is utilized, the reaction is complete in 30 min and similarly enantioselective (Scheme 2). The practicality of the catalytic process is underlined by the gram-scale transformation shown in Scheme 3. The reaction is performed with 0.25 mol% of the catalyst in a standard fume hood; treatment of the product mixture with aqueous HCl affords the homopropargyl amine (**5**) in 86% overall yield and 96:4 e.r. The desired product is isolated in analytically pure form after routine aqueous wash without the need for costly silica gel chromatography and the associated

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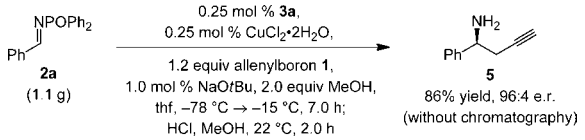
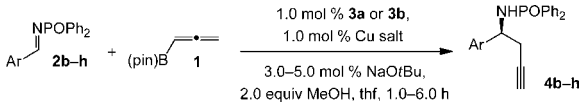


Scheme 3. Gram-scale NHC–Cu-catalyzed homopropargyl amine synthesis performed in a standard fume hood.

solvents. The amide can be obtained through simple trituration; such ease of isolation is due to the strong tendency of *N*-phosphinoyl amides to be crystalline.[11,12]

Enantioselective homopropargyl amine synthesis can be performed with a range of aryl-substituted imines; transformations proceed to completion with 1.0 mol % of the chiral catalyst (Table 1). Regardless of whether the substrate carries an electron-withdrawing (entries 2, 5 and 6), electron-donating (entries 4 and 7), or a sterically demanding aryl group (entries 1 and 3), products are isolated in 88–98 % yield and 93:7–98:2 e.r. Reaction times span from one to six hours; either CuCl or the more robust $CuCl_2{\cdot}2H_2O$ can be used. Homopropargyl amides are obtained in high yield regardless of the metal salt employed.

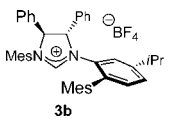
Table 1: NHC–Cu-catalyzed enantioselective propargyl additions to aryl-substituted aldimines.[a]



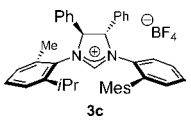
Entry	Substrate (Ar)	3	With CuCl		With $CuCl_2{\cdot}2H_2O$	
			yield [%][b]	e.r.[c]	yield [%][b]	e.r.[c]
1	**2b** (2-naphthyl)	**3b**	97	98:2	95	94:6
2	**2c** (*o*-FC_6H_4)	**3a**	96	97.5:2.5	96	95:5
3	**2d** (*o*-MeC_6H_4)	**3a**	93	97.5:2.5	92	94:6
4	**2e** (*o*-$MeOC_6H_4$)	**3a**	97	97:3	98	94:6
5	**2f** (*m*-BrC_6H_4)	**3a**	97	96:4	93	93:7
6	**2g** (*p*-ClC_6H_4)	**3a**	92	97:3	88	96:4
7	**2h** (*p*-$MeOC_6H_4$)	**3a**	98	97:3	92	96:4

[a] Reactions were performed in an N_2 atmosphere. Addition reactions with CuCl: 3.0 mol % NaO*t*Bu at −50 °C for 6.0 h; addition reactions with $CuCl_2{\cdot}2H_2O$: 5.0 mol % NaO*t*Bu at −78→−15 °C for 1.0 h; 1.4 equiv of **1** in all cases. Less than 2 % allene addition in all cases. [b] Yields of isolated purified products (±5 %). [c] Determined by HPLC analysis (±2 %). See the Supporting Information for all experimental details and analytical data.

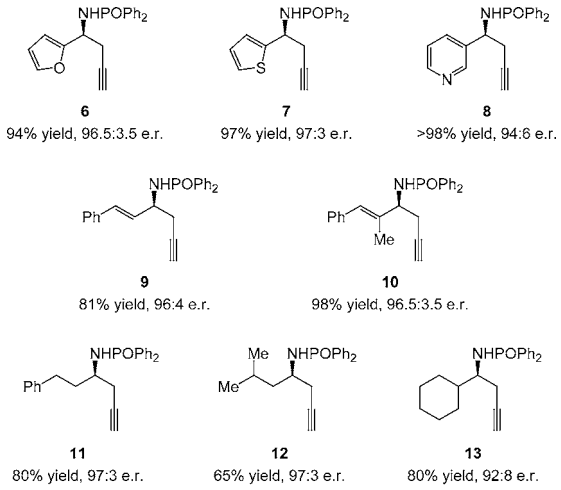
The occasional use of structurally modified imidazolinium salts, such as **3b** (Table 1, entry 1), is not because the catalyst derived from **3a** is ineffective. Rather, in some cases, slightly higher efficiency and/or enantioselectivity can be attained with modified NHC–Cu complexes **3b** and **3c**. For example, with **3a**, formation of **4b** proceeds to more than 98 % conversion, affording **4b** in 96 % yield and 95:5 e.r. (vs. 97 % yield and 98:2 e.r. with **3b**).



3b



3c

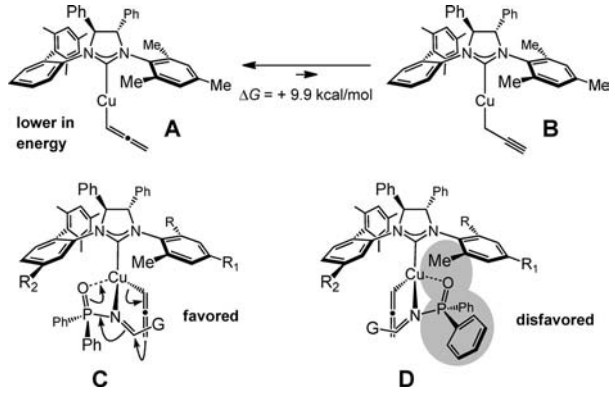


>98% conv. and >98% propargyl addition product in all cases

Scheme 4. NHC–Cu-catalyzed enantioselective synthesis of heteroaryl-, alkenyl-, and alkyl-substituted homopropargyl amines. (Conditions as in Table 1 with **3a** and $CuCl_2{\cdot}2H_2O$, except **3c** used for **13**. See the Supporting Information for details.)

Heterocycle-, alkenyl-, and alkyl-substituted *N*-phosphinoyl imines serve as substrates (Scheme 4). Enantioselective additions proceed readily with O-, as well as S- or N-substituted heterocyclic aldimines without detectable catalyst inhibition (**6**–**8**, Scheme 4); homopropargyl amides are isolated in 94 % to more than 98 % yield and 94:6–97:3 e.r. Allylamide **9** and the more sterically hindered **10** (Scheme 4) are obtained in similarly high yields and enantiomeric purities (81 % and 98 % yield, and 96:4 and 96.5:3.5 e.r., respectively). The catalytic protocol can be readily extended to substrates that bear a linear, β- or α-branched alkyl group (**11**–**13**, Scheme 4); products are isolated in 65–80 % yield and in 92:8–97:3 e.r. Optimal results for synthesis of **13** are obtained with the catalyst derived from imidazolinium salt **3c**; 90.5:9.5 and 90:10 e.r. and 76 % and 83 % yield are obtained, respectively, with **3a** and **3b**. In all transformations shown in Scheme 3, conditions involve the more robust Cu^{II} salt (1.0 mol % loading, 1.0 h). As with aryl-substituted imines (Scheme 2 and Table 1), the additions proceed with similar efficiency and slightly higher enantioselectivity when CuCl is used; for example, thienyl **7** and pyridyl **8** are generated in 91 % yield and 95 % yield and in more than 98:2 and 97:3 e.r., respectively (with **3a** as catalyst precursor; more than 98 % conversion and less than 2 % allene addition).[13]

The NHC–Cu-catalyzed processes likely involve allenyl–copper species, such as **A** (Scheme 5).[14] Complex **A** originates from the corresponding Cu–alkoxide, either by σ-bond metathesis with the allenylboron **1**, or through ligand exchange via allenylboronate derived from addition of a metal alkoxide to **1**.[15] Computational studies[16] point out that the Cu–allene is energetically favored as opposed to the alternative, and probably more nucleophilic, Cu–propargyl (**A** is 9.9 kcal mol^{-1} lower in energy compared to **B**; Scheme 5); the alkynyl complex would produce the unobserved allenyl amides. Examination of the geometry-optimized structures of **C** and **D** indicates that the mode of



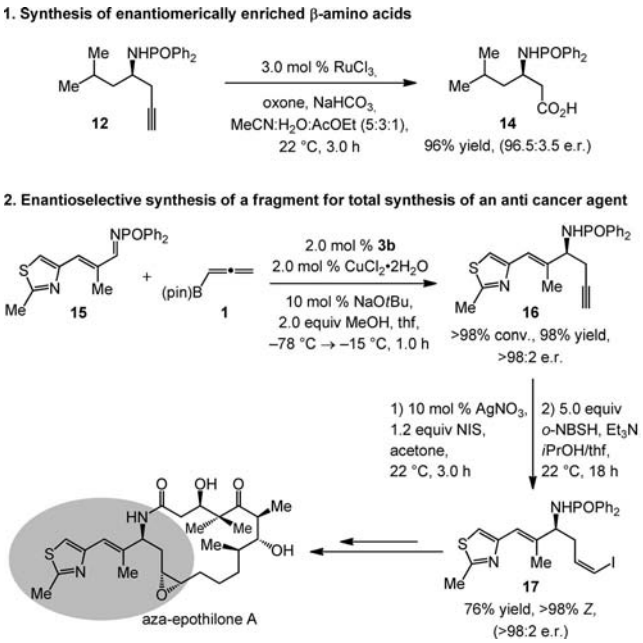
Scheme 5. Theoretical studies point to a strong energetic preference for the NHC–Cu–allenyl **A** versus the derived propargyl complex **B** and a model that accounts for the observed stereochemical outcomes.

reaction **C**, with the substrate coordinating from the most accessible quadrant of the chiral complex is preferred (vs. **D**);[16] such a scenario accounts for the identity of the observed major enantiomers.[17]

The strong preference for the intermediacy of allenyl–copper **A** (vs. the propargyl derivative **B**) might be the reason that the processes presented here are operationally more robust than the corresponding allyl additions.[10] Although the Cu^{II} salt can be used in either case, unless stringently controlled conditions are adopted, there is significant diminution in e.r. when allylcopper intermediates are involved. For example, when the reaction with (pinacolato)allylboron and **2a** is carried out under the conditions shown in Scheme 2 (bottom reaction), the desired homoallyl amide is generated in 84:16 e.r. (vs. 97:3 e.r. under strictly inert (glove box) conditions). Such disparity may originate from the higher sensitivity of the more nucleophilic allylmetals ($Cu–C_{sp^3}$ vs. $Cu–C_{sp^2}$ in allenylmetals; see Scheme 6). Moreover, when $CuCl_2 \cdot 2H_2O$ is used, transformations are likely catalyzed by an NHC–Cu^{I} complex,[18] a scenario supported by the close similarity of the stereochemical outcomes compared to processes involving CuCl. The in situ reduction of the transition metal thus occurs under the reaction conditions.[19]

The two instances depicted in Scheme 6 demonstrate utility. As illustrated by the formation of **14**, the homopropargyl amides can be transformed to the derived carboxylic acids through an efficient and mild Ru-catalyzed transformation.[20] The corresponding β-amino acids, building blocks in the preparation of biologically active molecules,[21] can be accessed by removal of the phosphinoyl group (see Scheme 3).

The second application is connected to the preparation of the amine segment of the anticancer agent aza-epothilone A (Scheme 6).[22] Catalytic enantioselective addition to heterocyclic aldimine **15** proceeds in 98% yield and more than 98:2 e.r. Homopropargyl amide **16** is then converted to the derived iodoalkyne and subsequently reduced[23] with complete *Z* selectivity to deliver **17** in 76% overall yield and exceptional enantiomeric purity. The *Z*-vinyl iodide (**17**) can be utilized in enantioselective synthesis of the biologically active target or



Scheme 6. Representative examples demonstrate the utility of the NHC–Cu-catalyzed method for enantioselective synthesis of homopropargyl amines; *o*-NBSH = *o*-nitrobenzenesulfonylhydrazide.

other members of the same family through a formerly reported strategy based on catalytic cross-coupling.[24]

In summary, we introduce the first practical, general, and efficient method for catalytic enantioselective preparation of homopropargyl amines. The protocol requires a catalyst composed of an inexpensive metal salt, a chiral ligand that can be prepared in four or five steps, and the allenylboron reagent, which can be purchased; product isolation is straightforward and inexpensive. Design and development of additional chiral catalysts for efficient and enantioselective C–C bond forming processes with readily accessible organoboron reagents is in progress.

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