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# Highly Enantioselective Access to Primary Propargylamines: 4-Piperidinone as a Convenient Protecting Group

**Patrick Aschwanden, Corey R. J. Stephenson, and Erick M. Carreira***

*Laboratorium für Organische Chemie, ETH Zurich, CH-8093 Zürich, Switzerland*

*carreira@org.chem.ethz.ch*

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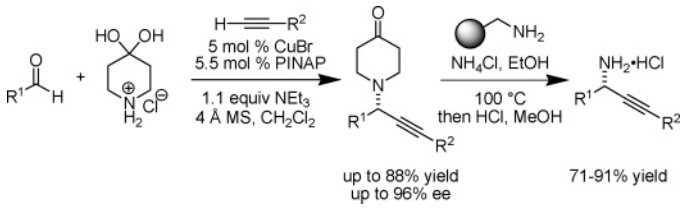
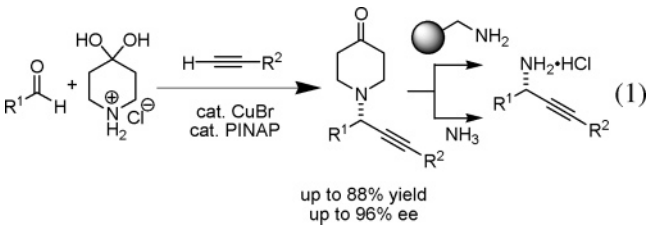
## ABSTRACT




**We report a highly enantioselective, catalytic three-component coupling of aldehydes, alkynes, and 4-piperidone hydrochloride hydrate to afford the corresponding tertiary propargylamines in useful yields. The selective cleavage of the piperidone protecting group using either ammonia/EtOH or a polymer-supported scavenger amine furnishes primary propargylamines.**

Propargylamines can serve as versatile building blocks and high-value-added intermediates for organic synthesis.[1] However, methods that provide reliable and convenient access to propargylamines are few.[2,3] First reported in 1963,[4] the Cu-catalyzed additions of terminal alkynes to in situ generated iminium ions have recently received increased attention.[5,6] Herein, we document that 4-piperidone can be used as the amine component in the Cu-catalyzed addition reactions of terminal alkynes to C═N electrophiles to provide aldimine adducts chemoselectively in useful yields and selectivities (eq 1). The fact that 4-piperidones can be employed in the addition reaction is surprising and leads to the production of useful building blocks for asymmetric synthesis. Significantly, we describe that the substituted 4-piperidone can be readily removed, conveniently furnishing optically active primary, propargylic amines.




We have recently reported the synthesis of a new class of P,N-ligands, which we have termed PINAP.[7] Our interest in the chemistry of terminal alkynes[8] compelled us to

(1) For a review, see: Aschwanden, P.; Carreira, E. M. Addition of Terminal Acetylides to C═O and C═N Electrophiles. In *Acetylene Chemistry: Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinski, R. R., Eds.; Wiley: Weinheim, 2005.

(2) For addition of alkynylides to imines, see: (a) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970. (b) Harwood, L. M.; Vines, K. J.; Drew, M. G. B. *Synlett* **1996**, 1051. (c) Brasseur, D.; Marek, I.; Normant, J.-F. *Tetrahedron* **1996**, *52*, 7235. (d) Sato, Y.; Nishimata, T.; Mori, M. *Heterocycles* **1997**, *44*, 443. (e) Cossy, J.; Poitevin, C.; Pardo, D. G.; Peglion, J.-L.; Dessinges, A. *Synlett* **1998**, *3*, 251. (f) Courtois, G.; Desre, V.; Miginiac, L. *J. Organomet. Chem.* **1998**, *570*, 279. (g) Florio, S.; Troisi, L.; Capriati, V.; Suppa, G. *Eur. J. Org. Chem.* **2000**, *65*, 3793. (h) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2001**, *123*, 5122. (i) For the copper-mediated addition of acetylene gas to *N*-alkyl imines at elevated temperatures, see: Rohm & Haas Co. U.S. Patent 2 665 311, 1950.

(3) For representative additions of other carbanions to imines, see: (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (b) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (c) Hamada, T.; Mizojiri, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2000**, *122*, 7138. (d) Knudsen, K.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (e) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984. (f) Wipf, P.; Stephenson, C. R. J.; Okumura, K. *J. Am. Chem. Soc.* **2003**, *125*, 14694.

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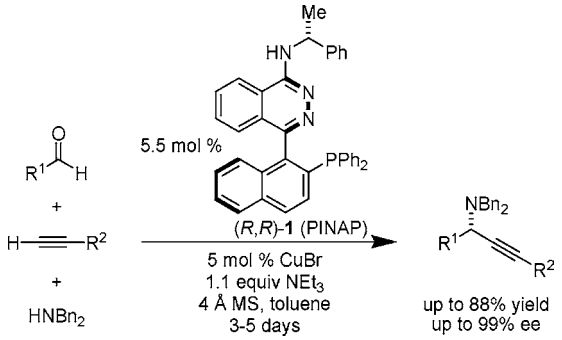
examine these ligands in the Cu-catalyzed three-component coupling of alkynes, aldehydes, and secondary amines. We have observed that the Cu$^{I}$ PINAP complexes of (*R*,*R*)-**1** and (*R*,*S*)-**1** catalyze the formation of the propargylamines in 90−99% ee, which are among the best values obtained to date (Scheme 1).

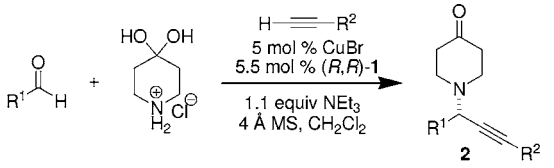
**Scheme 1.** CuBr-Catalyzed Three-Component Coupling




The tertiary propargylamines derived from the aldimines formed in situ in the condensation of *N*,*N*-dibenzylamine, and aldehyde reagents have a limitation: the selective cleavage of the *N*,*N*-dibenzyl protecting groups cannot be effected with ease without sacrificing the triple bond. Consequently, the addition reactions have also been performed with *N*,*N*-diallylamine; however, the utility of these alternative adducts is not without its own limitations because the enantioselectivities of the products isolated from the corresponding *N*,*N*-diallyl aldimines were at best 78% ee, and the deprotection could only be effected with Pd catalysts and a large excess (8 equiv) of allyl scavengers.[9] Although alternative amines have been employed, they all ultimately rely on the use of a noble metal catalyst (Pd) in the deprotection. It would seem regrettable that a process that benefits from the use of an inexpensive base metal (Cu) should resort to a subsequent deprotection step involving Pd catalysis. Thus, we sought alternative secondary amines for this process that would meet two criteria: (1) propargylamine formation in high yield and selectivities and (2) subsequent facile, chemoselective cleavage to give rise to primary propargylamines.

In a key experiment, commercially available 4-piperidone hydrochloride hydrate[10] was subjected to a suspension of 5 mol % of CuBr, triethylamine, isobutyraldehyde, phenylacetylene, and 4 Å molecular sieves in toluene giving rise to the corresponding tertiary propargylamine (Table 1). In the course of optimization studies, a variety of different ligands were examined in the reaction conditions described above revealing that ligand (*R*,*R*)-**1** afforded the desired products in the highest ee's and favorable yields. In addition, it was found that the complex formed between CuBr and

**Table 1.** Three-Component Coupling Using 4-Piperidone·HCl




| entry | $R^1$ | $R^2$ | product | time | yield | % ee |
|---|---|---|---|---|---|---|
| 1 | $^n$Bu | $SiMe_3$ | **2a** | 22 h | 73% | 90% ee[c] |
| 2 | *i*Pr | $SiMe_3$ | **2b** | 22 h | 83% | -95% ee[ce] |
| 3[a] | *i*Pr | $SiMe_3$ | ***ent*-2b** | 22 h | 88% | 96% ee[c] |
| 4 | Et, Et | $SiMe_3$ | **2c** | 22 h | 82% | 95% ee[c] |
| 5 | O | $SiMe_3$ | **2d** | 36 h | 58% | 90% ee |
| 6 | *c*-$C_6H_{11}$ | $SiMe_3$ | **2e** | 22 h | 75% | -93% ee[ce] |
| 7 | *c*-$C_3H_5$ | $SiMe_3$ | **2f** | 22 h | 92% | -89% ee[ef] |
| 8 | $C_6H_5(CH_2)_2$- | $SiMe_3$ | **2g** | 22 h | 84% | -85% ee[ce] |
| 9[ab] | *i*Pr | Ph | **2h** | 22 h | 82% | 85% ee |
| 10[ac] | *i*Pr | Ph | ***ent*-2h** | 22 h | 79% | -83% ee[d] |
| 11[ac] | *i*Pr | $(CH_2)_2Ph$ | **2i** | 22 h | 72% | 70% ee |

[a] Because of its volatility, isobutyraldehyde (1.0 mmol, 2.0 equiv) was used in slight excess under otherwise identical reaction conditions. [b] An equimolar amount of alkyne (0.50 mmol, 1.0 equiv) was used under otherwise identical reaction conditions. [c] After desilylation using $K_2CO_3$ in MeOH, ee's were determined by GC or HPLC. [d] PINAP ligand (*R*,*S*)-**1** was used. [e] PINAP ligand (*S*,*S*)-**1** was used. [f] Determined by conversion of the deprotected product to its corresponding MTPA amide.

(4) Brannock, K. C.; Burpitt, R. D.; Thweatt, J. G. *J. Org. Chem.* **1963**, *28*, 1462.

(5) (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (b) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268. (c) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (d) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473. (e) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (f) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem.−Eur. J.* **2003**, *9*, 2797. (g) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

(6) For the Ir-catalyzed addition of terminal alkynes to iminiums, see: Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319.

(7) Knöpfel, T. E.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.

(8) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245. (b) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (c) Boyall, D.; Lopez, F.; Sasaki, H.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 4233. (d) Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 964. (e) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017. (f) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687. (g) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605. (h) Diez, R. S.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, *58*, 8341. (i) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813. (j) Knöpfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054. (k) Fischer, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 1497. (l) Knöpfel, T.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682.

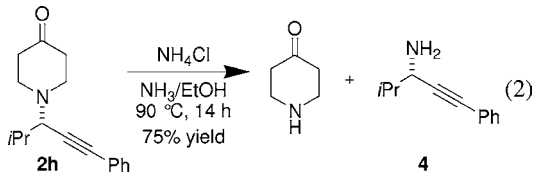
(9) For the use of bis(2-phenylallyl)amine in the asymmetric addition of Cu acetylides to iminium ions, see: Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175.

(10) To obtain fast conversion, the crystalline 4-piperidone hydrochloride hydrate had to be crushed to a fine powder.

(*R*,*R*)-**1** was completely soluble in dichloromethane thus leading to an increase (up to 5-fold) in reaction rate compared to that using toluene as solvent. This is well worth highlighting, as the reactions reported earlier prescribed long reaction times (>48 h). To determine the scope and limitations of the improved protocol, a representative set of aldehydes and terminal alkynes were subjected to the reaction conditions.

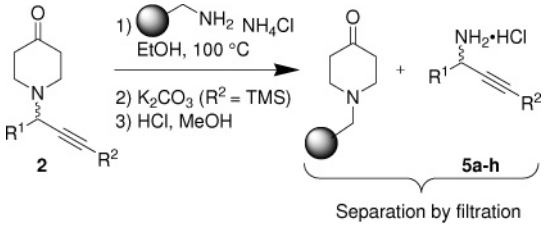
Trimethylsilylacetylene was the alkyne of choice in the three-component coupling as it not only allowed for subsequent cleavage to the terminal alkyne but also afforded the desired propargylamines in good yields and superior enantioselectivities. Subjecting phenylacetylene or 4-phenyl-1-butyne to the reaction conditions led to diminished ee's. The new protocol has been shown to tolerate a variety of different aldehydes to afford the desired products in useful optical purity and yields. Volatile aldehydes, such as isobutyraldehyde, can be used in excess to consistently obtain optimal yields. It is noteworthy that *n*-alkyl aldehydes were excellent substrates for this method (Table 1, entry 1). They are often challenging in other asymmetric processes because of low steric hindrance (leading to low ee's) and oligomerization side reactions (leading to low yields). Interestingly, 2-furaldehyde was also shown to participate in the three-component coupling affording the corresponding propargylamine in high enantiomeric excess. The use of benzaldehyde did not lead to satisfactory results even under prolonged stirring providing the desired product in only 22% yield after 48 h.

It is interesting to note that the additions are chemoselective for the aldehyde-derived iminium and that no addition is observed to either the aldehyde or the ketone. To the best of our knowledge, there is only one mention in the literature of the use of N-substituted piperidones as a precursor to primary amines.[11] It was reported that optimal conditions for deprotection involved the use of excess 2-butylamine. For the substrates we investigated, this was not the case. Thus, the application of this method to the deprotection of the tertiary propargylamines was unsuccessful because of difficulties in separating the desired primary propargylamine from 2-butylamine by either chromatography on silica or bulb-to-bulb distillation. We thus proceeded to examine other amines and their hydrochloride salts, which could be easily separated in the end from the desired primary products. We were particularly interested in the use of ammonia because it would enhance the practical aspects of the route to primary amines. In preliminary studies, a suspension of propargylamine **2h**, ammonium chloride, and ammonia-saturated ethanol was stirred at 90 °C in a pressure tube for 14 h (eq 2). Removal of the solvent under reduced pressure afforded a dark yellow oil which was purified by chromatography on silica gel (5% MeOH in EtOAc) to furnish the desired primary propargylamine **4** in 75% yield.[12]




Aside from the necessity of column chromatography, handling the low molecular weight primary amines proved difficult. Isolating the product as its hydrochloric acid salt was an attractive option; however, the desired propargylic amine salts were inseparable from the piperidone hydrochloride. The use of a solid-supported scavenger[13] to immobilize the piperidone byproduct was investigated to streamline the isolation process. Indeed, heating of a mixture of **2h**, amino-methylated polystyrene resin (1.5 equiv),[14] and $NH_4Cl$ (1 equiv) in EtOH at 100 °C (sealed tube) resulted in complete conversion of **2h** to the desired primary amine (Table 2, entry 1). After filtration of the mixture, the solution was cooled to 0 °C, treated with a solution of HCl in MeOH, and concentrated to afford **5h**. For the corresponding trimethylsilyl propargylamines (entries 2−7), partial desilylation of the alkyne was observed on treatment with the

**Table 2.** Deprotection Using a Resin-Bound Dienone Scavenger[a]




| entry | amine | $R^2$ | product | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | **2h** | Ph | **5h** | 5 | 91 |
| 2 | **2a** | $SiMe_3$ | **5a** | 14 | 82 |
| 3 | ***ent*-2b** | $SiMe_3$ | **5b** | 14 | 81 |
| 4 | **2c** | $SiMe_3$ | **5c** | 14 | 79 |
| 5 | **2e** | $SiMe_3$ | **5e** | 14 | 86 |
| 6 | **2f** | $SiMe_3$ | **5f** | 14 | 71 |
| 7 | **2g** | $SiMe_3$ | **5g** | 14 | 85 |

[a] A suspension of piperidone (1 equiv), PS-$NH_2$ (1.5 equiv), and $NH_4Cl$ (1 equiv) in EtOH was heated at 100 °C for 14 h, cooled, and filtered. $K_2CO_3$ (1.5 equiv) was added to the filtrate, and the reaction was stirred for 2−5 h followed by aqueous workup. The organic layer was cooled to 0 °C, treated with a solution of HCl in MeOH, and concentrated. The residue was dissolved in MeOH, treated with activated charcoal, filtered, and concentrated to afford the desired amine hydrochloride salts.

(11) Renaud, P.; Betrisey, I. *Synth. Commun.* **1995**, *25*, 3479.

(12) Hydrogenation of the triple bond in **4** afforded the known primary amine 3-amino-2-methyl-5-phenylpentane, which allowed for the assignment of the absolute configuration obtained in the three-component coupling reaction. The observed optical rotation for this amine was found to be in good agreement with the known value for the (*R*)-enantiomer. See: Son, Y. C.; Park, C. H.; Koh, J. S.; Choy, N. Y.; Lee, C. S.; Choi, H.; Kim, S. C.; Yoon, H. S. *Tetrahedron Lett.* **1994**, *35*, 3745.

(13) (a) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874. (b) Eames, J.; Watkinson, M. *Eur. J. Org. Chem.* **2001**, 1213. (c) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 573. (d) Cork, D.; Hird, N. *Drug Discovery Today* **2002**, *7*, 56. (e) *Handbook of Reagents for Organic Synthesis: Reagents for High-Throughput Solid-Phase and Solution-Phase Organic Synthesis*; Wipf, P., Ed.; Wiley: Chichester, 2005.

(14) Aminomethylated polystyrene EHL (200−400 mesh, 2.5% cross-linking with divinylbenzene, loading of 3 mmol/g) was purchased from Novabiochem.

supported amine. An intermediate step was thus introduced to complete desilylation, and treatment with a solution of HCl in MeOH and activated charcoal to remove colored impurities followed by concentration afforded the desired hydrochloride salts in 71−86% yield.

In summary, we have developed a highly enantioselective, catalytic three-component coupling of aldehydes, alkynes, and 4-piperidone hydrochloride hydrate using PINAP ligands and CuBr. The desired tertiary propargylamines are isolated in useful yields and enantioselectivity. The use of 4-piperidone as the amine component not only provides access to a useful building block but also highlights the exquisite chemoselectivity of the process. With respect to practicality, we have shown that the tertiary amine adducts undergo deprotection when treated with ammonia/ethanol as well as in the presence of a polymer-supported amine scavenger. The former method may find use on a larger scale, whereas the latter offers experimentally convenient access, particularly on a smaller scale, to optically active primary amines without the need for purification by chromatography. The use of 4-piperidinone as an ammonia equivalent sets the stage for further investigations in other processes where an ammonia equivalent may be necessary (such as arene amination and Strecker), the results of which will be reported as they become available.

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

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