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Enantioselective Addition of Terminal Alkynes to Isolated Isoquinoline Iminiums

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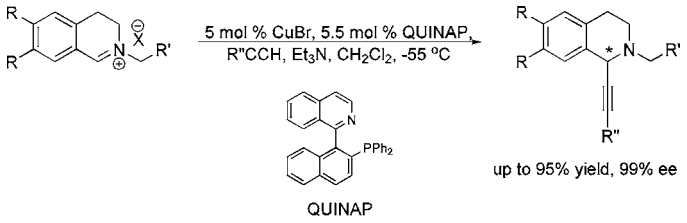
ABSTRACT



The asymmetric, catalytic addition of terminal alkynes to discrete alkyliminium species in the presence of copper bromide, QUINAP ligand, and triethylamine is reported. The reaction proceeds in high yield and high enantiomeric excess with a variety of substrates in solution and is also amenable to solid-phase synthesis.

A recently reported diversity-oriented synthetic pathway (Figure 1) uses the addition of a nucleophile to an isolated alkylisoquinolinium ion (**1**) to set the absolute stereochemistry of all the products of the pathway.[1] At the outset of the current study, we were not aware of a satisfactory method to control the absolute stereochemistry of this key reaction. Recently, Knochel and co-workers reported the copper-catalyzed, asymmetric addition of terminal alkynes to enamines and, in one pot, to aldehydes and amines.[2] Since these reaction conditions, involving the generation of an alkyliminium species generated in situ, are not directly applicable to our substrate, we investigated their modifcation for application to the isolated iminium intermediates of our pathway. Here, we report enantioselective additions of terminal alkynes to isolated alkylisoquinoliniums catalyzed by copper bromide and QUINAP. These conditions afford propargylamine products in high yield and high enantiomeric excess with substrates in solution. These conditions are also compatible with solid-phase synthesis and lead to resin-bound tetrahydroisoquinolines in high yield and purity with good enantioselectivity.

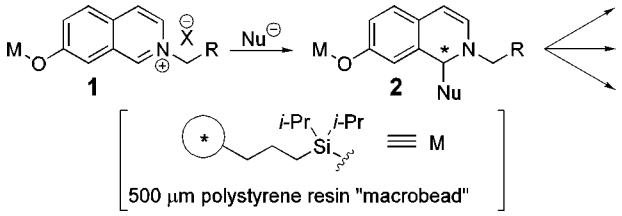


Figure 1. Previously reported diversity-oriented synthesis (DOS) of isoquinoline-derived alkaloids.[1] No general method existed to control the absolute stereochemistry of the addition reaction prior to the studies reported here.

In the DOS pathway depicted in Figure 1, alkylisoquinolinium intermediate **1** undergoes nucleophilic addition to

(1) Taylor, S. J.; Taylor, A. M.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1681.

(2) (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

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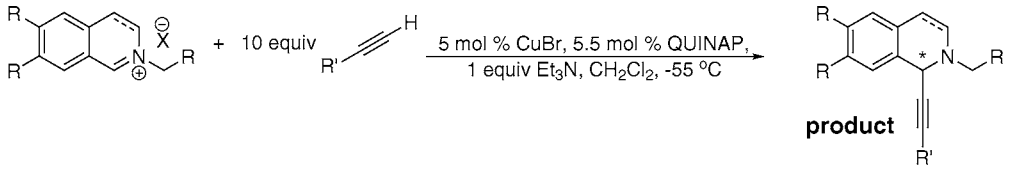
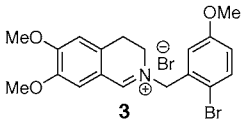
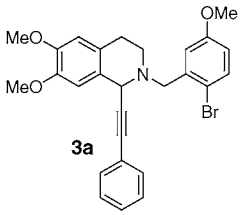
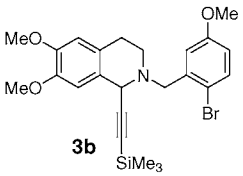
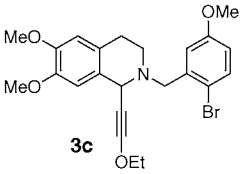
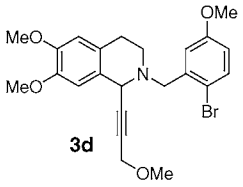
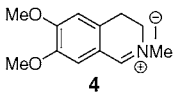
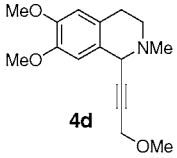
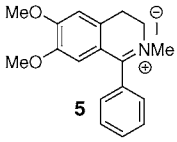
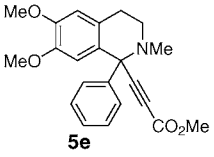
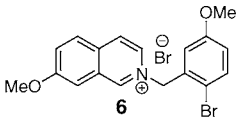
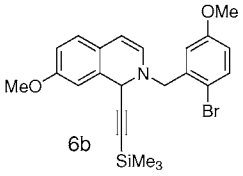
Table 1. CuBr-Catalyzed Addition of Terminal Alkynes to Selected Alkylisoquinolinium Salts



entry	isoquinolinium	alkyne (R^1)	product	yield (%)[a,b]	ee (%)[a,c]
1	 **3**	**Ph (a)**	 **3a**	**85**	**95**
2	**3**	**Si(Me)$_3$ (b)**	 **3b**	**91**	**99**
3	**3**	**OEt (c)**	 **3c**	**95**	**70**
4	**3**	**CH$_2$OMe (d)**	 **3d**	**78**	**98**
5	 **4**	**d**	 **4d**	**71**	**94**
6	 **5**	**CO$_2$Me (e)**	 **5e**	**75**	**0**[d]
7	 **6**	**b**	 **6b**	**67**[e]	**83**

[a] Based on the average of two experiments, each with the opposite enantiomer of the ligand. [b] Isolated yield of spectroscopically pure compound. [c] Enantiomeric excess determined by chiral HPLC. [d] Based on an experiment with only one enantiomer of ligand. [e] Conducted at −20 °C.

form enamine **2**, which is the branching substrate that leads to a number of different alkaloid skeletons. The lack of an accessible coordination site in the iminium species, such as from the lone pairs of a carbonyl (as in the system developed by Shibasaki and co-workers[3]), precludes asymmetric induction by the coordination of a chiral Lewis acid. Instead, we explored an enantioface-selective addition using a chiral

(3) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784.

nucleophile. For this addition, copper acetylides proved optimal because they can be generated in situ and because copper is known to bind well to a number of chiral ligands.[4]

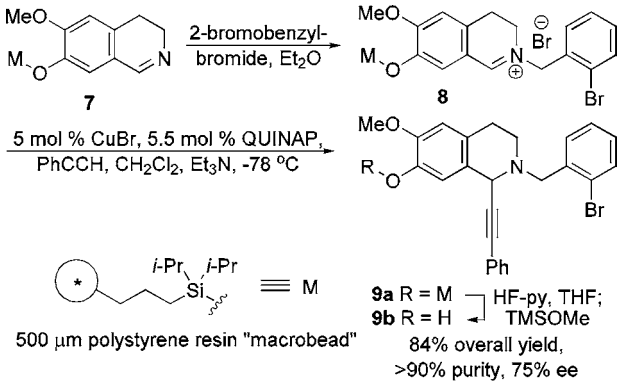
Although our studies began with investigations into the control of nucleophilic additions to isoquinolinium ions similar to **1**, such substrates proved unsuitable for optmization due to the instability of their enamine products.[5] Instead, 2-(2-bromo-5-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide **3** was selected as a model substrate because of the commercial availability of the precursor dihydroisoquinoline and the ease with which the propargylic amine products could be analyzed by chiral HPLC and SFC. These iminium salts were generated in high yield (typically greater than 90%) by isolation of the precipitate following treatment of commercially available 6,7-dimethoxy-3,4-dihydroisoquinoline with an alkylating agent such as 2-bromo-5-methoxy-3,4-dihydroisoquinoline in refluxing diethyl ether.[6]

Methylene chloride was chosen as the solvent for the copper-catalyzed additions because of its ability to solvate the starting iminium salts completely, which proved necessary for high yields. After a series of optimization experiments with various chiral ligands and copper(I) salts, we selected the ligand and metal system arrived at by Knochel: 5 mol % of CuBr, 5.5 mol % of QUINAP.[4a] Exposure of a 0.1 M solution of dihydroisoquinolinium **3** to excess phenylacetylene under these conditions in the presence of 1 equiv of triethylamine at −55 °C for 48 h afforded propargylamine **3a** in 85% isolated yield and 95% enantiomeric excess (Table 1, entry 1). The absolute stereochemistry of the addition products was inferred by comparison to that of homolaudanosine, a related natural product synthesized using the same conditions (see below).

We next examined the reactivity of these dihydroisoquinolinium salts with various alkynes under these conditions. Iminium **3** reacted with both trimethylsilylacetylene and methylpropargyl ether to afford propargylamines **3b** and **3d** in high yield and enantiomeric excess (Table 1, entries 2 and 4). Iminium **3** reacted with the electron-rich ethoxyethyne in high yield but with diminished enantiomeric excess (Table 1, entry 3), perhaps because of the actions of a more reactive, less selective corresponding copper acetylide. *N*-methyldihydroisoquinolinium **4** also reacted with methyl propargyl ether to form **4d** in good yield and high enantiomeric excess, which suggests that the conditions tolerate a degree of variation of the N-subsitutent (Table 1, entry 5). Treatment of 1-substituted dihydroisoquinolinium **5** with methylpropiolate under the reaction conditions proceeded in good yield but without stereoselection (Table 1, entry 6). Isoquinolinium **6** was exposed to trimethylsilylacetylene under the reaction conditions but reacted only at relatively elevated temperatures (−20 °C). Careful handling of the enamine product allowed for the isolation of **6b** in modest yield and enantiomeric excess (Table 1, entry 7).

To apply this method to the synthesis of a collection of diverse small molecules, we focused our attention to its optimization on substrates linked to a 500 μm diameter polystyrene resin (macrobeads) (Scheme 1). Using reported

Scheme 1. Solid-Phase Addition of Terminal Alkynes to Iminiums[a]



[a] Purity of the final compound was determined by UV/vis and TLC analysis. All intermediates were analyzed by MAS ^{1}H NMR. Enantiomeric excess is reported as the average of experiments with each ligand enantiomer.

procedures, we attached 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline to the macrobeads (**7**) and generated the corresponding iminium salt **8** by exposing the adducts to 2-bromobenzyl-bromide in ether.[7] Treatment of this alkyliminium salt with phenylacetylene in the presence of 5 mol % of CuBr, 5.5 mol % of QUINAP, triethylamine, and methylene chloride at −78 °C yielded propargylamine **9a**, which was characterized by ^{1}H magic angle spin (MAS) NMR prior to cleavage from the resin with HF-py for full characterization. Propargylamine **9b** was isolated in 84% yield (all steps), 75% enantiomeric excess, and >90% purity (as determined by UV/Vis and TIC analysis). Despite the diminished enantioselectivity of the solid-phase reaction, we anticipate that these conditions will be suitable for the synthesis of a collection of enantioenriched small molecules.

To determine the absolute configuration of the stereocenter established by this addition, we synthesized (*S*)-(−)-homolaudanosine (**11**), an isoquinoline-based natural product from a family of alkaloids with neurologic activity (Scheme 2). Commercially available 3,4-dihydro-6,7-dimethoxyisoquinoline hydrochloride was neutralized and alkylated with methyliodide to form isoquinolinium **4**. Addition of 3,4-dimethoxyphenylacetylene under the above reaction conditions

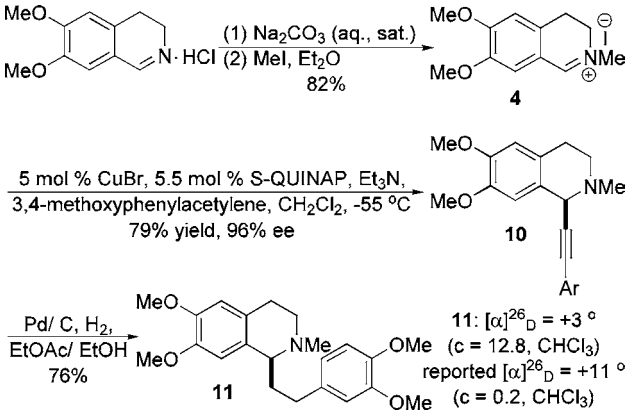
(4) Examples of copper-catalyzed enantioselective reactions include: (a) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797. (b) Li, C.-J.; Wei, C. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (c) Fu, G. C.; Suárez, A.; Downey, C. W. *J. Am. Chem. Soc.* **2005**, *127*, 11244.

(5) (a) Böhme, H.; Haake, M. In *Iminium Salts in Organic Chemistry*; Taylor, E. C., Ed.; Advances in Organic Chemistry: Methods and Results; John Wiley & Sons: New York, 1976; Vol. 1, p 112. (b) Thiessen, L. M. *Tetrahedron Lett.* **1974**, *15*, 59. (c) Onaka, T. *Tetrahedron Lett.* **1971**, *12*, 4395.

(6) See the Supporting Information for a general procedure.

(7) (a) Blackwell, H. E.; Perez, L.; Stavenger, R. A.; Tallarico, J. A.; Eatough, E. C.; Foley, M. A.; Schreiber, S. L. *Chem. Biol.* **2001**, *8*, 1167. (b) Clemons, P. A.; Koehler, A. N.; Wagner, B. K.; Sprigings, T. G.; Spring, D. R.; King, R. W.; Schreiber, S. L.; Foley, M. A. *Chem. Biol.* **2001**, *8*, 1183. (c) Reference 1.

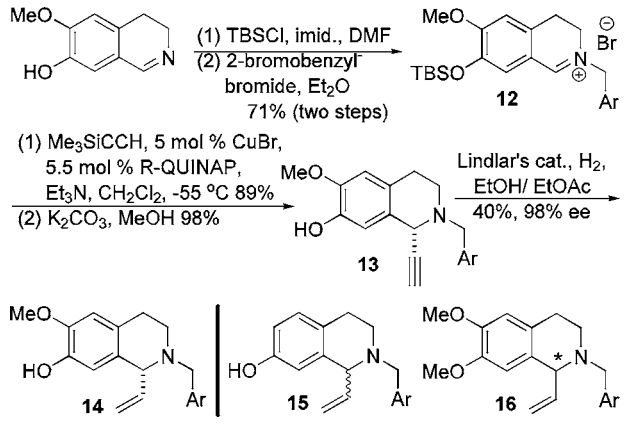
Scheme 2. Enantioselective Synthesis of Homolaudanosine



with *S*-QUINAP afforded the corresponding propargylamine tetrahydroisoquinoline **10** in good yield and high enantioselectivity. Complete reduction of this alkyne afforded homolaudanosine (**11**) in 76% yield. Synthetic homolaudanosine exhibited an optical rotation in the same direction as that reported for the natural product.[8] (*R*)-(+)-homolaudanosine was synthesized by the identical route using *R*-QUINAP and demonstrated a similar but opposite optical rotation.

In ongoing small-molecule screens at the Broad Institute Chemical Biology (BCB) Program using racemic tetrahydroisoquinoline products derived from the reported DOS pathway, we identified a small-molecule inhibitor of yeast proliferation (**15**).[9] As part of ongoing efforts to elucidate the target(s) of this compound, we synthesized both enantiomers of the derivative **14** (Scheme 3). Commercially

Scheme 3. Enantioselective Synthesis of Compounds Previously Discovered in Screens Using Proliferating Yeast Cells



available 7-hydroxy-6-methoxy-3,4-dihydroisoquinoline was protected as a silyl ether and alkylated with 2-bromobenzyl bromide to form alkyliminium **12** in 71% yield over two steps. Exposure to trimethylsilyacetylene under the above reaction conditions (using *R*-QUINAP) afforded in 89% yield the corresponding propargylamine, which was globally deprotected under basic conditions to form amine **13** (stereochemistry inferred from homolaudanosine synthesis). Partial hydrogenation formed **14** in 40% yield. These steps were repeated with *S*-QUINAP to yield *S*-**14**. Both enantiomers were isolated in 98% enantiomeric excess. Prelminary screens of **14** and *S*-**14** indicate that **14** has little effect on yeast growth, while *S*-**14** has activity comparable to the racemic mixture of **15**. *S*-**13** shows greater activity than either *S*-**14** or racemic **15**. Neither enantiomer of **16**, which differs only in substitution at the isoquinoline 7 position, had any detectable activity against yeast growth, suggesting that the active compounds of this series are acting in a specific manner on their target(s). Further experiments to determine basic structure−activity relationships and to identify the target(s) of these compounds are underway.

In summary, guided by earlier studies of Knochel and coworkers, we report the development of conditions for the asymmetric addition of terminal alkynes to discrete alkylisoquinolinium and alkyldihydroisoquinolinium ions in the presence of triethylamine and catalytic copper bromide and QUINAP. These conditions proceed with a variety of alkynes to yield propargylic amines in up to 95% isolated yield and 99% enantiomeric excess. Similar treatment of polystyrene resin-bound alkyliminiums also leads to highly pure propargylic amines in high yield and good enantiomeric excess. These conditions were used in solution to synthesize both enantiomers of naturally occurring homolaudanosine. Also, highly enantioenriched derivatives of a compound discovered to interfere with yeast proliferation were synthesized, indicating the applicability of these conditions toward resynthesis of active compounds from future screens. These conditions should allow for control of the absolute stereochemistry of a collection of isoquinoline-derived alkaloids derived from a previously reported DOS pathway, so that enantioenriched products can be screened directly soon.

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

OL0526165

(8) (a) Aladesamm, A. J., et al. *J. Nat. Prod.* **1983**, *46*, 127. (b) Meyers, A. I., et al. *Tetrahedron*. **1987**, *43*, 5095.

(9) Data shown in the Supporting Information. Preliminary experiments conducted with Ethan Perlstein.