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CuI-Catalyzed C1-Alkynylation of Tetrahydroisoquinolines (THIQs) by A^3 Reaction with Tunable Iminium Ions

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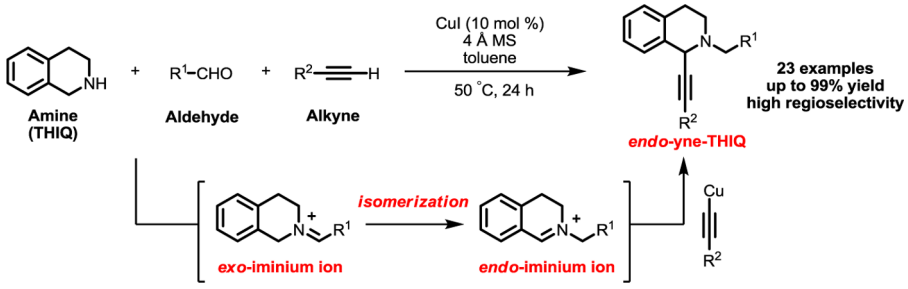
ABSTRACT



A CuI-catalyzed A^3 (amines, aldehydes and alkynes) reaction of tetrahydroisoquinolines (THIQs), aldehydes, and alkynes to give C1-alkynylated THIQ products (*endo*-yne-THIQs) was developed. This redox neutral C1-alkynylation of THIQs, which was conducted under mild conditions, has a broad scope for the used aldehydes and alkynes. It was proposed that the A^3 reaction first generates *in situ exo*-iminium ions, which then isomerize to *endo*-iminium ions and react with copper acetylides to give the *endo* alkynylated THIQs (*endo*-yne-THIQs).

Tetrahydroisoquinolines (THIQs) are among the most common skeletons in naturally existing alkaloids with various interesting biological activities.[1] Due to this, developing new methods of synthesizing THIQ derivatives or functionalizing THIQs is of tremendous significance. An appealing green-chemistry approach to attain C1-substituted THIQs is to use the cross-dehydrogenative coupling (CDC) strategy that directly activates the $C(sp^3)$–H bond at the C1 atom in the available THIQs.[2−4] One such CDC reaction to functionalize THIQs is the C1-alkynylation of THIQs by terminal alkynes catalyzed by Cu complexes (Reaction 1, Scheme 1).[5] This alkynylation reaction was proposed to proceed through addition of *in situ* generated copper acetylides to iminium ions, which were also generated *in situ* by the oxidation of the secondary amines.[6] A similar process was achieved via visible-light photoredox

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(3) For reviews of C–C bond formations involving CDC reactions, see: (a) Zhang, C.; Tang, C. H.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (b) Jones, K. M.; Klussmann, M. *Synlett* **2012**, *23*, 159. (c) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687. (d) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem.—Eur. J.* **2012**, *18*, 10092. (e) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (f) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490. (g) Compos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (h) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928.

(4) For mechanistic studies of CDC reactions, see: (a) Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256. (b) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648. (c) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (d) Ratnikov, M. O.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *125*, 1549.

(5) For alkynylation of THIQs by the CDC strategy, see: (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. For a recent example: Hudson, R.; Ishikawa, S.; Li, C.-J.; Moores, A. *Synlett* **2013**, *24*, 1637.

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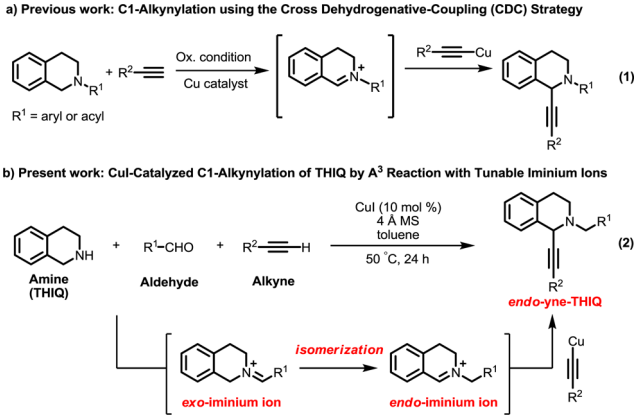
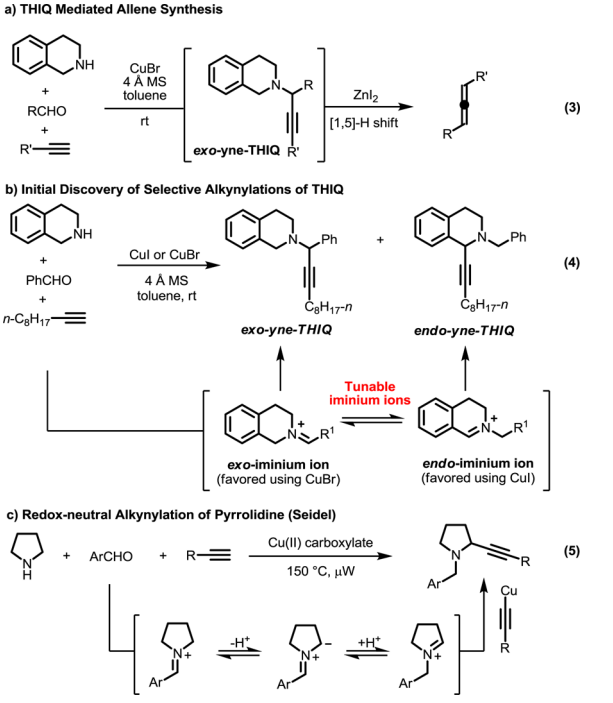
catalysis.[7] However, in both strategies, chemists have to use THIQs with *N*-aromatic or *N*-acyl substitutions, greatly limiting its use in synthesizing THIQs with various R^1 and R^2 groups. In addition, stoichiometric exogenous oxidants have to be used in the traditional CDC alkynylation reaction.[8] Here we report a new C1-alkynylation of THIQ through an A^3 reaction with tunable iminium ions (Reaction 2, Scheme 1). Four salient features of this new reaction are as follows: various aldehydes and alkynes can be used, leading to a broad library of THIQ derivatives; the reaction is redox-neutral; the reaction can be carried out under mild conditions (generally at 50 °C or even at rt); the substituent on the N-atom of the products can be the benzyl group, which can be easily removed and, consequently, would allow functionalization of THIQs to be realized.[9]

We recently developed a mild condition allene synthesis mediated by THIQ from aldehydes and alkynes (Reaction 3, Scheme 2).[10,11] In this reaction, an A^3 reaction occurs first to give *exo*-yne-THIQs, which can then give allenes via a [1,5]-H shift process promoted by ZnI_2. During our optimization of the A^3 reaction,[12−14] we found that the regioselectivity of this reaction can be, to some extent, well tuned by using different copper catalysts (Reaction 4, Scheme 2). When

Scheme 1. Two C1-Alkynylation Strategies of THIQs



Scheme 2. Discovery of this Work and a Previous Report with a Similar Iminium Isomerization Process



CuBr was utilized, *exo*-yne-THIQ was the major product. However, *endo*-yne-THIQ was the dominant product by using CuI as the catalyst. We proposed that the CuI-catalyzed reaction starts from generation of an *exo*-iminium ion from a secondary amine and aldehyde. The *exo*-iminium ion then isomerizes into an *endo*-iminium ion,[15,16] which reacts with copper acetylide to give *endo*-yne-THIQ. A similar iminium isomerization process has been proposed by Seidel in their Cu(II)-catalyzed alkynylation of pyrrolidines (Reaction 5, Scheme 2).[16a] Compared to Reaction 5, the synthesis of *endo*-yne-THIQ (Reaction 2, Scheme 1) was conducted under much milder conditions. More importantly, both *exo*- and *endo*-yne-THIQs can be

(6) Schreiber and Taylor described a direct reaction of the iminium ion and copper acetylides to give *endo*-yne-THIQs: Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143.

(7) (a) Condie, A. G.; Gónzalez-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (b) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94.

(8) An internal oxidant strategy was used by Nakamura for alkynylations of propargylic amines including only one example of THIQ; see: Sugiishi, T.; Nakamura, H. *J. Am. Chem. Soc.* **2012**, *134*, 2504.

(9) For discussions of removing protecting groups in CDC reactions of THIQs, see: (a) Tsang, A. S.-K.; Ingram, K.; Keiser, J.; Hibbert, D. B.; Todd, M. H. *Org. Biomol. Chem.* **2013**, *11*, 4921. (b) Schweitzer-Chaput, B.; Klussmann, M. *Eur. J. Org. Chem.* **2013**, 666.

(10) Jiang, G.-J.; Zheng, Q.-H.; Dou, M.; Zhuo, L.-G.; Meng, W.; Yu, Z.-X. *J. Org. Chem.*, in press, DOI: 10.1021/jo4018183.

(11) In the previous allene synthesis (ref 10), only two of all the *exo*-yne-THIQs were isolated and characterized. In the present paper, several *exo*-yne-THIQs as side products, shown in Schemes 2 and 3, were synthesized by using the CuBr catalyst and were characterized (see the Supporting Information), which is a demonstration that the A^3 reactions of THIQs can be tuned by using either CuI or CuBr as the catalyst.

(12) For selected reviews on the A^3 reaction, see: (a) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2012**, *41*, 3790. (b) Yoo, W. J.; Zhao, L.; Li, C.-J. *Aldrichimica Acta* **2011**, *44*, 43. (c) Kouznetsov, V. V.; Mendez, L. Y. V. *Synthesis* **2008**, 491. (d) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263. (e) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, *15*, 1472.

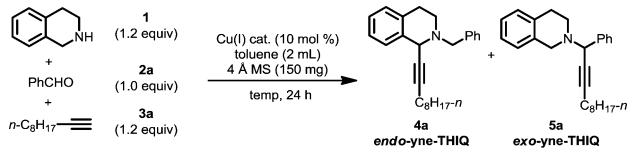
(13) For selected reports on A^3 reaction, see: (a) Dyatkin, A. B.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 3647. (b) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 676. (c) Li, C.-J.; Wei, C. M. *Chem. Commun.* **2002**, 268. (d) Wei, C. M.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (e) Gomermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

(14) For THIQ's A^3 reaction using a silver supermolecular catalyst, see: Zhao, Y.; Zhou, X.; Okamura, T.-A.; Chen, M.; Lu, Y.; Sun, W.-Y.; Yu, J.-Q. *Dalton Trans.* **2012**, *41*, 5889. Only two examples with moderate yields of *exo*-yne-THIQs were reported.

(15) B3LYP/6-311+G(d,p) calculations indicated the *endo*-iminium ion is more stable than the *exo*-iminium ion by 8.2 kcal/mol (in terms of enthalpy) in the gas phase with R^1=Ph in Reaction 4 of Scheme 2.

(16) (a) Das, D.; Sun, A. X.; Seidel, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3765. For other iminium isomerizations, see: (b) Zheng, L.; Yang, F.; Dang, Q.; Bai, X. *Org. Lett.* **2008**, *10*, 889. (c) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798. (d) Das, D.; Richers, M. T.; Ma, L.; Seidel, D. *Org. Lett.* **2011**, *13*, 6584. (e) Ma, L.; Chen, W.; Seidel, D. *J. Am. Chem. Soc.* **2012**, *134*, 15305. (f) Dieckmann, A.; Richers, M. T.; Platonova, A. Y.; Zhang, C.; Seidel, D.; Houk, K. N. *J. Org. Chem.* **2013**, *78*, 4132. (g) Das, D.; Seidel, D. *Org. Lett.* **2013**, *15*, 4358.

Table 1. Optimization of the THIQ C1-Alkynylation[a,b]



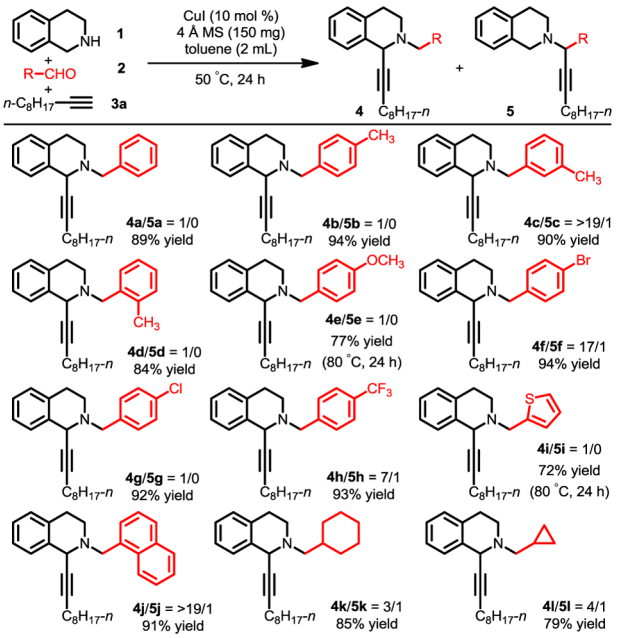
entry	catalyst	temp (°C)	yield[c] **4a** + **5a** (%)	ratio[d] **4a**/**5a**
1	CuCl	30	85	1:7
2	CuBr	30	92	<1:19
3	CuI	30	88	1:0
4	CuCN	30	41	1:0
5	$CuOTf \cdot 0.5C_6H_6$	30	21	3:1
6	$CuBF_4 \cdot 4MeCN$	30	24	10:1
7	$CuBr_2$	30	66	8:1
8	$Cu(OAc)_2$	30	58	8:1
9[e]	CuI	30	87	1:0
10[e]	CuI	22	83	1:0
11[e]	**CuI**	**50**	**89**	**1:0**
12[f]	CuI	30	0	N/A
13[g]	CuI	30	0	N/A

[a] Reactions were performed on a 0.5 mmol scale. [b] For screening of solvents and amounts of CuI, see Table S1 in the Supporting Information. [c] Isolated combined yields were calculated based on benzaldehyde. [d] Ratio was determined by NMR prior to purification, and in the case of 1:0, no **5a** could be observed in the mixture by NMR. [e] The molar ratio of **1**/**2a**/**3a** was 1.0/1.0/1.0 for the optimal conditions. [f] Reaction was performed in air atmosphere, showing that 1,3-diyne resulted from Glaser coupling as the only new compound generated (its yield was not measured). In other cases, no 1,3-diyne was observed. [g] Reaction was performed without 4 Å molecular sieves. N/A = not applicable.

obtained in a highly regioselective manner by choosing the appropriate catalyst, either CuBr or CuI. Previously we have shown that the CuBr-catalyzed A^3 reaction can give *exo*-yne-THIQs in the allene synthesis.[10,11] Here we report the scope of *endo*-yne-THIQ synthesis catalyzed by CuI.

In order to achieve the best reaction yield and regioselectivity for accessing *endo*-yne-THIQs, we reoptimized the reaction conditions (Table 1). At the very beginning of the exploration, an excess amount of THIQ and 1-decyne were used in order to consume all of the benzaldehyde, which was inseparable from products **4a** and **5a** by column chromatography. We first screened various copper(I) catalysts. Both CuCl and CuBr can catalyze the three-component reaction to give *exo*-yne-THIQ **5a** as the major product (entries 1−2), while the reactions catalyzed by CuI and CuCN generated the *endo*-yne-THIQ **4a** dominantly (entries 3−4). Apparently, CuBr and CuI catalyzed reactions gave very good yields, although with completely opposite regioselectivity. When using CuOTf and $CuBF_4$, both yields and selectivity were poor (entries 5−6). Cu(II) catalysts were also tested, with the finding that they were less effective compared with the Cu(I) catalysts (entries 7−8). Next, we decreased the amount of THIQ and 1-decyne to make all three components equivalent. To our delight, the reaction proceeded well and gave a good reaction yield as well as excellent regioselectivity (entry 9). By lowering the temperature further to a rigorously controlled 22 °C, which is widely regarded as rt, only a slight reduction of yield was observed, indicating the possibility of carrying out this reaction under even milder conditions (entry 10). Although we observed good results for the model substrates at rt, a later study of the reaction scope revealed that, in several cases, the C1-alkynylation reactions were slow at 30 °C, while the reactions at 50 °C could finish smoothly within 24 h with a very good yield and high regioselectivity (entry 11). Therefore, entry 9 was chosen as the optimal conditions for further investigation of the reaction scope. Control experiments demonstrated that an inert atmosphere and 4 Å molecular sieves were necessary for the success of the target reaction (entries 12−13). It is noteworthy that the CuI can be reduced to 2% and the reaction yield was lowered to 73% (see Supporting Information).

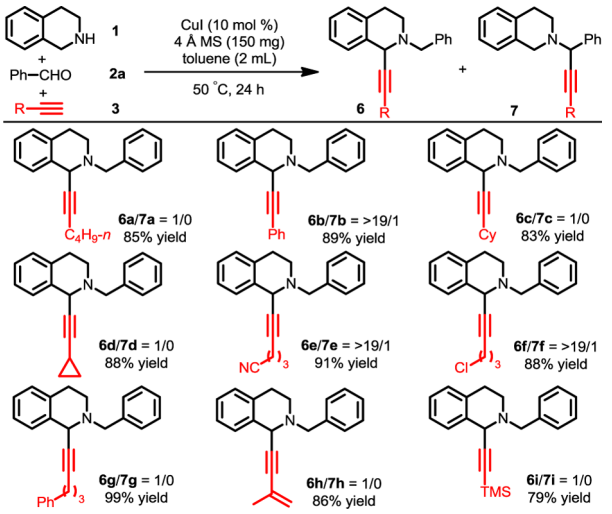
Scheme 3. Scope of Aldehydes in the THIQ C1-Alkynylation[a,b]



[a] Reactions were performed on 0.5 mmol scale, and the molar ratio of **1**/**2**/**3a** was 1.0/1.0/1.0. [b] Isolated combined yield of **4** and **5**, and the ratio of **4**/**5** was determined by NMR.

First, we studied the scope of the aldehydes for the target reaction. We were happy to note that tolualdehydes with different substitution patterns were well tolerated (**4b**−**d**, Scheme 3). The electronic effect of substituents on the benzene ring was also investigated, showing that electron-donating (**4e**, Scheme 3) and electron-withdrawing (**4h**, Scheme 3) groups can be applied in the reaction. It must be pointed out that, for electron-rich aromatic aldehydes, the reaction had to be carried out at 80 °C to gain a reasonable reaction rate. Unfortunately, poor selectivity was obtained when trifluoromethyl benzaldehyde was used (**4h**, Scheme 3), probably because of the slow isomerization of the *in situ* generated iminium. Apart from the variation of substituents on the benzene ring, a heterocyclic aldehyde (**4i**, Scheme 3) and polycyclic aromatic aldehyde (**4j**, Scheme 3) were also applicable under the standard reaction conditions

Scheme 4. Scope of Alkynes in the THIQ C1-Alkynylation[a,b]

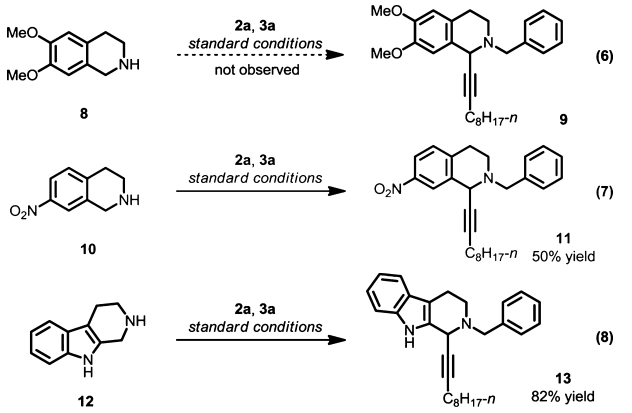


[a] Reactions were performed on 0.5 mmol scale, and the molar ratio of **1**/**2a**/**3** was 1.0/1.0/1.0. [b] Isolated combined yield of **6** and **7**, and the ratio of **6**/**7** was determined by NMR.

to give good yields and regioselectivity. Aliphatic aldehydes can be used in the target reaction with only a moderate preference for *endo*-yne-THIQs over the *exo*-yne-THIQs (**4k**–**l**, Scheme 3). Further study showed that an α,β-unsaturated aldehyde such as cinnamaldehyde failed to give the *endo*-yne-THIQ.

On the other hand, using THIQ and benzaldehyde as the fixed parteners, we studied the scope of terminal alkynes. When the 8C carbon chain in standard substrate 1-decyne was shortened to 4C, the reaction still performed well with a wonderful reaction yield and selectivity (**6a**, Scheme 4). Replacement of the nonbranched carbon chain by either a benzene ring (**6b**, Scheme 4) or a saturated ring (**6c**–**6d**, Scheme 4) gave excellent results. Aliphatic alkynes with different functional groups at the terminal position can participate in the C1-alkynylation reaction with very good yields and *endo*/*exo* selectivity (**6e**–**g**, Scheme 4). More excitingly, conjugated alkynes such as 2-methylbut-1-en-3-yne were applicable under the reaction conditions (**6h**, Scheme 4). In order to obtain a useful terminal-alkyne-type product, we tested trimethyl silyl acetylene as the alkyne partner, showing that the target *endo*-yne-THIQ can be formed exclusively in 79% yield (**6i**, Scheme 4).

A preliminary study showed that electron-rich THIQ **8** could give neither *endo*- nor *exo*-alkynylation products under CuI catalysis conditions (Reaction 6). In contrast, electron-deficient THIQ **10** could give *endo*-yne-THIQ **11** product under standard conditions in a moderate yield (Reaction 7). We were happy to observe that **12**, which has the skeleton of tryptoline widely found in natural products,[1a] can give the *endo*-alkynylation product exclusively (Reaction 8).[17]



In conclusion, we have developed a C1-alkynylation of THIQs through an A^3 reaction by using tunable iminium ions to attain *endo*-yne-THIQs with a broad scope and high regioselectivity. In addition, the scope of this reaction was successfully expanded from THIQs to its nitro-derivative and tryptoline. Further experimental and computational investigations of the scope, mechanism, and application of the C1-alkynylation of THIQs are ongoing. Developing an enantioselective version of this alkynylation reaction will also be explored.

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Supporting Information Available. General procedures, spectroscopy data, and copies of ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) (a) A^3 reactions of general secondary cyclic amines give traditional A^3 products without involving iminium ion isomerization. For a selected CuI-catalyzed example, see: Sreedhar, B.; Reddy, P. S.; Prakash, B. V.; Ravindra, A. *Tetrahedron Lett.* **2005**, *46*, 7019. (b) For a recent CuBr-catalyzed example, see: Gurubrahamam, R.; Periasamy, M. *J. Org. Chem.* **2013**, *78*, 1463. For CuBr-catalyzed reactions, see also refs 12–14. We found that, under our standard reaction conditions using CuI as the catalyst, the A^3 reaction of pyrrolidine gave also the traditional propargylamine product (see the Supporting Information).

The authors declare no competing financial interest.