Asymmetric Catalysis

DOI: 10.1002/ange.201308699

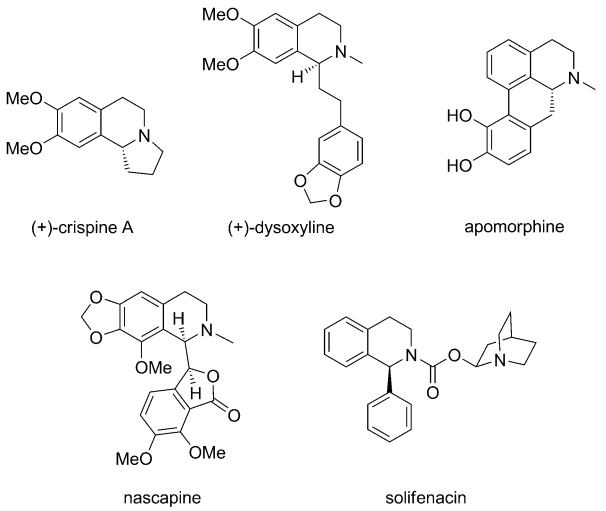
Enantioselective Double Manipulation of Tetrahydroisoquinolines with Terminal Alkynes and Aldehydes under Copper(I) Catalysis**

*Weilong Lin, Tao Cao, Wu Fan, Yulin Han, Jinqiang Kuang, Hongwen Luo, Bukeyan Miao, Xinjun Tang, Qiong Yu, Weiming Yuan, Jiasheng Zhang, Can Zhu, and Shengming Ma**

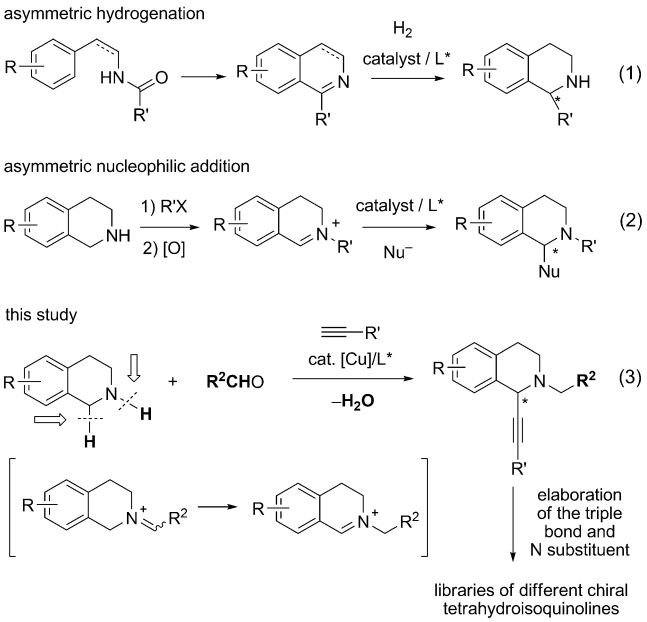
Abstract: *Tetrahydroisoquinoline alkaloids with a C1 stereogenic center are a common unit in many natural and non-natural compounds of biological importance. Herein we describe a novel Cu^{I}-catalyzed highly chemo- and enantioselective synthesis of chiral tetrahydroisoquinoline-alkaloid derivatives from readily available unsubstituted tetrahydroisoquinolines, aldehydes, and terminal alkynes in the presence of the ligand (R,R)-N-pinap. This synthetic operation installs two substituents in the 1- and 2-positions.*

1,2,3,4-Tetrahydroisoquinolines (THIQs) with a stereogenic center at the C1 position form a large class of natural and unnatural compounds with a great diversity of important biological properties.[1] Representative examples include (+)-crispine A,[1c] isolated from *Carduus crispus*, (+)-dysoxyline,[1d] isolated from *Dysoxylum lenticellare*, and the drugs apomorphine,[1e] nascapine,[1f] and solifenacin[1g] (Scheme 1).

Thus, much effort has been devoted to the synthesis of tetrahydroisoquinoline alkaloids.[2] Traditional synthetic methods for the preparation of this class of compounds are the Bischer–Napieralski cyclization/reduction[2b,3] and the Pictet–Spengler reaction.[2b,4] Two further enantioselective approaches towards such skeletons are the noble-transition-metal-catalyzed asymmetric hydrogenation of isoquinoline or dihydroisoquinoline derivatives [Scheme 2, Eq. (1)][5,6] and asymmetric nucleophilic addition to the preformed $C{=}N^{+}$ bond of cyclic precursors [Scheme 2, Eq. (2)].[7–11] During our recent study on the A^3 coupling of tetrahydroisoquinoline **3a**, terminal alkynes, and aldehydes, we observed that upon reduction of the Cu^{I} catalyst, besides the normal propargylic amine of type **5a**,[12,13] a product of tetrahydroisoquinoline α-alkynylation of type **4a** was unexpectedly formed as a by-product (Table 1), most probably through an in situ iminium-ion-isomerization process [Scheme 2, Eq. (3)]. If such a reaction is viable, the use of noble-metal catalysts, as in Equations (1) and (2), may be avoided, and the chemicals for such a manipulation of tetrahydroquinolines would just be



Scheme 1. Tetrahydroisoquinoline natural products and drugs.

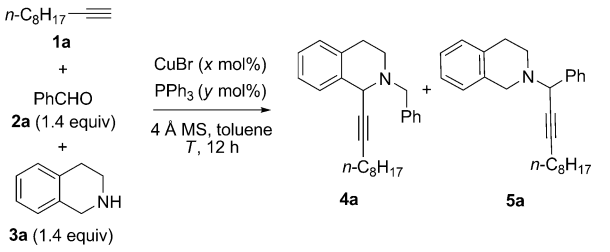


Scheme 2. Approaches to optically active tetrahydroisoquinolines.

[*] W. Lin, T. Cao,[+] Y. Han,[+] J. Kuang,[+] X. Tang,[+] J. Zhang,[+] C. Zhu,[+] Prof. Dr. S. Ma
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (P.R. China)
E-mail: masm@sioc.ac.cn
W. Fan,[+] H. Luo,[+] B. Miao,[+] Q. Yu,[+] W. Yuan,[+] Prof. Dr. S. Ma
Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry
East China Normal University
3663 North Zhongshan Lu, Shanghai 200062 (P.R. China)
[+] These authors contributed equally.

[**] Financial support from the National Basic Research Program (2011CB808700) and the National Natural Science Foundation of China (21232006) is acknowledged.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201308699.

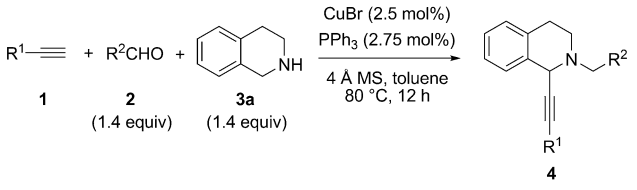
Table 1: Optimization of the catalytic alkynylation of tetrahydroisoquinolines.



Entry	*x*	*y*	*T* [°C]	Yield of **4a** [%][a]	Yield of **5a** [%][a]
1	15	0	RT	1	96
2	5	0	RT	9	13
3[b]	5	5.5	RT	23	1
4	5	5.5	80	88	1
5	2.5	2.75	80	90	N.D.

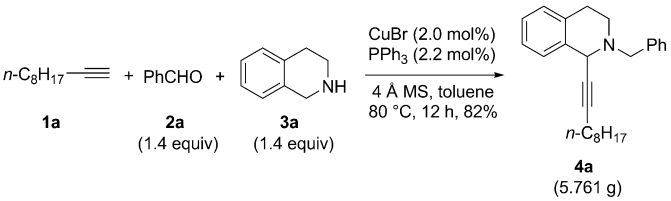
[a] Yields were determined by ^{1}H NMR spectroscopic analysis with nitromethane as the internal standard. [b] The reaction was conducted for 13 h. MS = molecular sieves, N.D. = not determined.

Table 2: Scope of the catalytic alkynylation of tetrahydroisoquinoline **3a**.



Entry	R^1 (**1**)	R^2 (**2**)	Yield [%][a]
1	*n*-C_8H_{17} (**1a**)	Ph (**2a**)	83 (**4a**)
2	Cy (**1b**)	Ph (**2a**)	81 (**4b**)
3	CH_3COOCH_2 (**1c**)	Ph (**2a**)	92 (**4c**)
4	$TBSO(CH_2)_2$ (**1d**)	Ph (**2a**)	81 (**4d**)
5	Ph (**1e**)	Ph (**2a**)	90 (**4e**)
6	4-FC_6H_4 (**1f**)	Ph (**2a**)	91 (**4f**)
7	4-$MeOC_6H_4$ (**1g**)	Ph (**2a**)	93 (**4g**)
8	*n*-C_8H_{17} (**1a**)	4-MeC_6H_4 (**2b**)	80 (**4h**)
9	*n*-C_8H_{17} (**1a**)	4-FC_6H_4 (**2c**)	93 (**4i**)
10	*n*-C_8H_{17} (**1a**)	2,6-$Cl_2C_6H_3$ (**2d**)	85 (**4j**)
11	*n*-C_8H_{17} (**1a**)	*N*-Ts-indole-3- (**2e**)	54 (**4k**)
12	*n*-C_8H_{17} (**1a**)	Cy (**2f**)	55 (**4l**)[b]

[a] Yield of the isolated product. [b] Compound **5l** was isolated in 15% yield. Cy = cyclohexyl, TBS = *tert*-butyldimethylsilyl, Ts = *p*-toluenesulfonyl.



Scheme 3. Large-scale synthesis of **4a**.

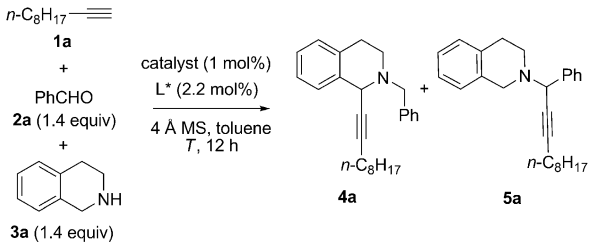
readily available common reagents, with water as the only by-product. Herein, we wish to report the realization of such a copper-catalyzed highly chemoselective α-alkynylation of tetrahydroisoquinolines with terminal alkynes and aldehydes, and the further development of an enantioselective procedure that provides different optically active 1-alkynyl-substituted tetrahydroisoquinolines with the simultaneous incorporation of a benzyl group on the nitrogen atom.

We observed that with CuBr (15 mol%) as the catalyst, the coupling of 1-decyne (**1a**), benzaldehyde (**2a**), and 1,2,3,4-tetrahydroisoquinoline (**3a**) afforded the normal propargylic amine **5a** in 96% yield as the major product (Table 1, entry 1).[12] Surprisingly, when 5 mol% of CuBr was used, the desired propargylic amine **4a** (9%) was obtained together with the normal propargylic amine **5a** (13%; Table 1, entry 2). When we used CuBr (5 mol%) together with PPh_3 (5.5 mol%) as the catalyst, the selectivity of the reaction was improved in favor of product **4a** (Table 1, entry 3), and the yield of **4a** was improved further to 88% when the reaction was conducted at 80°C (Table 1, entry 4). Surprisingly, a further decrease in the CuBr loading to 2.5 mol% completely suppressed the formation of **5a** (Table 1, entry 5). Thus, the optimized reaction conditions for further study were defined as the use of **1a** (1 equiv), **2a** (1.4 equiv), **3a** (1.4 equiv), CuBr (2.5 mol%), PPh_3 (2.75 mol%), and 4 Å MS (50 mg mL^{-1}) in toluene at 80°C. The reduction in the loading of CuBr and the addition of PPh_3 slowed down the normal A^3 coupling reaction, thus leaving more time for the isomerization of the iminium intermediate.

The scope of this non-asymmetric α-alkynylation of tetrahydroisoquinolines was investigated under the optimal reaction conditions. The reaction proceeded in good to excellent yield with aromatic aldehydes (Table 2, entries 1–10) and tolerated a variety of functional groups (Table 2, entries 3, 4, and 8–10). It was also successful with an indolecarbaldehyde and an aliphatic aldehyde (Table 2, entries 11 and 12), and could be readily conducted on a 2.7 g scale (with respect to **1a**; Scheme 3).

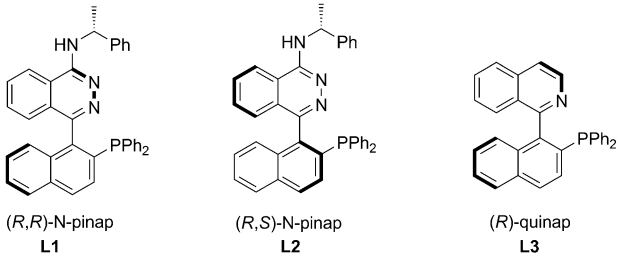
Having established this approach, we envisioned the further development of a catalytic enantioselective alkynylation by the use of chiral ligands. Interestingly, **4a** was obtained in 97% yield with 88% *ee* together with a trace amount of **5a** when (*R*,*R*)-N-pinap[13,14] was used instead of PPh_3 (Table 3, entry 1). When the loading of CuBr was further decreased, **4a** was obtained in 96% yield with 89% *ee*; **5a** was not detected (Table 3, entry 2). A decrease in the reaction temperature to 60°C improved the *ee* value to 92% but led to a lower yield (Table 3, entry 3). We next sought to optimize the catalyst system by examining various copper(I) salts together with (*R*,*S*)-N-pinap or (*R*)-quinap: CuI combined with (*R*,*R*)-N-pinap turned out to be the most efficient catalyst system (Table 3, entries 4–8). The reaction at a lower temperature (40°C) provided the product with a slightly higher *ee* value of 94% but in much lower yield (Table 1, entry 9). However, the addition of PhCOOH (5 mol%) improved the yield to 98% again, and the product was still obtained with 94% *ee* (Table 3, entry 10). The reaction at room temperature was rather poor in terms of the yield (Table 3, entry 11). Thus, the optimized reaction conditions for further study were defined as the use of **1a** (1 equiv), **2a** (1.4 equiv), **3a** (1.4 equiv), CuI

Table 3: Optimization of the catalytic asymmetric α-alkynylation of tetrahydroisoquinolines.



Entry	Catalyst	*T* [°C]	Ligand	Yield of **4a** [%][a]	Yield of **5a** [%][b]	*ee* [%][c]
1[d,e]	CuBr	80	**L1**	97	1	88
2	CuBr	80	**L1**	96	N.D.	89
3	CuBr	60	**L1**	76	N.D.	92
4	CuCl	60	**L1**	96	N.D.	89
5[f]	CuOTf	60	**L1**	98	N.D.	88
6	CuI	60	**L1**	97	N.D.	92
7	CuI	60	**L2**	93	N.D.	−83
8	CuI	60	**L3**	76	N.D.	64
9	CuI	40	**L1**	84	N.D.	94
10[g]	CuI	40	**L1**	98	N.D.	94
11	CuI	RT	**L1**	62	N.D.	95

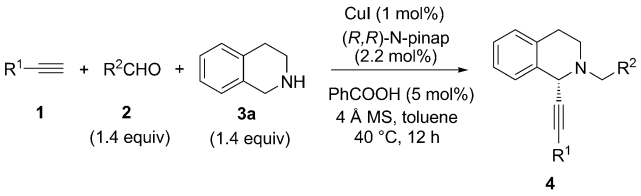
[a] Yield of the isolated product. [b] The yield of **5a** was determined by ^{1}H NMR spectroscopic analysis with nitromethane as the internal standard. [c] The *ee* value of **4a** was determined by HPLC analysis on a chiral stationary phase. [d] CuBr (5 mol%) was used. [e] The reaction was carried out with 5.5 mol% of the ligand. [f] Commercial copper(I) trifluoromethanesulfonate toluene complex (2:1) was used. [g] PhCOOH (5 mol%) was added.



(1 mol%), (*R*,*R*)-N-pinap (2.2 mol%), PhCOOH (5 mol%), and 4 Å MS (50 mg mL^{-1}) in toluene at 40 °C.

To examine the scope of the reaction, we first investigated diverse alkyne substrates under the optimal reaction conditions (Table 4). Terminal alkynes with *n*-alkyl (Table 4, entry 1) or cycloalkyl (Table 4, entry 2) and differently substituted aryl substituents (Table 4, entries 5–7) all afforded the corresponding products in good yield with high enantioselectivity (up to 95% *ee*). Furthermore, functionalized aliphatic alkynes, such as the TBS ether or acetate of propargylic or homopropargylic alcohols, also reacted smoothly to afford the desired products in excellent yield and enantioselectivity (Table 4, entries 3 and 4), thus providing opportunities for further attractive synthetic operations. In all these reactions, the formation of the undesired normal products of type **5** was not detected. We then investigated the use of a range of different aldehydes with 1-decyne (**1a**) and found that the reaction also showed broad scope with respect to the aldehyde substrate. Surprisingly, benzaldehyde deriv-

Table 4: Scope of the catalytic alkynylation of tetrahydroisoquinolines.

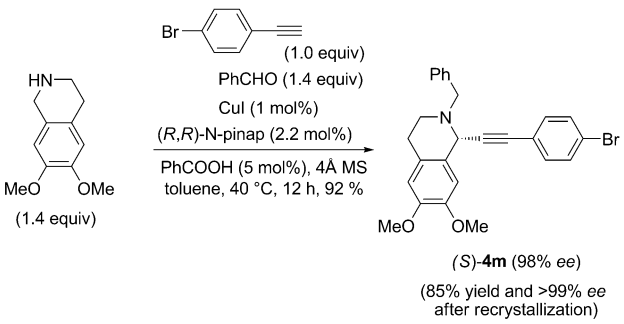


Entry	R^1 (**1**)	R^2 (**2**)	Yield [%][a]	*ee* [%][b]
1	*n*-C_8H_{17} (**1a**)	Ph (**2a**)	98 ((*R*)-**4a**)	94
2	Cy (**1b**)	Ph (**2a**)	94 ((*R*)-**4b**)	95
3	$MeCOOCH_2$ (**1c**)	Ph (**2a**)	91 ((*S*)-**4c**)	91
4	$TBSO(CH_2)_2$ (**1d**)	Ph (**2a**)	96 ((*R*)-**4d**)	93
5	Ph (**1e**)	Ph (**2a**)	94 ((*S*)-**4e**)	95
6	4-FC_6H_4 (**1f**)	Ph (**2a**)	95 ((*S*)-**4f**)	94
7	4-$MeOC_6H_4$ (**1g**)	Ph (**2a**)	97 ((*S*)-**4g**)	93
8	*n*-C_8H_{17} (**1a**)	4-MeC_6H_4 (**2b**)	95 ((*R*)-**4h**)	94
9	*n*-C_8H_{17} (**1a**)	4-FC_6H_4 (**2c**)	97 ((*R*)-**4i**)	95
10	*n*-C_8H_{17} (**1a**)	2,6-$Cl_2C_6H_3$ (**2d**)	89 ((*R*)-**4j**)	93
11	*n*-C_8H_{17} (**1a**)	*N*-Ts-indole-3- (**2e**)	80 ((*R*)-**4k**)	92

[a] Yield of the isolated product. [b] The *ee* value was determined by HPLC analysis on a chiral stationary phase.

atives with different substituents, such electron-donating *p*-Me and electron-withdrawing *p*-F groups as well as 2,6-dichloro groups, all afforded the desired products in good yield with high enantioselectivity (Table 4, entries 8–10). Interestingly, an aromatic heterocyclic aldehyde was also readily converted into the desired product in 80% yield with 92% *ee* (Table 4, entry 11).

For the purpose of accessing (+)-crispine A[1c] and (+)-dysoxyline,[1d] we used 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, and we were happy to observe that the desired product **4m** was afforded in 92% yield with 98% *ee* (85% yield and >99% *ee* after recrystallization; Scheme 4). The absolute configuration of the products in this study was determined by X-ray crystallographic analysis of (*S*)-**4m** (see the Supporting Information).[15]



Scheme 4. Enantioselective synthesis of (*S*)-**4m**.

In conclusion, we have succeeded in developing a novel CuI-catalyzed highly enantioselective synthesis of chiral tetrahydroisoquinolines through the α-alkynylation of 1,2-unsubstituted tetrahydroisoquinolines with aldehydes and terminal alkynes with readily available N-pinap as the chiral

ligand. The low catalyst loading, the mild reaction conditions, the broad scope of the reaction, the efficiency with which the tetrahydroisoquinoline skeleton can be accessed, and the potential for straightforward synthetic manipulation of the *N*-benzyl group and the C–C triple bond make this method of very broad interest to organic and medicinal chemists. This research opens a new and efficient entry to a broad range of tetrahydroisoquinolines, since, in principle, different nucleophiles may be applied instead of terminal alkynes. Further studies, including investigations into possible nucleophiles and synthetic applications to natural products (such as (+)-crispine A and (+)-dysoxyline) and drugs, are being actively pursued by our research group.

Experimental Section

Synthesis of (*R*)-**4a** (Table 4, entry 1): (*R*,*R*)-N-pinap (12.8 mg, 0.022 mmol) was placed in a flame-dried Schlenk tube inside a glove box. CuI (2.0 mg, 0.01 mmol), 4 Å MS (299.8 mg), and toluene (2 mL) were added sequentially under an Ar atmosphere outside of the glove box. The contents of the Schlenk tube were then stirred at room temperature for 30 min. PhCOOH (6.1 mg, 0.05 mmol), **2a** (147.9 mg, 1.4 mmol) in toluene (1 mL), **3a** (191.0 mg, 98% purity, 1.4 mmol) in toluene (1 mL), and **1a** (140.9 mg, 98% purity, 1.0 mmol) in toluene (2 mL) were then added sequentially under an Ar atmosphere. The Schlenk tube was then placed in a preheated oil bath at 40 °C, and the mixture was stirred for 12 h. The resulting mixture was cooled to room temperature and filtered through a short pad of silica gel with Et_2O (50 mL) as the eluent. The mixture was concentrated via evaporation, and the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate 100:1) to afford (*R*)-**4a** (351.8 mg, 98%, 94% *ee*) as a liquid. HPLC conditions: Chiralcel OD-H column, hexane/*i*PrOH (200:1), 1.0 mL min^{-1}, $\lambda = 214$ nm, t_R-(major) = 6.6 min, t_R(minor) = 7.2 min; $[\alpha]_D^{21} = -75.6$ ($c = 0.98$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J = 7.5$ Hz, 2H, Ar-H), 7.36–7.23 (m, 3H, Ar-H), 7.21–7.03 (m, 4H, Ar-H), 4.54 (s, 1H, NCH), 3.88 (d, $J = 13.2$ Hz, 1H, ArCH*H*N), 3.79 (d, $J = 13.2$ Hz, 1H, ArCH*H*N), 3.04–2.87 (m, 2H, $ArCH_2$), 2.81–2.65 (m, 2H, NCH_2), 2.23 (t, $J = 6.4$ Hz, 2H, CH_2), 1.59–1.20 (m, 12H, $6 \times CH_2$), 0.88 ppm (t, $J = 6.6$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 138.5, 136.3, 133.8, 129.2, 128.8, 128.2, 127.6, 127.0, 126.6, 125.6, 87.2, 77.8, 59.4, 54.0, 45.5, 31.8, 29.2, 29.1, 29.0, 28.94, 28.89, 22.6, 18.8, 14.1 ppm; IR (neat): $\tilde{\nu}$ =2924, 2854, 1494, 1453, 1357, 1328, 1289, 1262, 1131, 1105, 1075, 1051, 1028, 1010 cm^{-1}; HRMS: *m*/*z* calcd for $C_{26}H_{34}N$: 360.2686 $[M+H]^+$; found: 360.2701.

Received: October 6, 2013
Published online: November 29, 2013

Keywords: alkynylation · asymmetric catalysis · chirality · copper · tetrahydroisoquinoline alkaloids

[1] a) D. Jack, R. Williams, *Chem. Rev.* **2002**, *102*, 1669; b) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444; c) Q. Y. Zhang, G. Z. Tu, Y. Y. Zhao, T. M. Cheng, *Tetrahedron* **2002**, *58*, 6795; d) A. J. Aladesanmi, C. J. Kelly, J. D. Leary, *J. Nat. Prod.* **1983**, *46*, 127; e) A. Zhang, J. L. Neumeyer, R. J. Baldessarini, *Chem. Rev.* **2007**, *107*, 274; f) K. Ye, Y. Ke, N. Keshava, J. Shanks, J. A. Kapp, R. R. Tekmal, J. Petros, H. C. Joshi, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 1601; g) C. J. Kelleher, L. Cardozo, C. R. Chapple, F. Haab, A. M. Ridder, *BJU Int.* **2005**, *95*, 81.

[2] a) M. D. Rozwadowska, *Heterocycles* **1994**, *39*, 903; b) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341; c) P. Siengalewicz, U. Rinner, J. Mulzer, *Chem. Soc. Rev.* **2008**, *37*, 2676.

[3] a) B. S. Thyagarajan, *Chem. Rev.* **1954**, *54*, 1019; b) J. Gal, R. J. Wienkam, N. Castagnoli, Jr., *J. Org. Chem.* **1974**, *39*, 418.

[4] J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem.* **2011**, *123*, 8692; *Angew. Chem. Int. Ed.* **2011**, *50*, 8538.

[5] For representative reviews, see: a) Y. G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357; b) D. S. Wang, Q. A. Chen, S. M. Lu, Y. G. Zhou, *Chem. Rev.* **2012**, *112*, 2557.

[6] For selected examples of the asymmetric hydrogenation of isoquinolines, see: a) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, T. Ohta, H. Takaya, *J. Am. Chem. Soc.* **1986**, *108*, 7117; b) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 4916; c) S. M. Lu, Y. Q. Wang, X. W. Han, Y. G. Zhou, *Angew. Chem.* **2006**, *118*, 2318; *Angew. Chem. Int. Ed.* **2006**, *45*, 2260; d) C. Q. Li, J. L. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 13208; e) P. C. Yan, J. H. Xie, G. H. Hou, L. X. Wang, Q. L. Zhou, *Adv. Synth. Catal.* **2009**, *351*, 3243; f) L. Evanno, J. Ormala, P. M. Pihko, *Chem. Eur. J.* **2009**, *15*, 12963; g) M. X. Chang, W. Li, X. M. Zhang, *Angew. Chem.* **2011**, *123*, 10867; *Angew. Chem. Int. Ed.* **2011**, *50*, 10679; h) F. Berhal, Z. Wu, Z. G. Zhang, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett.* **2012**, *14*, 3308; i) A. Iimuro, K. Yamaji, S. Kandula, T. Nagano, Y. Kita, K. Mashima, *Angew. Chem.* **2013**, *125*, 2100; *Angew. Chem. Int. Ed.* **2013**, *52*, 2046; j) Z. Wu, M. Perez, M. Scalone, T. Ayad, V. Ratovelomanana-Vidal, *Angew. Chem.* **2013**, *125*, 5025; *Angew. Chem. Int. Ed.* **2013**, *52*, 4925.

[7] For selected examples of oxidative cross-dehydrogenative coupling at the C1 position, see: a) S. I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.* **2003**, *125*, 15312; b) Z. P. Li, C. J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810; c) Z. P. Li, C. J. Li, *Org. Lett.* **2004**, *6*, 4997; d) Z. P. Li, C. J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968; e) Z. P. Li, P. D. MacLeod, C. J. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590; f) S. Murarka, I. Deb, C. Zhang, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 13226; g) J. Xie, H. M. Li, J. C. Zhou, Y. X. Cheng, C. J. Zhu, *Angew. Chem.* **2012**, *124*, 1278; *Angew. Chem. Int. Ed.* **2012**, *51*, 1252; h) J. M. Zhang, B. Tiwari, C. Xing, X. K. Chen, Y. R. Chi, *Angew. Chem.* **2012**, *124*, 3709; *Angew. Chem. Int. Ed.* **2012**, *51*, 3649; i) G. Zhang, Y. X. Ma, S. L. Wang, Y. H. Zhang, R. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 12334; j) A. J. Neel, J. P. Hehn, P. F. Tripet, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 14044.

[8] For selected examples of organocatalytic addition to the C1 position, see: a) K. Frisch, A. Landa, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 6212; *Angew. Chem. Int. Ed.* **2005**, *44*, 6058; b) M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 6858; *Angew. Chem. Int. Ed.* **2005**, *44*, 6700.

[9] For selected examples of the direct nucleophilic addition of organometallic compounds to the C1 position, see: a) A. M. Taylor, S. L. Schreiber, *Org. Lett.* **2006**, *8*, 143; b) S. Wang, C. T. Seto, *Org. Lett.* **2006**, *8*, 3979; c) S. Wang, M. B. Onaran, C. T. Seto, *Org. Lett.* **2010**, *12*, 2090; d) T. Hashimoto, M. Omote, K. Maruoka, *Angew. Chem.* **2011**, *123*, 9114; *Angew. Chem. Int. Ed.* **2011**, *50*, 8952.

[10] For selected examples with others nucleophiles, see: a) K. Funabashi, H. Ratni, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 10784; b) S. I. Murahashi, Y. Imada, T. Kawakami, K. Harada, Y. Yonemushi, N. Tomita, *J. Am. Chem. Soc.* **2002**, *124*, 2888; c) N. Sasamoto, C. Dubs, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2006**, *128*, 14010; d) C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume, M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859; e) M. Miyazaki, N. Ando, K. Sugai, Y. Seito, H. Fukuoka, T. Kanemitsu, K. Nagata, Y. Odanaka, K. T. Nakamura, T. Itoh, *J. Org. Chem.* **2011**, *76*, 534.

[11] For reviews, see: a) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069; b) C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; c) C. Zhang, C. H. Tanga, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464; d) L. Shi, W. J. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687.
[12] W. Fan, S. Ma, *Chem. Commun.* **2013**, *49*, 10175.
[13] For a recent review on the normal three-component reaction of aldehydes, terminal alkynes, and amines for the synthesis of propargylic amines, see: V. A. Peshkov, O. P. Perehivko, E. V. van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790.
[14] T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 6097; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971.
[15] Crystal data for (*S*)-**4m**: $C_{26}H_{24}BrNO_2$, MW = 462.37, monoclinic, space group *P*2(1), final *R* indices [$I > 2\sigma(I)$]: $R1 = 0.0757$, $wR2 = 0.1683$; *R* indices (all data): $R1 = 0.2088$, $wR2 = 0.2379$; $a = 11.100(3)$, $b = 13.908(3)$, $c = 29.172(7)$ Å, $\alpha = 90.00$, $\beta = 94.769\ (4)$, $\gamma = 90.00°$, $V = 4488.0\ (18)$ Å^3, $T = 273(2)$ K, $Z = 8$, reflections collected/unique: 26252/6222 ($R_{int} = 0.0686$), number of observations [$> 2\sigma(I)$]: 16259, parameters: 1119. CCDC 962647 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

