DOI: 10.1002/adsc.201000015

Efficient and General Synthesis of 3-Aminoindolines and 3-Aminoindoles *via* Copper-Catalyzed Three-Component Coupling Reaction

Dmitri Chernyak,[a] Natalia Chernyak,[a] and Vladimir Gevorgyan[a,*]

[a] Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607-7061, USA
Fax: (+1)-312-355-0836; phone: (+1)-312-355-3579; e-mail: vlad@uic.edu

Received: January 7, 2010; Revised: March 11, 2010; Published online: April 7, 2010

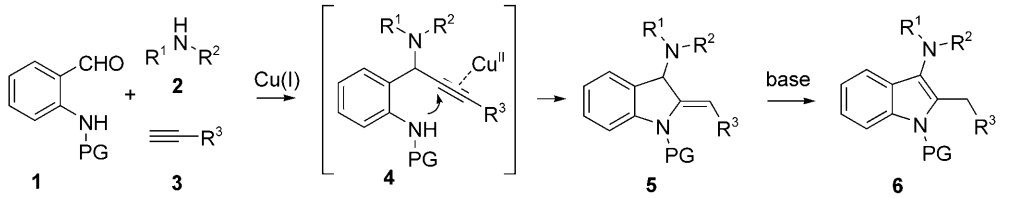
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000015.

Abstract: An efficient three-component coupling (TCC) reaction toward a variety of 3-aminoindoline and 3-aminoindole derivatives has been developed. This cascade transformation proceeds *via* the copper-catalyzed coupling reaction between 2-aminobenzaldehyde, a secondary amine, and an alkyne leading to a propargylamine intermediate which, under the reaction conditions, undergoes cyclization into the indoline core. The latter, upon treatment with a base, smoothly isomerizes into the indole. Alternatively, the indole can directly be synthesized in a one-pot sequential reaction.

Keywords: 3-aminoindolines; 3-aminoindoles; copper; synthetic methods; three-component coupling

Indole and indoline structural motifs are ubiquitously found in a wide range of natural products and pharmaceuticals.[1] In particular, 3-aminoindoles and indolines have found a broad application in medicinal chemistry as effective anticancer agents, compounds with analgesic properties, and agents for prevention of type II diabetes. However, the reported examples on the synthesis of 3-aminoindoles[2] and 3-aminoindolines[3] are limited in scope and require multistep preparation of starting materials. Thus, the development of a simple and general synthesis of 3-aminoindoles and 3-aminoindolines from easily available starting materials is warranted. One of the reasonable solutions to this problem would be the assembly of indole and indoline cores *via* a multicomponent coupling reaction (MCR).[4]

Herein, we wish to report an efficient Cu-catalyzed three-component coupling reaction of *N*-protected 2-aminobenzaldehydes **1** with secondary amines **2** and terminal acetylenes **3** into the 3-aminoindolines **5** and their subsequent isomerization into indoles **6** (Scheme 1). The multicomponent Mannich reaction between benzaldehydes, secondary amines and acetylenes is well-documented.[5] Recently, the synthesis of benzofurans *via* a three-component coupling reaction of *o*-hydroxybenzaldehydes, acetylenes and secondary amines catalyzed by copper salts has been reported.[6] However, analogous multicomponent reactions of 2-aminobenzaldehydes are unknown. We envisioned that a TCC reaction of *N*-protected 2-aminobenzaldehydes **1**, secondary amine **2** and terminal alkyne **3** would lead to the formation of propargylamine intermediate **4**,[7] which, upon activation of the triple bond with a π-philic metal, would undergo an intramolecular 5-*exo-dig* cyclization[8,9,10] into indoline **5**. It was expected that under the reaction conditions, a subsequent isomerization of **5** into 3-aminoindoles **6** would occur (Scheme 1).

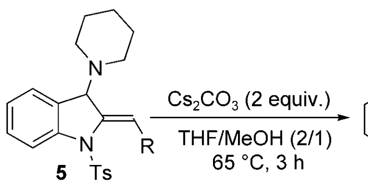


Scheme 1. Proposed synthesis of 3-aminoindoles.

To test this hypothesis, the reaction of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide, piperidine and phenylacetylene in the presence of different metal salts has been examined (Table 1). It was found that employment of gold(I) and (III), as well as silver and copper salts, was not effective resulting in formation of propargylamine intermediate **4** only (entries 1–6). The TCC reaction in the presence of CuCl and $Cu(OTf)_2$ produced trace amounts of **5** (entry 7). Substantial improvement of the yields was achieved in the presence of stoichiometric amounts of Et_3N and Cs_2CO_3 (entries 8 and 9). Furthermore, employment of DMAP led to the nearly quantitative formation of indoline **5** (entry 10)! Employment of a sole copper source in the presence of DMAP (entries 11 and 12) was less efficient as compared to the use of a Cu(I)/Cu(II) binary system.[11]

Surprisingly, no formation of indole **6** was observed under these reaction conditions. Next, under the optimized conditions, the scope of this new TCC reaction has been examined (Table 2). Gratifyingly, we found that this transformation is very general for a wide range of different acetylenes, aldehydes and secondary amines providing an easy access to densely-substituted indolines **5**. Thus, employment of piperidine, morpholine, and pyrrolidine produced aminoindolines in good to excellent yields. Acyclic dibenzyl-, diallyl-, diethyl- and diisobutylamines were similarly effective. Different alkynes, bearing alkyl or aryl substituents, displayed high reactivity in this transformation. A variety of different groups at the aromatic moiety of the aldehyde, such as chloro (entries 18 and 19), bromo (entries 20–23), methyl (entry 24), methoxy (entry 25), and fluoro (entry 26), were also perfectly tolerated. Additionally, we have shown that the *N*-4-nitrobenzenesulfonyl group can be tolerated under our reaction conditions resulting in the formation of indoline **5aa** in good yield (entry 27). Reaction of *N*-tosylamino-3-naphtalaldehyde resulted in the formation of tricyclic indoline **5ab** although in slightly decreased yield (entry 28). Employment of 1,2,3,4-tetrahydroquinoline resulted in the formation of the corresponding indoline **5ac** in 68% isolated yield (entry 29). Furthermore, by utilizing trimethylsilylacetylene as acetylene surrogate,[12] an exomethylene moiety-possessing indoline **5ad** was obtained in 64% yield (entry 30).

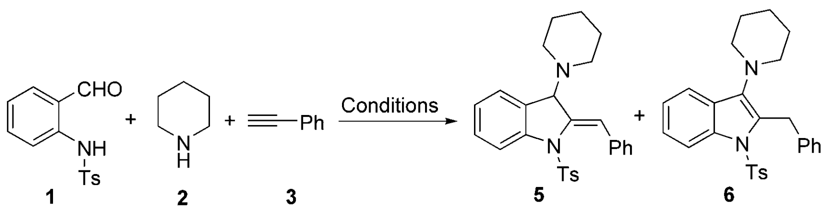
Next, conversion of indolines **5** into their more stable aromatic isomers, indoles **6**, was explored [Eq. (1)]. We reasoned that this isomerization reaction should occur in the presence of a base.[13] Indeed, it



(1)

6a, R = Ph, **95%**
6b, R = *p*-Tol, **98%**
6d, R = CH_2OMe, **89%**

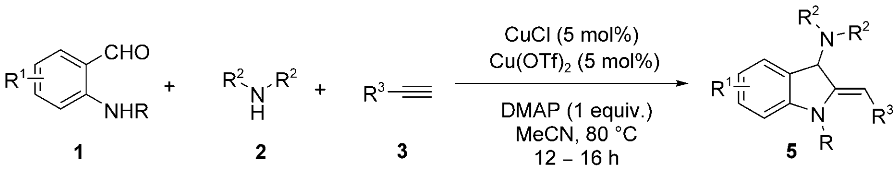
Table 1. Optimization of TCC coupling.[a]



#	Conditions – Catalyst (mol%)	Additive (equiv)	**5**, Yield [%][b]
1	AuCl (5)	none	– (83)[c]
2	$AuCl_3$ (5)	none	– (75)[c]
3	$NaAuCl_4 \cdot 2H_2O$ (5)	none	traces
4	AgOTf (5)	none	– (70)[c]
5	CuCl (5)	none	– (60)[c]
6	$Cu(OTf)_2$ (5)	none	– (51)[c]
7	CuCl (5), $Cu(OTf)_2$ (5)	none	7 (80)[c]
8	CuCl (5), $Cu(OTf)_2$ (5)	NEt_3 (1.0)	48
9	CuCl (5), $Cu(OTf)_2$ (5)	Cs_2CO_3 (1.0)	51
10	CuCl (5), $Cu(OTf)_2$ (5)	DMAP (1.0)	98
11	CuCl (5)	DMAP (1.0)	70 (10)[c]
12	$Cu(OTf)_2$ (5)	DMAP (1.0)	47 (21)[c]

[a] All reactions were performed with **1** (0.3 mmol), **2** (0.3 mmol) and **3** (0.45 mmol) in MeCN at 80 °C.
[b] Yield of the isolated product after flash chromatography on silica gel.
[c] Yield in parentheses given for formation of the corresponding propargylamine **4**.

Table 2. TCC synthesis of 3-aminoindolines.[a]



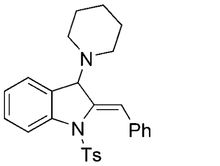
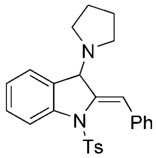
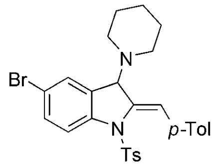
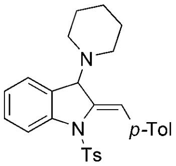
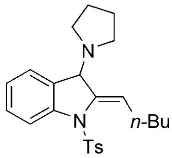
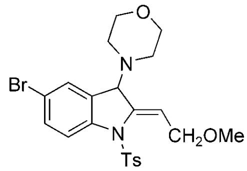
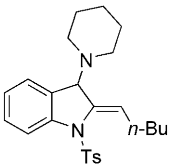
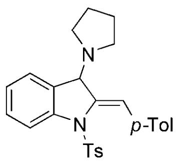
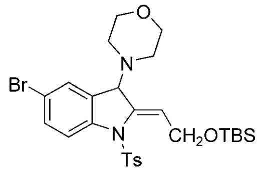
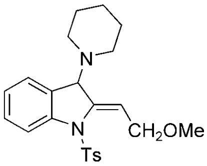
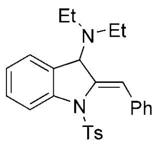
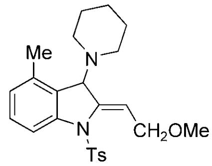
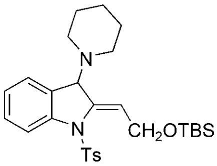
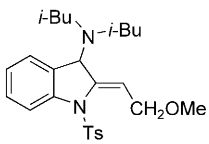
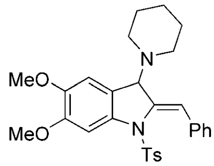
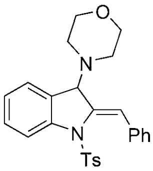
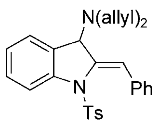
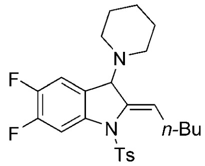
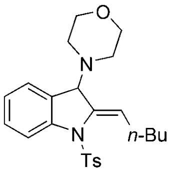
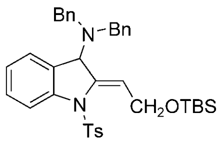
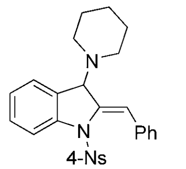
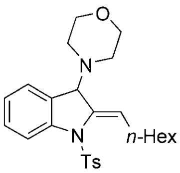
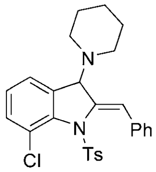
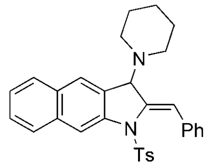
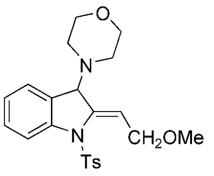
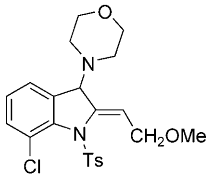
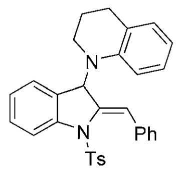
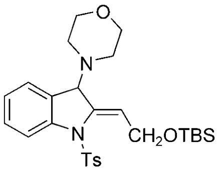
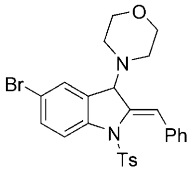
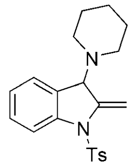
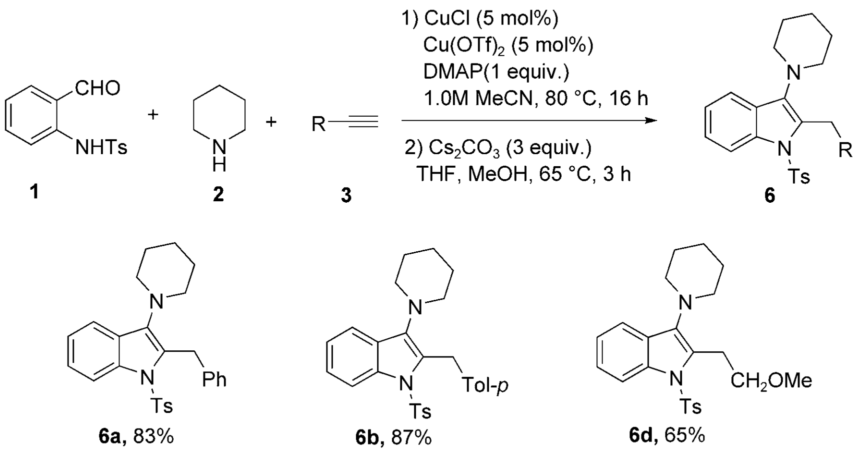
Entry	Product		Yield[b] [%]	Entry	Product		Yield[b] [%]	Entry	Product		Yield[b] [%]
1		**5a**	98	11		**5k**	75	21		**5u**	80
2		**5b**	94	12		**5l**	77	22		**5v**	89
3		**5c**	78	13		**5m**	78	23		**5w**	80
4		**5d**	92	14		**5n**	70	24		**5x**	97
5		**5e**	90	15		**5o**	74	25		**5y**	34
6		**5f**	61	16		**5p**	68	26		**5z**	32
7		**5g**	78	17		**5q**	90	27		**5aa**	73
8		**5h**	84	18		**5r**	68	28		**5ab**	45

Table 2. (Continued)

Entry	Product		Yield[b] [%]	Entry	Product		Yield[b] [%]	Entry	Product		Yield[b] [%]
9		**5i**	95	19		**5s**	57	29		**5ac**	68
10		**5j**	87	20		**5t**	82	30		**5ad**	64[c]

[a] All reactions were performed with **1** (0.3 mmol), amine **2** (0.3 mmol), acetylene **3** (0.45 mmol) in MeCN (1 M) at 80 °C for 12–16 h.
[b] Yield of the isolated product after flash chromatography on silica gel.
[c] Reaction was performed with trimethylsilylacetylene (1.5 equiv.).



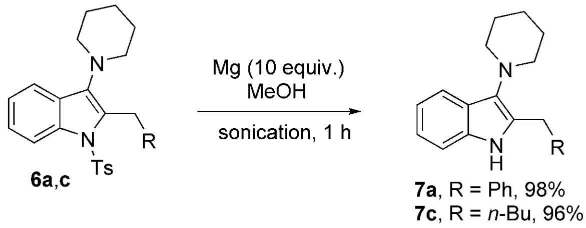
Scheme 2. One-pot TCC synthesis of indoles **6**.

was found that heating indolines **5** with cesium carbonate in THF/MeOH mixture at 65 °C resulted in formation of the corresponding indoles **6a–c** in excellent yields.

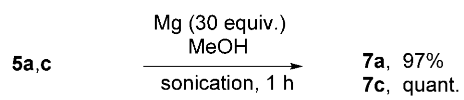
Encouraged by these results, we attempted a three-component one-pot synthesis of 3-aminoindoles **6** (Scheme 2).

Thus, the Cu-catalyzed TCC reaction of *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **1**, piperidine **2**, and acetelynes **3** produced indolines **5**. Subsequent base-assisted one-pot isomerization of the latter produced indoles **6a**, **b**, **d** in good to high yields (Scheme 2). It deserves mentioning that *N*-tosylindoles **6** upon treatment with magnesium powder[14] could smoothly be detosylated into the corresponding N–H indoles **7a**, **c** [Eq. (2)]. Interestingly, treatment of *N*-tosylindolines **5a**, **c** with Mg not only caused *N*-detosylation, but also highly efficient isomerization into indoles **7a**, **c** [Eq. (3)].

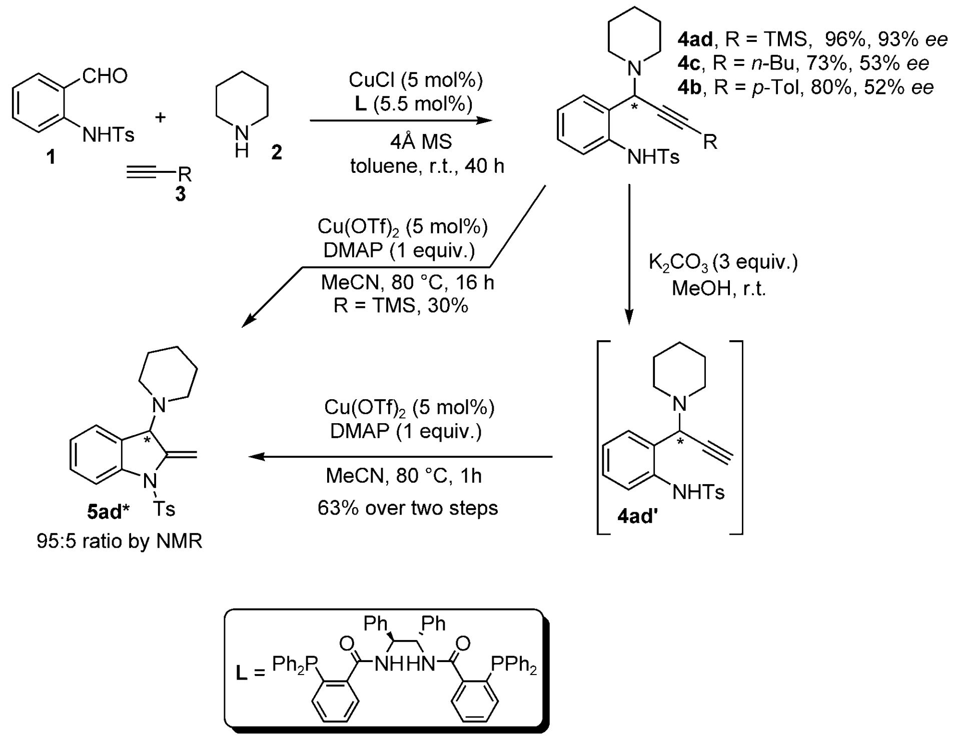
With the new efficient methodology for assembly of the 3-aminoindoline core in hand, we performed



(2)



(3)



Scheme 3. Enantioselective TCC synthesis of indoline **5***.

initial studies toward an enantioselective version of this transformation (Scheme 3). It was found that under a modified Knochel's protocol for enantioselective TCC assembly of propargylamines[15,16] (with Trost's C_2-symmetrical ligand[17]), *N*-(2-formylphenyl)-4-methylbenzenesulfonamide **1**, piperidine **2**, and trimethylsilylacetelyne **3** underwent smooth coupling reaction to produce **4ad** in high yield and 93% enantioselectivity. Employment of alkyl- and arylacetylenes **3** in the synthesis of propargylamines (**4c** and **4b**) resulted in good chemical yields, but moderate enantioselectivity (53 and 52% *ee*, respectively). Direct cycloisomerization of **4ad** gave poor yield of the desired indoline **5ad*** (30%). However, desilylation of **4ad** into **4ad′** followed by its cyclization under standard conditions produced enantioenriched indoline **5ad*** in good yield with virtually complete preservation of enantioselectivity (Scheme 3).

In summary, we have developed a novel highly efficient and general copper-catalyzed three component coupling reaction of *N*-protected 2-aminobenzaldehydes with secondary amines and terminal acetylenes into 3-aminoindolines. It was shown that the 3-aminoindolines, under basic conditions, could highly efficiently be transformed into the isomeric 3-aminoindoles. Alternatively, the latter can be obtained *via* a one-pot TCC procedure. In addition, we have demonstrated that the optically active indoline could be synthesized via a stepwise enantioselective version of this novel TCC protocol.

Experimental Section

General Procedure

In a dry and argon-flushed Wheaton 1-mLV-vial, equipped with a magnetic stirring bar and a screw cap, CuCl (0.015 mmol, 5 mol%), $Cu(OTf)_2$ (0.015 mmol, 5 mol%), DMAP (0.3 mmol, 1 equiv.) and aldehyde (0.3 mmol, 1 equiv.) were suspended in dry acetonitrile (0.3 mL). Secondary amine (0.3 mmol, 1 equiv.) and alkyne (0.45 mmol, 1.5 equiv.) were added and the reaction mixture was stirred at 80 °C until TLC analysis showed full conversion of an aldehyde. The reaction mixture then was filtered through Celite and washed with dichloromethane. The crude product was concentrated under vacuum and purified by column chromatography on silica gel.

Acknowledgements

We gratefully acknowledge the financial support of the National Institute of Health (1P50 GM-086145).

References

[1] a) H. Takayama. M. Kitajima, N. Kogure, *Curr. Org. Chem.* **2005**, *9*, 1445; b) S. E. Lewis, *Tetrahedron* **2006**, *62*, 8655; c) C. Sánchez, C. Méndez, J. A. Salas, *Nat. Prod. Rep.* **2006**, *23*, 1007; d) K. Higuchi, T. Kawasaki, *Nat. Prod. Rep.* **2007**, *24*, 843; e) L. Gupta, A. Talwar,

P. M. S. Chauchan, *Curr. Med. Chem.* **2007**, *14*, 1789; f) S. A. Patil, R. Patil, D. D. Miller, *Curr. Org. Chem.* **2008**, *12*, 691.

[2] a) N. M. Przheval'skii, N. S. Skvortsova, I. V. Magedov, *Chem. Heterocycl. Comp.* **2002**, *38*, 1055; b) N. M. Przheval'skii, N. S. Skvortsova, I. V. Magedov, *Chem. Heterocycl. Comp.* **2004**, *40*, 1435; c) C. M. Seong, C. M. Park, J. Choi, N. S. Park, *Tetrahedron Lett.* **2009**, *50*, 1029; d) A. Couture, E. Deniau, Y. Gimbert, P. Grandclaudon, *Tetrahedron* **1993**, *49*, 1431.

[3] a) Z. Gan, P. T. Reddy, S. Quevillon, S. Couve-Bonnaire, P. Arya, *Angew. Chem.* **2005**, *117*, 1390; *Angew. Chem. Int. Ed.* **2005**, *44*, 1366; b) T. Sunazuka, T. Hirose, S. Omura, *Acc. Chem. Res.* **2008**, *41*, 302; c) S. P. Marsden, E. L. Watson, S. A. Raw, *Org. Lett.* **2008**, *10*, 2905.

[4] For reviews on MCR, see: a) G. Posner, *Chem. Rev.* **1986**, *86*, 831; b) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123; c) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321; d) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115; e) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

[5] a) B. Yan, Y. Liu *Org. Lett.* **2007**, *9*, 4323; b) R.-V. Nguyen, C.-J. Li, *Synlett* **2008**, 1897; c) M. M. Salter, J. Kobayashi, Y. Shimizu, S. Kobayashi, *Org. Lett.* **2006**, *8*, 3533; d) N. Azizi, L. Torkiyan, M. R. Saidi, *Org. Lett.* **2006**, *8*, 2079; e) D. A. Black, B. A. Arndtsen, *J. Org. Chem.* **2005**, *70*, 5133; f) T. Ollevier; E. Nadeau, *J. Org. Chem.* **2004**, *69*, 9292; g) T.-P. Loh, S.-L. Chen, *Org. Lett.* 2002, 4, 3647; h) T.-P. Loh, S. B. K. W. Liung, K.-L. Tan, L.-L. Wei, *Tetrahedron* **2000**, *56*, 3227; i) S. Kobayashi; T. Busujima, S. Nagayama, *Synlett* **1999**, 545; j) T.-P. Loh, L.-L. Wei, *Tetrahedron Lett.* **1998**, *39*, 323.

[6] a) N. Sakai, N. Uchida, T. Konakahara, *Tetrahedron Lett.* **2008**, *49*, 3437; b) H. Li, J. Liu, B. Yan, Y. Li, *Tetrahedron Lett.* **2009**, *50*, 2353.

[7] For selected examples of Cu-catalyzed syntheses of propargylamines *via* TCC, see: a) M. K. Patil, M. Keller, B. M. Reddy, P. Pale, J. Sommer, *Eur. J. Org. Chem.* **2008**, 4440; b) M. L. Kantam, S. Laha, J. Yadav, S. Bhargava, *Tetrahedron Lett.* **2008**, *49*, 3083; c) M. Niu, Z. Yin, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 3961; d) S. B. Park, H. Alper, *Chem. Commun.* **2005**, 1315; e) L. W. Bieber, M. F. da Silva, *Tetrahedron Lett.* **2004**, *45*, 8281; f) A. S.-Y. Lee, G.-A. Chen, Y.-T. Chang, S.-F. Chu, *Synlett* **2009**, 441; for gold-catalyzed reaction, see: g) V. K.-Y. Loa, K. K.-Y. Kung, M.-K. Wong, C.-M. Che, *J. Organomet. Chem.* **2009**, *694*, 583; h) X. Zhang, A. Corma, *Angew. Chem.* **2008**, *120*, 4430; *Angew. Chem. Int. Ed.* **2008**, *47*, 4358; i) M. Kidwai, V. Bansal, A. Kumarb, S. Mozumdar, *Green Chem.* **2007**, *9*, 742; j) B. Huang, X. Yao, C.-J. Lib, *Adv. Synth. Catal.* **2006**, *348*, 1528; k) V. K.-Y. Lo, Y. Liu, M.-K. Wong, C.-M. Che, *Org. Lett.* **2006**, *8* 1529; l) B. T. Elie, C. Levine, I. Ubarretxena-Belandia, A. Varela-Ramírez, R. J. Aguilera, R. Ovalle, M. Contel, *Eur. J. Inorg. Chem.* **2009**, 3421; for other transition metal-catalyzed reactions, see: m) Y. Zhang, P. Li, M. Wang, L. Wang, *J. Org. Chem.* **2009**, *74*, 4364; n) P. Li, Y. Zhang, L. Wang, *Chem. Eur. J.* **2009**, *15*, 2045.

[8] For example, on the Pt-catalyzed 5-*exo-dig*/aza-Cope rearrangement cascade toward indoles, see: K. Cariou, B. Ronan, S. Mignani, L. Fensterbank, M. Malacria, *Angew. Chem.* **2007**, *119*, 1913; *Angew. Chem. Int. Ed.* **2007**, *46*, 1881.

[9] For selected reviews on palladium catalyzed 5-*endo-dig* cyclizations into indoles, see: a) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873; b) M. Lautens, D. Alberico, C. Bressy, *Pure Appl. Chem.* **2006**, *78*, 351.

[10] L. Yu. Ukhin, V. N. Komissarov, G. I. Orlova, G. S. Borodkin, S. V. Lindeman, V. N. Khrustalev, Yu. T. Struchkov, *Izv. Akad. Nauk Ser. Khim.* **1995**, 2236.

[11] Apparently, CuCl is a more efficient catalyst for the assembly of propargylamine **4** from 2-aminobenzaldehyde, secondary amine, and terminal alkyne; while $Cu(OTf)_2$ is a more active catalyst for the following 5-*exo-dig* cyclization of **4** into indoline **5** (Scheme 1).

[12] For desilylation of TMS-alkynes during cycloisomerizations, see, for example: a) R. C. Larock, E. K. Yum, M. D. Refvic, *J. Org. Chem.* **1998**, *63*, 7652; b) M. L. Crewley, I. Goljer, D. J. Jenkin, J. F. Mehlmann, L Nogle, R. Dooley, P. E. Mahaney, *Org. Lett.* **2006**, *8*, 5837. See also ref.[6a]

[13] For an analogous base-assisted isomerization of dihydrofurans into furans, see: M. Tiecco, L. Testaferri, M. Tingoli, F. Marini, *J. Org. Chem.* **1993**, *58*, 1349.

[14] B. Nyasse, L. Grehn, U. Ragnarsson, *Chem. Commun.* **1997**, 1017.

[15] For the synthesis of propargylamines *via* an enantioselective TCC reaction, see: a) C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268; b) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763; c) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 6097; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971; d) A. Bisai, V. K. Singh, *Org. Lett.* **2006**, *8*, 2405.

[16] For a recent review on enatioselective addition of alkynes to carbonyl compounds, see: B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963.

[17] a) B. M. Trost, D. L. Van Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327; b) B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res.* **2006**, *39*, 747; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921; d) Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264; *Angew. Chem. Int. Ed.* **2008**, *47*, 258.

