JOC*Note*

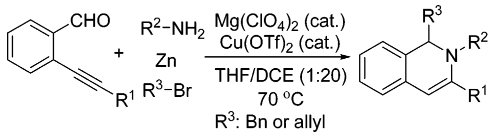
Synthesis of Functionalized 1,2-Dihydroisoquinolines via Multicomponent One-Pot Reaction of 2-Alkynylbenzaldehyde, Amine, Zinc, and Allylic Bromide or Benzyl Bromide

Ke Gao[†] and Jie Wu*[,†,‡]

Department of Chemistry, Fudan University, 220 Handan Road,
Shanghai 200433, China, and State Key Laboratory of
Organometallic Chemistry, Shanghai Institute of Organic
Chemistry, Chinese Academy of Sciences, 354 Fenglin Road,
Shanghai 200032, China

jie_wu@fudan.edu.cn

Received August 1, 2007



A multicomponent one-pot reaction of 2-alkynylbenzaldehydes, amines, zinc, and allylic bromide or benzyl bromide using the combination of $Mg(ClO_4)_2$/$Cu(OTf)_2$ as catalyst in THF/DCE (1:20) is described, which provides an efficient and practical route for the synthesis of functionalized 1,2-dihydroisoquinolines.

As a prevailed scaffold, the 1,2-dihydroisoquinoline ring was found in many natural products and pharmaceuticals with remarkable biological activities.[1] Because of their importance as substructures[1] which was mentioned above and as synthetic intermediates[2] in total synthesis of natural alkaloids, significant effort continues to be given to the development of new 1,2-dihydroisoquinoline-based structures and new methods for their construction.[3] For instance, recently it was reported that 1,2-dihydroisoquinoline skeletons could be obtained through the direct addition of various carbon pronucleophiles to *ortho*-alkynylaryl aldimines catalyzed by Lewis acid.[3a−c] When chloroform was utilized as a carbon pronucleophile, the reaction could even be performed in the absence of a catalyst.[3d] The scaffold also could be generated from isoquinolines via multicomponent reaction.[3i−l] Larock and co-workers have reported the palladium-catalyzed synthetic methods for related isoquinoline formation using *o*-alkynylarylaldimines, having a *tert*-butyl group on the nitrogen atom.[4] As part of a continuing effort in our laboratory toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds,[5,6] we also discovered that 2,3-disubstituted-1,2-dihydroisoquinolin-1-ylphosphonates could be generated from three-component reactions of 2-alkynylbenzaldehydes, amines, and diethylphosphite.[6] Meanwhile, recently we reported an efficient synthesis of homobenzylamines and homoallylamines via three-component benzylation and allylation of aromatic, aliphatic aldehydes and amines[7] (Scheme 1, eq 1). Prompted by this result and our efforts for the 1,2-dihydroisoquinoline synthesis,[6] we conceived that functionalized 1,2-dihydroisoquinolines **4** may be synthesized from multicomponent reaction[8] of 2-alkynylbenzaldehyde **1**, amine **2**, zinc dust, and allylic bromide or benzyl bromide **3** under suitable conditions (Scheme 1, eq 2). The results are disclosed herein.

To test this idea, our studies commenced with the reaction of 2-alkynylbenzaldehyde **1a**,[4e] aniline **2a**, zinc dust, and allylic bromide **3a** (Scheme 2). To our surprise, in contrast to our previous report,[7] compound **5a** was obtained instead of product **5b** when the reaction was performed at room temperature in THF. This is presumably due to the existence of a triple bond,

---

[†] Fudan University.

[‡] Shanghai Institute of Organic Chemistry.

(1) For selected examples, see: (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Australia, 1998; Vol 1. (b) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. *J. Med. Chem.* **2006**, *49*, 6954. (c) Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y. *J. Nat. Prod.* **1999**, *62*, 780. (d) Oi, S.; Ikedou, K.; Takeuchi, K.; Ogino, M.; Banno, Y.; Tawada, H.; Yamane, T. PCT Int. Appl. 2002, 600 pp (WO 2002062764 A1).

(2) For selected examples, see: (a) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (b) Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596. (c) Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476. (d) Zheng, S.; Chan, C.; Furuuchi, T.; Wright, B. J. D.; Zhou, B.; Guo, J.; Danishefsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1754. (e) Vincent, G.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1517.

(3) (a) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462 and references cited therein. (b) Asao, N.; Yudha, S. S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526. (c) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822. (d) Asao, N.; Iso, K.; Yudha, S. S. *Org. Lett.* **2006**, *8*, 4149. (e) Mori, S.; Uerdingen, M.; Krause, N.; Morokuma, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4715. (f) Asao, N.; Chan, C. S.; Takahashi, K.; Yamamoto, Y. *Tetrahedron* **2005**, *61*, 11322. (g) Ohtaka, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 7339. (h) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4257. (i) Yavari, I.; Ghazanfarpour-Darjani, M.; Sabbaghan, M.; Hossaini, Z. *Tetrahedron Lett.* **2007**, *48*, 3749. (j) Shaabani, A.; Soleimani, E.; Khavasi, H. R. *Tetrahedron Lett.* **2007**, *48*, 4743. (k) Wang, G.-W.; Li, J.-X. *Org. Biomol. Chem.* **2006**, *4*, 4063. (l) Diaz, J. L.; Miguel, M.; Lavilla, R. *J. Org. Chem.* **2004**, *69*, 3550.

(4) (a) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920. (c) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042. (d) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (e) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86. (f) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042. (g) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553.

(5) (a) Zhang, L.; Wu, J. *Adv. Synth. Catal.* **2007**, *349*, 1047. (b) Wang, W.; Ding, Q.; Fan, R.; Wu, J. *Tetrahedron Lett.* **2007**, *48*, 3647. (c) Wang, Z.; Wang, B.; Wu, J. *J. Comb. Chem.* **2007**, *9*, 811.

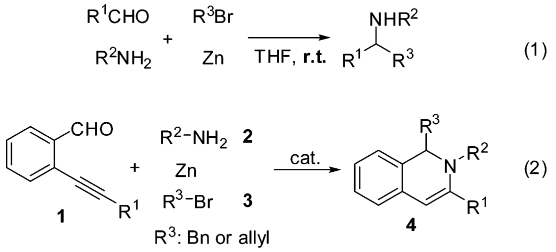
(6) (a) Sun, W.; Ding, Q.; Sun, X.; Fan, R.; Wu, J. *J. Comb. Chem.* **2007**, *9*, 690. (b) Ding, Q.; Ye, Y.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 5439.

(7) Fan, R.; Pu, D.; Qin, L.; Wen, F.; Yao, G.; Wu, J. *J. Org. Chem.* **2007**, *72*, 3149.

(8) For selected examples, see: (a) *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (b) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (c) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekenth, A. R.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (d) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (e) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101. (f) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (g) Bienayme, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.−Eur. J.* **2000**, *6*, 3321. (h) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366. (i) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647. (j) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133.

10.1021/jo7016839 CCC: $37.00

SCHEME 1



SCHEME 2

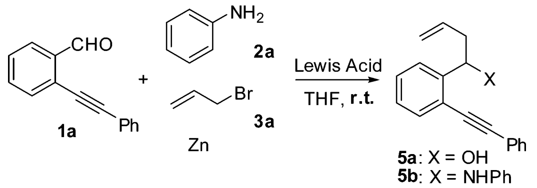
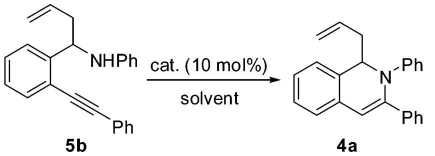


TABLE 1. Reaction of Compound 5b Catalyzed by Various Lewis Acids



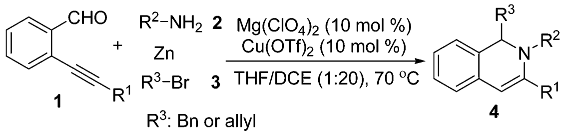
entry	Lewis acid	solvent	temp (°C)	time (h)	yield (%)[a]
1	$Zn(OTf)_2$	DCE	25	24	59
2	$In(OTf)_3$	DCE	25	24	50
3	AgOTf	DCE	60	24	46
4	$PdCl_2$	DCE	25	12	26
5	$Cu(OTf)_2$	DCE	25	18	87
6	CuI	DCE	25	24	trace
7	$Mg(ClO_4)_2$	DCE	25	24	15
8	$Yb(OTf)_3$	DCE	25	24	trace
9	$Dy(OTf)_3$	DCE	25	24	trace
10	$LiClO_4$	DCE	25	24	trace
11	TsOH	DCE	25	24	trace
12	$Cu(OTf)_2$	THF	25	24	NR
13	$Cu(OTf)_2$	Toluene	60	10	58
14	$Cu(OTf)_2$	MeCN	25	24	NR
15	$Cu(OTf)_2$	CH_2Cl_2	25	19	80
16	$Cu(OTf)_2$	EtOH	25	30	62

[a] Isolated yield based on compound **5b**. DCE: 1,2-dichloroethane.

which may deactivate the organozinc reagent generated in situ. The presence of Lewis acid should enhance the activity of imine. After screening various Lewis acids (10 mol %) [$Zn(OTf)_2$, AgOTf, $AgBF_4$, $Cu(OTf)_2$, $Mg(ClO_4)_2$, $LiClO_4$, $Yb(OTf)_3$, $Dy(OTf)_3$, $In(OTf)_3$, $Bi(OTf)_3$, $Sn(OTf)_2$, I_2], we still could not observe the formation of desired product **4**, even at higher temperature. Only addition product **5b** was generated in most cases. $Mg(ClO_4)_2$ (10 mol %) was the most efficient catalyst in this reaction, and the corresponding product **5b** was obtained in 87% yield after 3 h. However, a complicated mixture was obtained when $Cu(OTf)_2$ was utilized as catalyst in this reaction.

With compound **5b** in hand, we started to investigate the possibility of cyclization, and the results are shown in Table 1. To our delight, we observed the formation of the desired product **4a** in 59% isolated yield when $Zn(OTf)_2$ was employed as catalyst (Table 1, entry 1). The result was dramatically improved when the reaction was performed in the presence of $Cu(OTf)_2$ as catalyst at room temperature in DCE (Table 1, entry 5, 87% yield). Inferior results were observed when other catalysts were used. Different solvents were also screened for the $Cu(OTf)_2$-catalyzed reaction of **5b**. DCE was demonstrated to be the best choice of solvent. No reaction occurred when THF or MeCN was used as solvent (Table 1, entries 12 and 14).

TABLE 2. Multicomponent One-Pot Reaction of 2-Alkynylbenzaldehyde 1, Amine 2, Zinc Dust, and Allylic Bromide or Benzylic Bromide 3 Catalyzed by $Mg(ClO_4)_2$ (10 mol %)/$Cu(OTf)_2$ (10 mol %)



entry	R^1	R^2	R^3	product	yield (%)[a]
1	C_6H_5 **1a**	C_6H_5 **2a**	allyl **3a**	**4a**	90
	C_6H_5 **1a**				
2	C_6H_5 **1a**	4-$MeOC_6H_4$ **2b**	allyl **3a**	**4b**	68
3	C_6H_5 **1a**	4-MeC_6H_4 **2c**	allyl **3a**	**4c**	71
4	C_6H_5 **1a**	4-FC_6H_4 **2d**	allyl **3a**	**4d**	81
5	C_6H_5 **1a**	4-ClC_6H_4 **2e**	allyl **3a**	**4e**	73
6	C_6H_5 **1a**	Bn **2f**	allyl **3a**	**4f**	35
7	C_6H_5 **1a**	$(Me)_2CHCH_2$ **2g**	allyl **3a**	**4g**	20
8	C_6H_5 **1a**	C_6H_5 **2a**	Bn **3b**	**4h**	79
9	C_6H_5 **1a**	4-$MeOC_6H_4$ **2b**	Bn **3b**	**4i**	75
10	C_6H_5 **1a**	4-FC_6H_4 **2d**	Bn **3b**	**4j**	78
11	4-$MeOC_6H_4$ **1b**	C_6H_5 **2a**	allyl **3a**	**4k**	70
12	4-$MeOC_6H_4$ **1b**	4-$MeOC_6H_4$ **2b**	allyl **3a**	**4l**	76
13	*n*-Bu **1c**	4-$MeOC_6H_4$ **2b**	allyl **3a**	**4m**	68
14	cyclopropyl **1d**	4-$MeOC_6H_4$ **2b**	allyl **3a**	**4n**	75

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

After successful generation of 1,2-dihydroisoquinoline **4a** from **5b**, we embarked on the one-pot multicomponent reaction of 2-alkynylbenzaldehyde **1a**, aniline **2a**, zinc dust, and allylic bromide **3a** catalyzed by the combination of $Mg(ClO_4)_2$ (10 mol %) and $Cu(OTf)_2$ (10 mol %). Because THF is crucial for the allylzinc bromide generation[7] and the cyclization gave the best result in DCE, the solvent combination of THF/DCE was considered in the reaction. After screening the ratio of solvent, it was found that this one-pot reaction proceeded most efficiently in THF/DCE (1:20), and the desired product **4a** could be prepared in 70% yield after 9 h at room temperature. Further studies revealed that the yield could be increased to 90% when the reaction was performed at 70 °C, and only 2 h was needed for completion of the reaction. Decreasing the amount of catalyst retarded the reaction.

To demonstrate the generality of this method, we started to investigate the scope of this reaction under the optimized reaction conditions [$Mg(ClO_4)_2$ (10 mol %), $Cu(OTf)_2$ (10 mol %), THF/DCE (1:20), 70 °C], and the results are shown in Table 2. From Table 2, it was found that, for most cases, the one-pot reactions of 2-alkynylbenzaldehydes **1**, aromatic amines **2**, zinc dust, allylic bromide, or benzyl bromide **3** catalyzed by $Mg(ClO_4)_2$/$Cu(OTf)_2$ furnished the corresponding functionalized 1,2-dihydroisoquinolines **4** in good yields. Additionally, the reaction of aniline derivatives was found to tolerate a range of different groups with different electronic demands on the aromatic rings involving electron-donating and electron-withdrawing groups. For example, 2-alkynylbenzaldehydes **1a** reacted with *p*-anisidine **2b**, zinc, and allylic bromide **3a** leading to the desired 1,2-dihydroisoquinolines **4b** in 68% yield (Table 2, entry 2). Reaction of 2-alkynylbenzaldehydes **1a** with 4-fluorobenzeneamine **2d** in the presence of zinc and allylic bromide **3a** proceeded smoothly to generate compound **4d** in 81% yield (Table 2, entry 4). Inferior results were displayed when aliphatic amines were employed in this reaction. For instance, a 35% yield of 1,2-dihydroisoquinolines **4f** was obtained when benzylamine was utilized in the reaction (Table 2, entry 6). Only 20% of compound **4g** was isolated when *iso*-butylamine was employed (Table 2, entry 7). Besides allylic bromide **3a**, benzyl bromide **3b** was also a good partner for this kind of transformation (Table 2, entries 8−10). We also tried other 2-alkynylbenzaldehydes, such as **1b**−**d**, in the reactions of aromatic amines, zinc, and allylic bromide **3a**. Good yields were observed for each case (Table 2, entries 11−14).

In conclusion, we have described a facile and efficient route for the synthesis of functionalized 1,2-dihydroisoquinolines via the multicomponent one-pot reaction of 2-alkynylbenzaldehydes, amines, zinc dust, allylic bromides, or benzyl bromides catalyzed by $Mg(ClO_4)_2/Cu(OTf)_2$. We anticipate that this method will be readily applicable to combinatorial library synthesis due to the efficiency and novelty of this method, combined with the operational simplicity of the present process. Efforts along this line are currently in progress.

Experimental Section

General Procedure: A solution of 2-alkynyl benzaldehyde **1** (0.2 mmol), amine **2** (0.4 mmol), $Cu(OTf)_2$ (7.2 mg, 0.02 mmol), and $Mg(ClO_4)_2$ (4.5 mg, 0.02 mmol) in DCE (2.0 mL) was added to a mixture of allylic bromide or benzyl bromide **3** (1.2 mmol) and zinc dust (91.5 mg, 1.4 mmol) in THF under an N_2 atmosphere at 70 °C. After completion of the reaction as indicated by TLC, the reaction mixture was cooled and partitioned between ethyl acetate and saturated NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluting with PE/EA = 100/1 to 50/1) to provide the desired product **4**. Selected example: 1-allyl-3-phenyl-2-*p*-tolyl-1,2-dihydroisoquinoline (**4c**), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.30−2.34 (m, 1H), 2.73−2.76 (m, 1H), 4.92−4.94 (m, 1H), 5.16−5.24 (m, 2H), 6.12−6.19 (m, 1H), 6.62 (s, 1H), 6.82 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 11.4 Hz, 2H), 7.15 (t, J = 7.2 Hz, 1H), 7.21−7.28 (m, 5H), 7.58−7.60 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 39.4, 65.8, 111.3, 117.7, 117.9, 122.3, 124.2, 125.5, 126.1, 127.1, 127.6, 128.2, 129.1, 129.8, 131.2, 131.7, 132.5, 135.6, 137.9, 140.6, 145.2; m/z 337 (M^+); HRMS calcd for $C_{25}H_{23}N$ 337.1830, found 337.1842. (For details, please see Supporting Information.)

Acknowledgment. Financial support from the National Natural Science Foundation of China (20502004) and the Science & Technology Commission of Shanghai Municipality (05ZR14013) is gratefully acknowledged.

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

JO7016839