Tetrahedron Letters 49 (2008) 5495–5497

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A three-component synthesis of homoallylic amines catalyzed by CuI

Pabitra Kumar Kalita, Prodeep Phukan *

Department of Chemistry, Gauhati University, Guwahati 781 014, Assam, India

ARTICLE INFO

Article history:
Received 31 May 2008
Revised 26 June 2008
Accepted 5 July 2008
Available online 9 July 2008

Keywords:
CuI
Aldehyde
Benzyl amine
Allyltributylstannane
Homoallylic amine

ABSTRACT

Cuprous iodide is a very effective catalyst for the three-component condensation of an aldehyde, benzylamine and allyltributylstannane in DMF to produce homoallylic amines in high yields.

© 2008 Elsevier Ltd. All rights reserved.

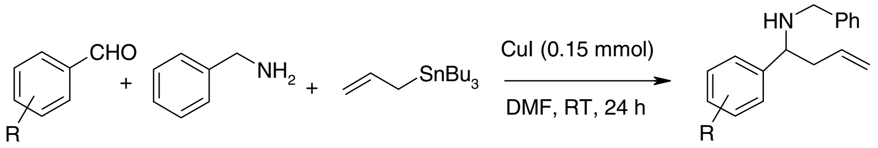
The nucleophilic addition of allyl metal reagents to aldimines has emerged as an important carbon–carbon bond forming reaction in organic synthesis.[1] The resulting homoallylic amines are useful intermediates that can be converted to synthetically and biologically important compounds such as statin,[2] conine,[3] epothilone,[4] β-amino acids[5] and many others.[6] These amino compounds are synthesized by nucleophilic addition of organoallyl reagents of several metals such as Mg, Si, Sn, Sm, Li, Zn, Ce, Cr, B or Cr to an imine.[7] Allyltributylstannane is one of the most common reagents used for the synthesis of homoallylic amines. Generally, strong Lewis acids such as $TiCl_4$ and $BF_3 \cdot OEt_2$, and other metal complexes such as $PdCl_2(PPh_3)_2$, $PtCl_2(PPh_3)_2$, bis-π-allyl palladium complex, lanthanide salts and $LiClO_4$ are used for the preparation of homoallylic amines.[8] However, these reactions cannot be carried out in a one-pot operation with a carbonyl compound, an amine and an allyl metal reagent because the amines and water that exist during imine formation can decompose or deactivate the Lewis acid.[9] In order to overcome these problems, several lanthanide triflates are used as catalysts;[10] however, metal triflates are highly expensive. Lectka has reported a method for the addition of allylsilane to *N*-tosyl iminoesters catalyzed by $CuClO_4$.[11] A similar method has been reported by Jørgensen for the addition of allylstannane to *N*-tosyl iminoesters using $CuPF_6$.[12] Kobayashi employed a 1,2-diphenyl-diamine/Cu(II) complex for addition of a functionalized allylsilane to *N*-acyliminoesters.[13] However, these methods can only be utilized in the case of highly active iminoesters. Several attempts have been made to modify the Barbier-like protocol for the synthesis of homoallylic amines, wherein reactive organometals are generated in situ.[1,14] Very recently, Roy developed a method for the Barbier-type allylation of sulfonimines using $Pd(dba)_3 \cdot CHCl_3$ as the catalyst.[15] The major drawback of this method was that the palladium catalyst is very expensive. Moreover, this method is only applicable to highly reactive sulfonimines in the presence of 1.5 equiv of $SnCl_2$ and 2 equiv of allyl bromide for in situ generation of the allylstannane. Therefore, the development of new, general, less expensive, high yielding and practical catalytic methods is of interest. CuI has emerged as a very effective catalyst for various organic transformations.[16] In continuation of our work on CuI-catalyzed reactions,[16h,i] we report herein a three-component synthesis of homoallylic amines using CuI as the catalyst (Scheme 1).

In order to find optimum reaction conditions, a screen was performed varying several parameters including concentration of the catalyst, amount of substrate, solvent and temperature. The results are summarized in Table 1. In a typical reaction, allyltri(*n*-butyl)stannane (1 equiv) was added to a mixture of benzaldehyde (1 equiv), benzylamine (1 equiv) and CuI (10 mol % based on the amount of benzaldehyde) in DMF at room temperature. The reaction was monitored by TLC. After 24 h, the yield of the homoallyl amine was found to be just 60%. Hence, the reaction was evaluated by varying the concentration of the catalyst (5–20 mol %) keeping the reaction time (24 h) constant. Although the optimal amount of catalyst was found to be 15 mol %, the yield was not satisfactory. Thereafter, we examined the reaction by changing the concentrations of the amine and allyltributylstannane. An improvement in the yield was observed when the amount of allylating agent was increased from 1 equiv to 1.1 equiv (based on benzaldehyde) but

---

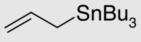
* Corresponding author. Tel.: +91 361 2674360; fax: +91 361 2700311.
E-mail address: pphukan@yahoo.com (P. Phukan).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.07.032



Scheme 1.

Table 1
Synthesis of homoallylic amines from benzaldehyde under various reaction conditions[a]

Entry	PHCH$_2$NH$_2$ (mmol)	CuI (mmol)	 (mmol)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	1	0.05	1	DMF	25	24	10
2	1	0.1	1	DMF	25	24	60
3	1	0.15	1	DMF	25	24	70
4	1	0.2	1	DMF	25	24	58
5	1	0.25	1	DMF	25	24	40
6	1	0.3	1	DMF	25	24	35
7	1	0.15	1.1	DMF	25	24	81
8	1.1	0.15	1.1	DMF	25	24	77
9	1	0.15	1.2	DMF	25	24	78
10	1	0.15	1.1	DMF	50	8	70
11	1	0.15	1.1	MeCN	25	24	0
12	1	0.15	1.1	DCM	25	24	20
13	1	0.15	1.1	DMSO	25	24	0
14	1	0.15	1.1	THF	25	24	0
15	1	0.15	1.1	H_2O	25	24	0

[a] 1 mmol of benzaldehyde was used.

[b] Isolated yield after chromatographic purification.

the yield did not improve with a further increase to 1.2 equiv. Increasing the benzylamine concentration did not improve the yield. Hence, the optimum conditions were 0.15 equiv (15 mol %) of CuI and 1.1 equiv of allyltributylstannane (based on benzaldehyde) (Table 1, entry 7). We also studied the effect of various solvents such as MeCN, DMSO, THF and H_2O on the yield of the product (Table 1), and DMF was found to be the solvent of choice in terms of yield and reactivity.

Next, we examined the scope of the reaction using various aldehydes and the results are summarized in Table 2.[17] In general, this procedure works well for a variety of aromatic aldehydes to produce the corresponding homoallylic amines. The reaction time can be shortened significantly by increasing the reaction temperature up to 50 °C; however, the yield was not improved. Aromatic substrates bearing functional groups such as $-CH_3$, –OMe, –Cl, NO_2 and –F all reacted successfully to give the corresponding homoallylic amine in good to high yields irrespective of the substituent position on the aromatic ring. The presence of an $-NO_2$ group on the aromatic ring lowers the yield of the product. Although the present method works well with aromatic aldehydes, the reaction was sluggish with aliphatic aldehydes (Table 2, entries 10 and 11), giving lower yields after much longer reaction times.

Table 2
CuI-catalyzed three-component synthesis of homoallylic amines

Entry	R	Temp (°C)	Time (h)	Yield (%)
1	H	25	24	81
		50	8	70
2	4-OMe	25	24	88
		50	6	78
3	4-Cl	25	24	82
		50	7	78
4	3-Cl	25	24	85
		50	5	80
5	2-Cl	25	24	88
		50	5	85
6	4-NO_2	25	24	65
		50	9	55
7	2-NO_2	25	24	68
		50	8	59
8	4-Me	25	24	78
		50	6	72
9	4-F	25	24	79
		50	5	75
10	*n*-Octanal	25	72	70
		50	24	50
11	3-Phenylpropanal	25	72	73
		50	24	52

The merits of this method are (a) a very simple, one-pot and high yielding room temperature process; (b) CuI is very cheap and is easily available and (c) a low amount of the catalyst (15 mol %) is needed.

In conclusion, we have developed an efficient protocol for the three-component synthesis of homoallylic amines using CuI as the catalyst. The workup procedure for this method is very simple. This method has wide scope for further applications as the catalyst is cheap and easily available commercially.

Acknowledgement

Financial Support from DST (Grant No. SR/S1/RFPC-07/2006) is gratefully acknowledged.

References and notes

1. (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763; (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163; (c) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095.
2. Yamamoto, Y.; Schmid, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1310.
3. Yamaguchi, R.; Moriyasu, M.; Kawanisi, M. *J. Org. Chem.* **1985**, *50*, 287.
4. Borzilleri, R. M.; Zheng, X.; Schmidt, R. J.; Johnson, J. A.; Kim, S.-H.; DiMarco, J. D.; Fairchild, C. R.; Gougoutas, J. Z.; Lee, F. Y. F.; Long, B. H.; Vite, G. D. *J. Am. Chem. Soc.* **2000**, *122*, 8890.
5. Laschat, S.; Kunz, H. *J. Org. Chem.* **1991**, *56*, 5883.
6. (a) Wright, D. L.; Schulte, J. P., II; Page, M. A. *Org. Lett.* **2000**, *2*, 1847; (b) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305; (c) Jain, R. P.; Williams, R. M. *J. Org. Chem.* **2002**, *67*, 6361; (d) Di Fabio, R.; Alvaro, G.; Bertani, B.; Donati, D.; Giacobbe, S.; Marchioro, C.; Palma, C.; Lynn, S. M. *J. Org. Chem.* **2002**, *67*, 7319; (e) Ramachandran, P. V.; Burghardt, T. E.; Bland-Berry, L. *J. Org. Chem.* **2005**, *70*, 7911; (f) Ryan, S. J.; Zhang, Y.; Kennan, A. J. *Org. Lett.* **2005**, *7*, 4765; (g) Besada, P.; Mamedova, L.; Thomas, C. J.; Costanzi, S.; Jacobson, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2016.
7. (a) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895; (b) Jones, P.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 186; (c) Wang, D.-K.; Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **1999**, *64*, 4233; (d) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614; (e) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242; (f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207; (g) Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 4187; (h) Negoro, N.; Yanada, R.; Okaniwa, M.; Yanada, K.; Fujita, T. *Synlett* **1998**, 835; (i) Itsuno, S.; Yokoi, A.; Kuroda, S. *Synlett* **1999**, 1987; (j) El-Shehawy, A. A.; Omara, M. A.; Ito, K.; Itsuno, S. *Synlett* **1998**, 367; (k) Yanada, R.; Negoro, N.; Okaniwa, M.; Ibuka, T. *Tetrahedron* **1999**, *55*, 13947; (l) Fang, X.; Johannsen, M.; Yao, S.; Gatherhood, N.; Hazel, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844; (m) Akiyama, T.; Iwai, J. *Synlett* **1998**, 273.
8. (a) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146; (b) Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehaway, A. A.; Sarhan, A. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 109; (c) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641; (d) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242; (e) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049; (f) Chaudary, B. M.; Chidara, S.; Sekhar, C. V. R. *Synlett* **2002**, 1694; (g) Aspinall, H. C.; Bissett, J. S.; Greeves, N.; Levin, D. *Tetrahedron Lett.* **2002**, *43*, 323; (h) Yadav,

J. S.; Reddy, B. V. S.; Reddy, P. S. R.; Rao, M. S. *Tetrahedron Lett.* **2002**, *43*, 6245; (i) Veenstra, S. J.; Schmid, P. *Tetrahedron Lett.* **1997**, *38*, 997.

9. Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.
10. (a) Colombo, F.; Annunziata, R.; Benaglia, M. *Tetrahedron Lett.* **2007**, *48*, 2687; (b) Kalita, H. R.; Phukan, P. *Synth. Commun.* **2005**, *35*, 475; (c) Kulkarni, N. A.; Yao, C.-F.; Chen, K. *Tetrahedron* **2007**, *63*, 7816; (d) Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, *44*, 9003; (e) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 19.
11. (a) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168; (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67.
12. Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844.
13. Kiyohara, H.; Nakamura, Y.; Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1615.
14. (a) Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 4187; (b) Giammaruco, M.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1993**, *34*, 3635; (c) Bhuyan, P. J.; Prajapati, D.; Sandhu, J. *Tetrahedron Lett.* **1993**, *34*, 7975; (d) Benchet, P.; Le Marrec, N.; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959; (e) Tanaka, H.; Inoue, K.; Pokorski, U.; Taniguchi, M.; Torii, S. *Tetrahedron Lett.* **1990**, *31*, 3023; (f) Tanaka, H.; Nakahara, T.; Dhimane, H.; Torii, S. *Tetrahedron Lett.* **1989**, *30*, 4161; (g) Tanaka, H.; Yamashita, S.; Ikemoto, Y.; Torii, S. *Chem. Lett.* **1987**, 673.
15. Roy, U. K.; Roy, S. *Tetrahedron Lett.* **2007**, *48*, 7177.
16. (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421; (b) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844; (c) Äirakovic, J. C.; Driver, T. G.; Woerpel, K. A. *J. Org. Chem.* **2004**, *69*, 4007; (d) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888; (e) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139; (f) Li, J.-H.; Wang, D.-P.; Xie, Y.-X. *Tetrahedron Lett.* **2005**, *46*, 4941; (g) Taniguchi, N. *J. Org. Chem.* **2006**, *71*, 7874; (h) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609; (i) Kalita, H. R.; Phukan, P. *Catal. Commun.* **2007**, *8*, 179; (j) Kalita, H. R.; Borah, A. J.; Phukan, P. *Tetrahedron Lett.* **2007**, *48*, 5047.
17. *General procedure:* To a solution of aldehyde (1 mmol) in DMF (1 mL), benzylamine (1.1 mmol), CuI (0.15 mmol) and allyltributylstannane (1 mmol) were added successively at room temperature. After stirring the reaction for 24 h at room temperature, water was added and the mixture was extracted with diethyl ether. The organic phase was dried over sodium sulfate, filtered and evaporated. The crude product was purified by column chromatography over silica gel (60–120 mesh) using ethyl acetate–petroleum ether (5:95) as eluent.