JOC*Note*

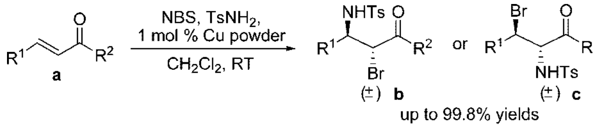
Copper Powder-Catalyzed Regio- and Stereoselective Aminobromination of α,*β*-Unsaturated Ketones with $TsNH_2$ and NBS as Nitrogen and Halogen Sources

Zhan-Guo Chen,† Jun-Fa Wei,*,† Run-Tao Li,‡
Xian-Ying Shi,† and Peng-Fei Zhao†

School of Chemistry and Materials Science, Shaanxi Normal University, Xi'an, 710062, People's Republic of China, and School of Pharmaceutical Sciences, Peking University, Beijing, 100083, People's Republic of China

weijf@snnu.edu.cn

Received August 24, 2008



up to 99.8% yields

The regio- and stereoselective aminobromination of α,*β*-unsaturated ketones catalyzed by copper powder has been established with 4-$TsNH_2$ and NBS as the nitrogen/bromine sources, respectively. This method provides an easy access for preparation of vicinal aminohalo derivatives in the presence of 1 mol % catalyst. Electron-rich α,*β*-unsaturated ketones afforded the corresponding aminobrominated products in excellent yields (up to 99.8%), revealing that the addition has an electrophilic feature.

The functionalization of carbon−carbon double bonds with amine and halogen groups in α,*β*-unsaturated ketones has long been an important topic in organic and medicinal chemistry.[1−3] Although many synthetic approaches to the vicinal aminohalo functionality have been developed,[4−6] the study of efficient and highly regio- and stereoselective methods still remains challenging.[7] The catalysts are currently believed to play a key role in the aminohalogenation of α,*β*-unsaturated ketones and many efficient catalysts have been reported in the literature in the past two decades, such as CuI, $CuCl_2 \cdot 2H_2O$, CuCN, $Cu(OAc)_2$, CuOTf, V_2O_5, $MnSO_4$, Mn(III)-salen, $Co(OAc)_2 \cdot 4H_2O$, $FeCl_3$, $NiCl_2 \cdot 6H_2O$, $ZnCl_2$, dichloro(1,10-phenanthroline)palladium(II), and so on.[7b,8] However, these catalysts still appeared to have several shortcomings, such as high molecular weight (Mn(II)-salen), hygroscopicity (e.g., CuOTf, $FeCl_3$), high cost (e.g., dichloro(1,10-phenanthroline)palladium(II)), and high catalyst loadings (5−10 mol %).

TABLE 1. The Catalytic Activity of Copper Powder in Aminobromination of Chalcone 9a[a]

entry	cat. (amt., mol %)	time, h	temp, °C	atmosphere	yield,[b] %
1	Cu (10)	4	25	air	83
2	Cu (5)	6	25	air	82
3	Cu (1)	9	25	air	82
4	CuI (5)	10	25	N_2	68[c]
5	CuOTf (10)	8	0 to r.t.	N_2	71[c]

[a] Conditions: chalcone (5 mmol), $TsNH_2$ (5 mmol), NBS (6 mmol), amount of catalyst in paratheses, CH_2Cl_2 (10 mL), at 25 °C and aerial condition. [b] Isolated yield after chromatographic separation. [c] Yield reported in refs 7b and 7c.

Considering that copper powder (Cu^0) can be oxidized by NBS into Cu^+ or Cu^{2+}, we employed copper powder to displace Cu(I)- or Cu(II)-containing compounds as catalyst in the aminohalogenation of α,*β*-unsaturated ketones with NBS and *p*-toluenesulfonamide (4-$TsNH_2$) as halogen and nitrogen sources. The results showed that the reactions were carried out smoothly at room temperature to afford the desired aminobrominated products in good yields. We herein wish to report, for the first time, a practical process for the regio- and stereoselective aminobromination of α,*β*-unsaturated ketones catalyzed by elemental copper powder with $TsNH_2$ and NBS as the nitrogen/bromine sources, respectively.

The catalytic activity of copper powder in aminobromination of α,*β*-unsaturated ketone was initially investigated by using chalcone (1,3-diphenyl-propen-1-one, **9a**) as the substrate under the common conditions reported in the literature[7b] except for protection of inert gaseous atmosphere. The results are listed in Table 1.

It can be seen from Table 1 that copper powder was an efficient catalyst for the aminobromination of chalcone. Even though a 1 mol % amount of copper powder was used, the reaction proceeded smoothly at ambient conditions and completed within 9 h, affording the desired product in a higher yield compared with previous reports in which Cu(I) or Cu(II) salts were used as the catalyst.[7b,c] It was worthy to note that the reactions were carried out under aerial conditions with use of commercial reagents.

To explore the scope and the limitation of copper powder-catalyzed aminobromination of α,*β*-unsaturated ketones and gain an insight into the mechanism of the reaction, a series of enones bearing electron-donating groups and/or electron-withdrawing groups on the carbon−carbon bond have been investigated. The results are summarized in Table 2.

---

† Shaanxi Normal University.
‡ Peking University.

[1] (a) Daniher, F. A.; Butler, P. E. *J. Org. Chem.* **1968**, *33*, 4336. (b) Daniher, F. A.; Butler, P. E. *J. Org. Chem.* **1968**, *33*, 2637.

[2] (a) Lessard, J.; Driguez, H.; Vermes, J.-P. *Tetrahedron Lett.* **1970**, *11*, 4887–4891. (b) Barton, D. H. R.; Britten-Kelly, M. R.; Ferreira, D. *J. Chem. Soc., Perkin Trans. I* **1978**, 1090. (c) Driguez, H.; Vermes, J.-P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119.

[3] Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863.

[4] (a) Orlek, B. S.; Stemp, G. *Tetrahedron Lett.* **1991**, *32*, 4045–4048. (b) Bach, T.; Schlummer, B.; Harms, K. *Eur. J. Org. Chem.* **2001**, *66*, 2581–2594.

[5] Karur, S.; Kotti, S. R. S. S.; Xu, X.; Cannon, J. F.; Headley, A. D.; Li, G. *J. Am. Chem. Soc.* **2003**, *125*, 13340–13341.

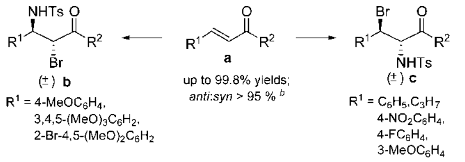
[6] (a) Li, G.; Wei, H.-X.; Kim, S. H.; Neighbors, M. *Org. Lett.* **1999**, *1*, 395–397. (b) Wei, H.-X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, *57*, 3869–3973. (c) Li, G.; Wei, H.-X.; Kim, S. H. *Org. Lett.* **2000**, *2*, 2249–2252.

[7] (a) Qi, X.; Lee, S. H.; Kwon, J. Y.; Kim, Y.; Kim, S. J.; Lee, Y. S.; Yoon, J. *J. Org. Chem.* **2003**, *68*, 9140–9143. (b) Thakur, V. V.; Talluri, S. K.; Sudalai, A. *Org. Lett.* **2003**, *5*, 861–864. (c) Chen, D.; Timmons, C.; Chao, S.; Li, G. *Eur. J. Chem.* **2004**, 3097–3101.

[8] Wei, H.-X.; Kim, S. H.; Li, G. *Tetrahedron* **2001**, *57*, 3869–3873.

10.1021/jo8023768 CCC: $40.75 © 2009 American Chemical Society
Published on Web 12/24/2008

TABLE 2. **Copper Powder-Catalyzed Aminobromiation of Varies α,β-Unsaturated Ketones**[a]



substituted chalcones	R^1	R^2	product	t (h)	yield,[d] %
1a	4-$MeOC_6H_4$	C_6H_5	**1b**	24 (24)[c]	98.0 (92.5)[c]
2a	4-$MeOC_6H_4$	4′-$MeOC_6H_4$	**2b**	1	97.5
3a	4-$MeOC_6H_4$	4′-ClC_6H_4	**3b**	2 (24)[c]	98.9 (95.5)[c]
4a	4-$MeOC_6H_4$	4′-$NO_2C_6H_4$	**4b**	1 (24)[c]	99.8 (96.0)[c]
5a	4-$NO_2C_6H_4$	C_6H_5		48 (48)[c]	NR (NR)[c]
6a	4-$NO_2C_6H_4$	4′-$MeOC_6H_4$		48 (48)[c]	NR (NR)[c]
7a	4-$NO_2C_6H_4$	4′-ClC_6H_4		48	NR
8a	4-$NO_2C_6H_4$	4′-$NO_2C_6H_4$		48	NR
9a	C_6H_5	C_6H_5	**9c**	9	82.0
10a	C_6H_5	4′-$MeOC_6H_4$	**10c**	24	69.8
11a	C_6H_5	4′-ClC_6H_4	11c	48	40.0
12a	C_6H_5	4′-$NO_2C_6H_4$		48	NR
13a	4-FC_6H_4	C_6H_5	**13c**	48	15.7
14a	4-FC_6H_4	4′-$MeOC_6H_4$	**14c**	24	58.0
15a	4-FC_6H_4	4′-ClC_6H_4		48	NR
16a	4-FC_6H_4	4′-$NO_2C_6H_4$		48	NR
17a	3,4,5-$(MeO)_3C_6H_2$	C_6H_5	17b	1	71.2
18a	3,4,5-$(MeO)_3C_6H_2$	4′-$NO_2C_6H_4$	**18b**	2	85.2
19a	3-$MeOC_6H_4$	C_6H_5	**19d**[e]	24	99.2
20a	3-$MeOC_6H_4$	4′-$MeOC_6H_4$	**20c**	13 (24)[c]	94.5 (94.5)[c]
21a	3-$MeOC_6H_4$	4′-$NO_2C_6H_4$	**21d**[e]	12	78.0
22a	3,5-$(MeO)_2C_6H_3$	C_6H_5	**22d**[e]	1	99.4
23a	4-$MeOC_6H_4$	Me	**23b**	1	98.1
24a	2-Br-4,5-$(MeO)_2$ C_6H_2	Me	**24b**	3	82.3
25a	3,4,5-$(MeO)_3C_6H_2$	Me	**25b**	0.5	85.4
26a	C_3H_7	Me	**26b**	4	90[f]

[a] Conditions: α,β-unsaturated ketone (5.0 mmol), $TsNH_2$ (5.0 mmol), NBS (6.0 mmol), catalyst (1 mol % Cu powder or 5 mol % CuI), CH_2Cl_2 10 mL, 25 °C. [b] The ratio of *anti:syn* products, >95% means no *syn*-isomer was detected by ^1H NMR. [c] Data of CuI as catalyst in parentheses. NR: no reaction. [d] Isolated yield after chromatography separation, data of CuI as catalyst in parentheses. [e] 4-Bromo-substituted products. [f] Decomposed during purification by column chromatography, the yield was estimated by crude ^1H NMR spectroscopic determination.

As can be seen in Table 2, the reactivity of the substituted chalcones depends greatly on the substituents of both benzene rings, especially those on the 4-position of the phenyl attached directly to the double bond. The chalcones bearing a strong electron-donating group (e.g., OCH_3) on the 4-position of the benzene ring afforded the trans isomer as the sole adductive products in nearly quantitative yields, no matter what substituent was on another benzene ring that links to the carbonyl group (**1a**−**4a**). On the contrary, no reaction occurred for the chalcones which have a strong electron-withdrawing group (NO_2) on the 4-positon of the benzene ring (**5a**−**8a**), even with prolonged reaction time up to 48 h.

For the chalcones without a substituent on the 4-position of the benzene ring but with a strong electron-donating group or a poor electron-withdrawing group such as CH_3O or Cl on the 4′-position of the benzene ring (**10a** and **11a**), the addition reaction occurred in a lower yield than that of chalcone (**9a**). However, the reaction cannot be carried out with a strong electron-withdrawing group (NO_2) on the 4′-position of the benzene ring (**12a**). For the chalcones bearing a poor electron-withdrawing group (F) on the 4-position of the benzene ring, a strong electron-donating group (CH_3O) on the 4′-position increased the yield from 15.7% to 58.0% (**13a** and **14a**). However, an electron-withdrawing group such as a chlorine or nitro group on the 4′-position could completely inhibit the reaction (**15a** and **16a**).

3,4,5-Trimethoxy chalcone and its 4′-NO_2 analogue (**17a** and **18a**), which has a strong electron-donating group (e.g., OCH_3) on the 4-position of the benzene ring, afforded the desired aminobrominated products in 71.2% and 85.2% yield, respectively.

The 3-methoxy chalcones (**19a**, **21a**) underwent the electrophilic substitution of the phenyl ring rather than the desired aminobromination of the carbon−carbon double bond, affording the corresponding 4-bromo chalcones as the sole products in excellent yields under the same condition (**19d** and **21d**). Similarly, the 3,5-dimethoxy chalcone (**22a**) produced the substituted product in excellent yield (**22d**, 99.4%). However, its 3,4′-dimethoxy isomer gave the expected addition product in a nearly quantitative yield (**20a**, 94.5%). This means that the double bond is activated by 4′-methoxy in this case.

To compare the effectiveness of copper powder with CuI and the influence of the substituents on the reaction yields, the aminobromination of some chalcones was carried out with CuI as catalyst under the same condition except for the protection of nitrogen gas. In the cases with CuI as catalyst, the aminobromination of activated chalcones (**1a**, **3a**, **4a**, **20a**) afforded the expected addition products, but the yields were slightly lower than those with copper powder as catalyst. Notably, the CuI-catalyzed reactions were carried out under harsher conditions such as more catalyst (5 mol %), longer reaction time (≥24 h), and protection with inert atmosphere. For the deactivated chalcones (**5a** and **6a**), no product was observed in the CuI-catalyzed aminobromination until 48 h, similar to the copper powder-catalyzed reactions.

The above observations indicate that the catalytic activity of copper powder is better than that of CuI and, more importantly, the reactivity of chalcones catalyzed by either copper powder or CuI depends significantly on the electron density on the double bond of the substrate. Strong electron-donating substituents on the benzene ring attaching to the double bond can activate the chalcones remarkably toward aminohalogenation addition, whereas strong electron-withdrawing substituents deactivate them. Such experimental evidence reinforces that aminobromination of chalcones catalyzed by transition metal powder is an electrophilic addition, as the literature reported previously.[9−14]

Further investigation revealed that the aromatic enones underwent the copper powder-catalyzed aminobromination readily and gave the aminobromo products in good to excellent yields under the same condition (**23b**−**25b**). The reaction of aromatic enones was much faster and the enones were completely consumed within 3 h. In the case of aliphatic enone, 3-hepten-2-one (**26a**), the reaction was found to be complete within 4 h by detecting the starting material. However, the pure product has not been obtained due to its easy decomposition during purification by column chromatography, similar to the

---

(9) (a) Wei, H.-X.; Kim, S. H.; Li, G. *J. Org. Chem.* **2002**, *67*, 4777–4781. (b) Wei, H.-X.; Siruta, S.; Li, G. *Tetrahedron Lett.* **2002**, *43*, 3809–3812.

(10) (a) Chen, D.; Timmons, C.; Wei, H.-X.; Li, G. *J. Org. Chem.* **2003**, *68*, 5742–5745. (b) Timmons, C.; Chen, D.; Xu, X.; Li, G. *Eur. J. Org. Chem.* **2003**, *68*, 3850–3854.

(11) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.

(12) (a) Booker-Milburn, K. I.; Guly, D. J.; Cox, B.; Procopiou, P. A. *Org. Lett.* **2003**, *5*, 3313–3315. (b) Muniz, K.; Nieger, M. *Synlett* **2003**, 211–214.

(13) Viso, A.; de la Pradilla, R. F.; Garci, A.; Guerrero-Strachan, C.; Alonso, A.; Tortosa, M.; Flores, A.; Martinez-Ripoll, M.; Fonseca, I.; Andre, I.; Rodriguez, A. *Chem. Eur. J.* **2003**, *9*, 2867–2876.

(14) Chuang, T. H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555–3557.

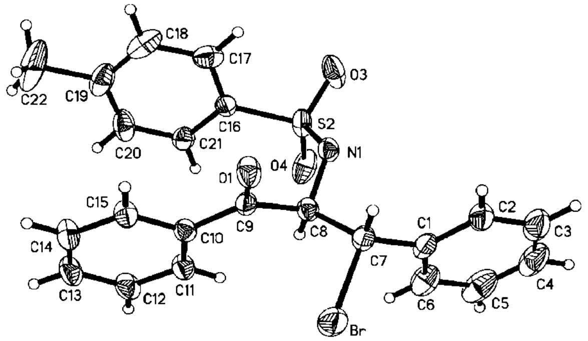


FIGURE 1. X-ray crystal structure of product **9c**.

aminochlorination of aliphatic enone with $TsNCl_2$.[7c] Thus, the exact structure of the product was not confirmed. ^1H NMR analysis of both starting material and crude product showed that the absorption peaks of hydrogen atoms on the carbon−carbon double bond of 3-hepten-2-one [δ 6.81−6.73 (m, 1H), 6.08−6.03 (m, 1H)] disappeared and the new absorption peaks [δ 7.71 (d, J = 6.0 Hz, 2H), 7.21 (d, J = 6.0 Hz, 2H), 5.45 (s, 1H), 4.44−4.41 (m, 1H), 2.67 (s, 3H)] belonging to the addition product appeared, indicating that the addition reaction has taken place indeed.

The absolute stereochemistry of a typical addition product, 3-bromo-1,3-diphenyl-2-(*p*-toluenesulfonamido)propan-1-one, was confirmed by X-ray crystallographic analysis (Figure 1). The result showed that the bromine atom was added to the β-carbon while the nitrogen atom was added to the α-carbon of chalcone, and the reaction proceeded with *anti*-stereochemistry.

The regio- and stereoselectivity of the other aminohalo products were confirmed by ^1H NMR in accordance with the coupling constants of protons on both carbon atoms of bonding a *N*-hydrogen-*N*-toluenesulfonamide group and a bromine atom. Interestingly, for the 4-position of the benzene ring bearing an OCH_3 group, the aminobromination afforded reversed products (**1b**−**4b**, **17b**−**18b**, **23b**−**25b**) in regioselectivity, as confirmed by their corresponding MS analysis. Wherein two prominent fragmented ions, $[R^1CHNHTs]^+$ and $[R^2CO]^+$, were clearly identified.

The exact mechanism of the copper powder-catalyzed aminobromination of α,β-unsaturated ketone is not clear now. However, we consider that Cu(II) formed via an oxidation of copper (Cu^0) by NBS might be the actual catalytic species in this reaction. Indeed, the water washings of the reaction mixture showed the light blue typical color of Cu^{2+} in all cases. The existence of Cu^{2+} has been confirmed by the visible spectrum of water washings containing Cu^{2+} in which the maximum absorption appeared at 800 nm, in agreement with the $CuBr_2$ aqueous solution (see Figure 2 in the Supporting Information). Actually, the aminohalogenation of the carbon−carbon double bond catalyzed by Cu(II)-containing compound has been reported recently.[15]

In conclusion, we have found that copper powder is an efficient catalyst toward the aminobromination of α,β-unsaturated ketones with high regio- and stereoselectivities. The nearly quantitative yields were obtained under mild conditions and without the protection of an inert gaseous atmosphere. This method provides an easy access for preparation of vicinal aminohalo derivatives. Strong electron-donating substituents activated the double bond of α,β-unsaturated ketones remarkably to the addition reactions, whereas strong electron-withdrawing substituents deactivated them, revealing that the addition reaction has an electrophilic feature.

Experimental Section

General Experimental Procedure. Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. A mixture of a chalcone (5 mmol), Cu powder catalyst (1 mol %), $TsNH_2$ (855 mg, 5 mmol), and NBS (1068 mg, 6 mmol) was put into a dried convenience vessel. Then, 10 mL of commercial and not degassed CH_2Cl_2 was added to the vessel with stirring at room temperature without protection with inert gas. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with EtOAc (20 mL) and washed with water (3 × 15 mL) and brine (3 × 15 mL). The organic layer was dried by anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography packed with silica gel with petroleum ether and EtOAc as eluent to afford pure product.

Preparation of 3-Bromo-1,3-diphenyl-2-(*p*-toluenesulfonamido)propan-1-one (9c) Catalyzed by Copper Powder. A mixture of chalcone **9a** (1040 mg, 5 mmol), Cu powder catalyst (3.2 mg, 1 mol %), $TsNH_2$ (855 mg, 5 mmol), and NBS (1068 mg, 6 mmol) was put into a dried convenience vessel. Then, 10 mL of CH_2Cl_2 was added to the vessel with stirring at room temperature and under aerial condition. The reaction was monitored by TLC. After completion of the reaction (9 h), the reaction mixture was diluted with EtOAc (20 mL) and washed with water (3 × 15 mL) and brine (3 × 15 mL). The organic layer was dried by anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography packed with silica gel with petroleum ether and EtOAc as eluent to afford the pure product (white solid 1878 mg, 82% yield). Analytical data for **9c**: mp 124−126 °C (recrystallized in EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.50 Hz, 2H), 7.59−7.40 (m, 10H), 7.00 (d, J = 8.10 Hz, 2H), 5.50 (d, J = 3.60 Hz, 1H), 5.12−5.10 (dd, J = 3.00 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$) δ 196.3, 143.6, 136.7, 136.4, 135.2, 134.1(2), 129.0(2), 129.5(2), 128.9(2), 128.7(2), 128.6(2), 127.1(2), 60.8, 51.7, 21.4. Anal. Calcd for $C_{22}H_{20}BrNO_3S$: C, 57.64; H, 4.37; N, 3.06. Found: C, 57.62; H, 4.36; N, 3.05.

Acknowledgment. The authors are grateful to the National Foundation of Natural Science in China (Grant No. 20572066) and the Innovation Foundation of Postgraduate Cultivation of Shaanxi Normal University (No. 2008CXB009).

Note Added after ASAP Publication. There were errors in the Supporting Information file published ASAP December 24, 2008; the corrected version was published ASAP January 14, 2009.

Supporting Information Available: Experimental procedures, copy of ^1H and ^{13}C NMR spectra, analytical data for compounds (**1b**−**4b**, **9c**−**11c**, **13c**−**14c**, **17b**−**18b**, **20c**, **19d**, **21d**−**22d**, **23b**−**25b**), the visible spectrum of the water washing containing Cu^{2+}, and crystallographic data of compound **9c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8023768

---

[15] Han, J. L.; Zhi, S. J.; Wang, L. Y.; Pan, Y.; Li, G. *Eur. J. Org. Chem.* **2007**, *8*, 1332–1337.