Copper-catalyzed aminobromination/elimination process: an efficient access to α,β-unsaturated vicinal haloamino ketones and esters†

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A novel copper-catalyzed aminobromination-elimination process has been developed, which provides an easy access to α,β-unsaturated vicinal haloamindes derivatives from readily available α,β-unsaturated ketones and esters in good to excellent yields. The isolated intermediate discloses that the current system proceeds through the aminobromination process.

The functionalization of olefins, especially those involving amino functionalities, has been widely served as powerful tool in organic synthesis and medicinal chemistry, because those reactions can convert readily available unsaturated petroleum products into important organic building blocks and biologically precursors.[1–3] Despite great progress has been achieved in this field during the past decade,[4–6] developing one-pot procedures or tandem reactions for those structural units still remain great challenges.[7] Particularly, the α-vinylic functionalization of α,β-unsaturated systems with amino and halogen moieties has not been discovered so far.

Over the past few years, catalytic aminohalogenation reaction has been developed as an efficient tool for the synthesis of vicinal haloamines from olefins by using N,N-dihalogen sulfonamides,[8–10] N-alkyl,N-halogen sulfonamides[11] or related combinations as nitrogen/halogen sources.[12–14] Furthermore, the resulting haloamines can be converted into aziridines[7b,7c] or α,β-dehydroamino acid derivatives[7a] through one-pot procedure. In this communication, we reported a copper-catalyzed aminohalogenation/elimination reaction with N-alkyl,N-bromo-*p*-toluenesulfonamide as nitrogen source (Scheme 1). The reaction serves as the first example of the system through aminohalogenation reaction. And it is noteworthy that this reaction provides an easy access to α,β-unsaturated vicinal haloamino ketones and esters, which represent a novel kind of building block for the unusual amino acids and many biologically active natural products.[15–17]

Initial study was carried out on the reaction of 4-methoxychalcone (**1a**) with N-alkyl-*p*-toluenesulfonamide under the usual aminohalogenation condition.[11a] Almost all the starting material was consumed in the reaction, and the product was carefully isolated, and ^{1}H NMR analysis of this compound showed that the two characteristic double peaks of coupling hydrogen disappeared. The X-ray crystal structure analysis of the product (**2aa**) showed that the α- and β- hydrogen atoms were eliminated, and resulted in (*E*)-α,β-unsaturated haloamino ketone derivative (Fig. 1)

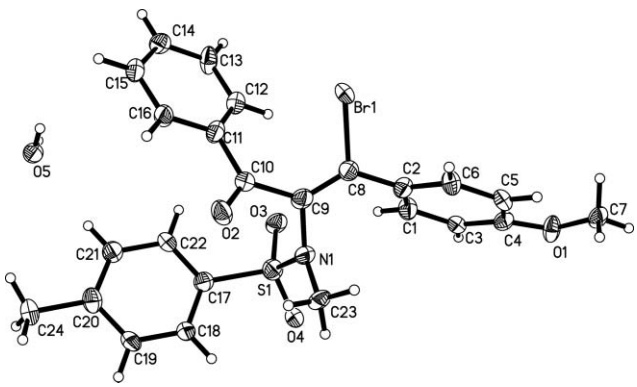
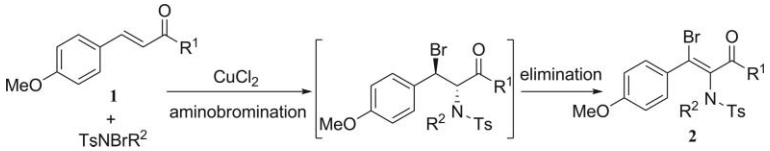


Fig. 1 ORTEP diagram showing **2aa**.

To improve the yield, several metal catalysts, such as $Ni(OAc)_2$, $CuCl_2$, $CuBr_2$, CuCl, CuI, $Mn(OAc)_2$ and $MnSO_4$ were test for this system (Table 1). $CuCl_2$ was found to be the most efficient catalyst and gave 76% yield (entry 7, Table 1). $CuBr_2$ can also promote this reaction, and gave a slightly lower yield (entry 5). However, lower chemical yields were observed when copper(I) salts were used as catalysts (entries 4, 6 and 8). Increasing the loading amount of $CuCl_2$ to 10 mol% did not give obvious improvement on the chemical yield (entry 9).

To further improve the reaction condition, several common organic solvents were examined in the catalytic system. CH_2Cl_2 was found to be the best choice for this reaction, and 76% yield was obtained (entry 6, Table 2). The other solvents, including



Scheme 1 Cu-catalyzed reaction of α,β-unsaturated ketone.

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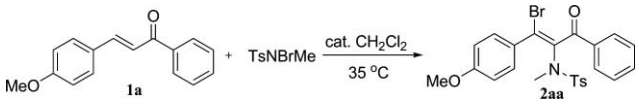
† Electronic supplementary information (ESI) available: General experimental procedures, spectral data and copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c0ob00283f

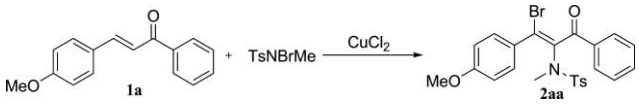
Table 1 Optimization of catalyst[a]



Entry	Catalyst	Amount (mol%)	Yield (%)[b]
1	$Ni(OAc)_2$	5	70
2	$Cu(OAc)_2$	5	64
3	$Mn(OAc)_2$	5	58
4	CuI	5	58
5	$CuBr_2$	5	73
6	$CuI(PPh_3)_2$	5	61
7	$CuCl_2$	5	76
8	CuCl	5	56
9	$CuCl_2$	10	77

[a] Conditions: **1a** (1.0 mmol), TsNBrMe (1.8 mmol), 4 Å molecular sieves (0.5 g) in 6 mL CH_2Cl_2 at 35 °C for 36 h. [b] Isolated yields.

Table 2 Optimization of reaction conditions[a]

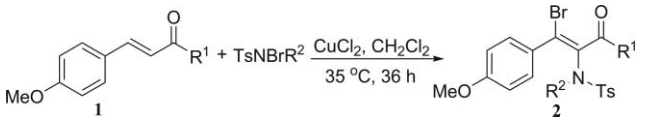


Entry	Substrate[b]	Solvent	Time/h	T/°C	Yield (%)[c]
1	1 : 1.8	CH_3CN	36	35	62
2	1 : 1.8	EtOAc	36	35	70
3	1 : 1.8	Toluene	36	35	52
4	1 : 1.8	Benzene	36	35	45
5	1 : 1.8	THF	36	35	65
6	1 : 1.8	CH_2Cl_2	36	35	76
7	1 : 1.8	CH_2Cl_2	36	45	73
8	1 : 1.8	CH_2Cl_2	36	30	65
9	1 : 1.8	CH_2Cl_2	36	25	15
10	1 : 1.8	CH_2Cl_2	24	35	64
11	1 : 1.8	CH_2Cl_2	48	35	78
12	1 : 2.0	CH_2Cl_2	36	35	74
13	1 : 1.5	CH_2Cl_2	36	35	63

[a] Conditions: 1 mmol **1a** in 6 mL solvent with 0.5 g 4 Å molecular sieves. [b] The ratio of **1a** to TsNBrMe. [c] Isolated yields.

CH_3CN, EtOAc, toluene, benzene and THF gave no improvement on yields at all. It seemed that temperature also plays an important role in the current system. The reaction can proceed well when the temperature was higher than 30 °C and the best result was found at 35 °C (entries 6–9). 36 h was necessary for the completion of the reaction. Although no improvement was achieved when extended the reaction time to 48 h, an obviously lower chemical yield would be found when the reaction was stopped at 24 h (entries 10–11). Furthermore, the loading amount of TsNBrMe was investigated and it was found that the use of 1.8 equiv. of TsNBrMe gave the highest yield (entries 12–13).

Table 3 The reaction with α,β-unsaturated ketones and esters[a]



Entry	R^1	R^2	Product	E : Z[b]	Yield (%)[c]
1	Ph	Me	**2aa (2ab)**[d]	5 : 1	76
2	Ph	Et	**2b**	>20 : 1	64
3	4-Cl-Ph	Me	**2c**	12 : 1	72
4	4-Br-Ph	Me	**2da (2db)**[d]	8 : 1	68
5	4-F-Ph	Me	**2e**	17 : 1	78
6	4-NO_2-Ph	Me	**2f**	>20 : 1	81
7	4-Me-Ph	Me	**2g**	7 : 1	72
8	4-MeO-Ph	Me	**2ha (2hb)**[d]	4 : 1	58
9	OMe	Me	**2i**	>20 : 1	64
10	OEt	Me	**2j**	>20 : 1	62

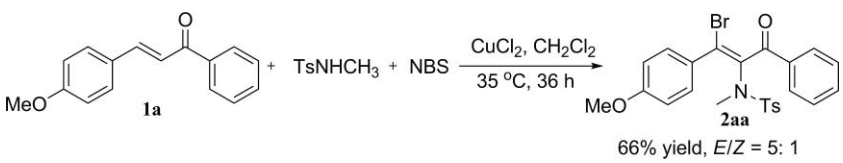
[a] Conditions: **1** (1.0 mmol), nitrogen source (1.8 mmol) and $CuCl_2$ (0.05 mmol) in 6 mL CH_2Cl_2 in the presence of 4 Å molecular sieves (0.5 g) at 35 °C for 36 h. [b] Determined by crude ^1H NMR. > 20 : 1 means no minor isomer was detected. [c] Isolated yields. [d] Products in the parentheses are the *Z*-isomers.

After obtaining the optimized reaction condition, varieties of α,β-unsaturated alkenes with *p*-methoxy substituents on the aromatic rings were used as substrates to investigate the scope of the reaction (Table 3).

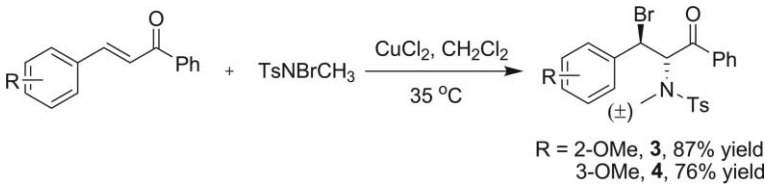
As shown in Table 3, both α,β-unsaturated ketones and α,β-unsaturated esters worked well in this system, and good to excellent chemical yields were obtained. The substitutions on the 1-aromatic rings have no obvious effects on either chemical yields or reaction rates. The substrates showed good to excellent stereoselectivities with *E*/*Z* ratios ranging from 4 : 1 to >20 : 1. In three cases (entries 6, 9 and 10), only the *E*-isomers were observed. It was also found that the geometry of the product was completely controlled with TsNBrEt as nitrogen source (entry 2). The minor *Z* isomers for three cases were successfully isolated and fully characterized (entries 1, 4 and 8). Their stereochemistry has also been unambiguously confirmed by X-ray structural analysis of the single crystal analysis of **2ab**.[18]

Then, the combination of $TsNHCH_3$/NBS was employed as nitrogen/halogen source, instead of TsNBrMe, for the current system, which has been reported as efficient nitrogen/halogen source for the previous aminohalogenation system.[11,12] The combination of $TsNHCH_3$/NBS also can work well as nitrogen/halogen source in the current system, and the corresponding product was obtained with 66% chemical yield and 5 : 1 *E*/*Z* ratio (Scheme 2). The advantage of such replacement is that the catalytic system becomes more practical and facile.

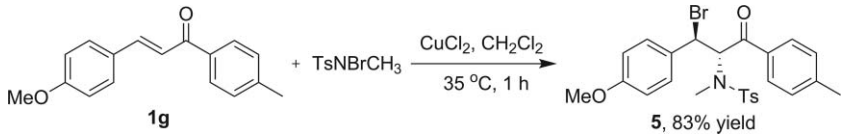
Then, the optimized reaction condition was applied to the other α,β-unsaturated ketones with methoxy substituent at the different position on the aromatic rings (Scheme 3). Unfortunately, no



Scheme 2 Reaction with TsNHMe/NBS.



Scheme 3 Reaction of ketone with methoxy group at different position.

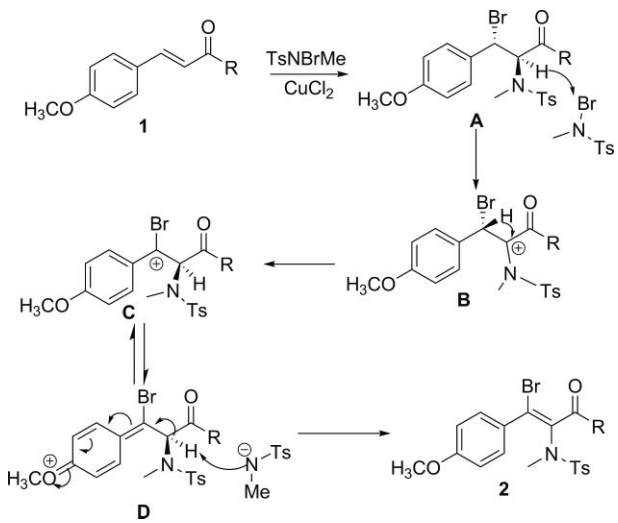


Scheme 4 Reaction for isolation of intermediate.

expected α,β-dehydro haloamines were observed at all, and only the usual haloamines products were obtained when the methoxy group was at *ortho* or *meta* position, which disclosed that the existence of *para* methoxy group on the aromatic plays a key role in the formation of corresponding α,β-unsaturated haloamide products.

The mechanism of the copper-catalyst reaction still remains unclear at this stage. To explain the formation of the unusual product, the following experiment was carried out for attempting to obtain reaction intermediate. **1g** was chosen to react with $TsNBrCH_3$ under the typical condition (Scheme 4). The reaction was stopped at 1 h, and adduct formed in the reaction mixture was carefully isolated which was characterized to be usual haloamide (**5**) by X-ray structural analysis.[19] This result strongly suggests that the bromoamide is the most probable intermediate.

One proposed pathway to account for this new process was offered in Scheme 5, which probably includes the aminobromination and elimination process. In the initial step of the catalytic process, $CuCl_2$ activates TsNBrMe, followed by reacting with α,β-unsaturated ketone, resulting in haloamine **A**, which is similar to our previous reported aminohalogenation process.[9,11a] Then is the step for the removal of hydrogen occurred on α-position with the aid of TsNBrMe to form the intermediate **B**. The intermediate **B** transforms into the more stable intermediate **C**. The methoxy



Scheme 5 Suggested reaction mechanism.

group on the *para* position of aromatic ring can stabilize the positive charged intermediate through the formation of a strong conjugated system **D**. This may be the reason why the existence of *para* methoxy group is necessary for the current system. The intermediate **D** next undergoes the α-deprotonation to give the final product **2**. The steric hindrance of the methyl group may be responsible for the excellent stereoselectivities of the current system.

In conclusion, a novel copper-catalyzed aminohalogenation and elimination system was reported. This is the first example of the system proceeds through aminohalogenation process. This reaction is also easy and convenient to carry out, which provides the first practical halo and sulfonylamino functionalization of α,β-unsaturated system. Further study on the mechanism of this process and application of this reaction is in progress in our group.

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Notes and references

1 (*a*) T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675–704; (*b*) A. Ricci, *Modern Amination Methods*. Wiley VCH: Weinheim, 2000; (*c*) Y. Yamamoto and U. Radhakrishnan, *Chem. Soc. Rev.*, 1999, **28**, 199–207; (*d*) F. Pohlki and S. Doye, *Chem. Soc. Rev.*, 2003, **32**, 104–114; (*e*) D. A. Griffith and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1990, **112**, 5811–5819; (*f*) D. A. Griffith and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1991, **113**, 5863–5864.

2 (*a*) J. E. G. Kemp, In *Comprehensive Organic Synthesis*, Vol. 3 (Eds: B. M. Trost, I. Fleming), Pergamon: Oxford, 1991, pp. 471; (*b*) I. Ojima, In *The Organic Chemistry of* β-*Lactams*, (Ed: G. I. Georg), VCH Publishers, New York, 1992, pp 197–255; (*c*) I. Ojima, *Acc. Chem. Res.*, 1995, **28**, 383–389; (*d*) D. Lucet, T. Le Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2580–2627; (*e*) K. Muñiz, *New J. Chem.*, 2005, **29**, 1371–1385.

3 (*a*) Y. Y. Yeung, X. Gao and E. J. Corey, *J. Am. Chem. Soc.*, 2006, **128**, 9644–9645; (*b*) J. Lessard, H. Driguez and J. P. Vermes, *Tetrahedron Lett.*, 1970, **11**, 4887–4891; (*c*) H. Driguez, J. P. Vermes and J. Lessard, *Can. J. Chem.*, 1978, **56**, 119–130; (*d*) F. A. Daniher and P. E. Butler, *J. Org. Chem.*, 1968, **33**, 4336–4340; (*e*) F. A. Daniher, M. T. Melchior and P. E. Butler, *Chem. Commun.*, 1968, 931–932; (*f*) B. S. Orlek and G. Stemp, *Tetrahedron Lett.*, 1991, **32**, 4045–4048.

4 (*a*) H. Pellissier, *Tetrahedron*, 2010, **66**, 1509–1555; (*b*) J. A. Halfen, *Curr. Org. Chem.*, 2005, **9**, 657–669.

5 (*a*) R. M. D. Figueiredo, *Angew. Chem., Int. Ed.*, 2009, **48**, 1190–1193; (*b*) F. Cardona and A. Goti, *Nat. Chem.*, 2009, **1**, 269–275; (*c*) H. F. Du, W. C. Yuan, B. G. Zhao and Y. Shi, *J. Am. Chem. Soc.*, 2007, **129**, 7496–7497; (*d*) G. Li, H. X. Wei, S. H. Kim and M. Carducci, *Angew.*

Chem., Int. Ed., 2001, **40**, 4277–4280; (*e*) H. X. Wei, S. H. Kim and G. Li, *J. Org. Chem.*, 2002, **67**, 4777–4781; (*f*) K. I. Booker-Milburn, D. J. Guly, B. Cox and P. A. Procopiou, *Org. Lett.*, 2003, **5**, 3313–3315.

6 (*a*) G. Li, S. R. S. S. Kotti and C. Timmons, *Eur. J. Org. Chem.*, 2007, 2745–2758; (*b*) M. R. Manzoni, T. P. Zabawa, D. Kasi and S. R. Chemler, *Organometallics*, 2004, **23**, 5618–5621; (*c*) H. Danielec, J. Klügge, B. Schlummer and T. Bach, *Synthesis*, 2006, 551–556.

7 (*a*) D. J. Chen, L. Guo, J. Y. Liu, S. Kirtane, J. F. Cannon and G. Li, *Org. Lett.*, 2005, **7**, 921–924; (*b*) D. J. Chen, C. Timmons, L. Cuo, X. Xu and G. Li, *Synthesis*, 2004, 2479–2484; (*c*) J. L. Han, S. J. Zhi, Y. Pan, C. Timmons and G. Li, *Tetrahedron Lett.*, 2006, **47**, 7225–7228; (*d*) A. Kamimura, T. Yoshida and H. Uno, *Tetrahedron*, 2008, **64**, 11081–11085.

8 (*a*) G. Li, S. H. Kim and H. Wei, *Tetrahedron Lett.*, 2000, **41**, 8699–8701; (*b*) J. Liu, Y. Wang and G. Li, *Eur. J. Org. Chem.*, 2006, 3112–3115.

9 (*a*) G. Li, H. X. Wei, S. H. Kim and M. Neighbors, *Org. Lett.*, 1999, **1**, 395–397; (*b*) X. Xin, S. Kotti, Y. Liu, J. F. Cannon, A. D. Headley and G. Li, *Org. Lett.*, 2004, **6**, 4881–4884; (*c*) D. Chen, C. Timmons, S. Chao and G. Li, *Eur. J. Org. Chem.*, 2004, 3097–3101; (*d*) J. L. Han, S. J. Zhi, L. Y. Wang, Y. Pan and G. Li, *Eur. J. Org. Chem.*, 2007, 1332–1337; (*e*) Q. J. Li, M. Shi, C. Timmons and G. Li, *Org. Lett.*, 2006, **8**, 625–628; (*f*) S. J. Zhi, H. Sun, G. Q. Zhang, G. Li and Y. Pan, *Org. Biomol. Chem.*, 2010, **8**, 628–631.

10 (*a*) A. Yamasaki, H. Terauchi and S. Takemura, *Chem. Pharm. Bull.*, 1976, **24**, 2841–2849; (*b*) H. Terauchi, A. Yamasaki and S. Takemura, *Chem. Pharm. Bull.*, 1975, **23**, 3162–3169; (*c*) L. Revesz, E. Blum and R. Wicki, *Tetrahedron Lett.*, 2005, **46**, 5577–5580; (*d*) R. Shen and X. Huang, *J. Org. Chem.*, 2007, **72**, 3961–3964.

11 (*a*) H. Sun, S. J. Zhi, J. L. Han, G. Li and Y. Pan, *Chem. Biol. Drug Des.*, 2010, **75**, 269–276; (*b*) G. Q. Zhang, G. H. An, J. Zheng, Y. Pan and G. Li, *Tetrahedron Lett.*, 2010, **51**, 987–989.

12 (*a*) V. V. Thakur, S. K. Talluri and A. Sudalai, *Org. Lett.*, 2003, **5**, 861–864; (*b*) X. L. Wu, J. J. Xia and G. W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 548–553; (*c*) J. F. Wei, L. H. Zhang, Z. G. Chen, X. Y. Shi and J. J. Cao, *Org. Biomol. Chem.*, 2009, **7**, 3280–3284; (*d*) Z. Wang, Y. M. Zhang, H. Fu, Y. Y. Jiang and Y. F. Zhao, *Synlett*, 2008, 2667–2670; (*e*) X. L. Wu and G. W. Wang, *Tetrahedron*, 2009, **65**, 8802–8807; (*f*) J. F. Wei, Z. G. Chen, W. Lei, L. H. Zhang, M. Z. Wang, X. Y. Shi and R. T. Li, *Org. Lett.*, 2009, **11**, 4216–4219; (*g*) Z. G. Chen, J. F. Wei, M. Z. Wang, L. Y. Zhou, C. J. Zhang and X. Y. Shi, *Adv. Synth. Catal.*, 2009, **351**, 2358–2368; (*h*) T. M. Shaikh, P. U. Karabal, G. Suryavanshi and A. Sudalai, *Tetrahedron Lett.*, 2009, **50**, 2815–2817; (*i*) Z. G. Chen, J. F. Wei, R. T. Li, X. Y. Shi and P. F. Zhao, *J. Org. Chem.*, 2009, **74**, 1371–1373.

13 (*a*) Z. G. Chen, Y. Wang, J. F. Wei, P. F. Zhao and X. Y. Shi, *J. Org. Chem.*, 2010, **75**, 2085–2088; (*b*) X. L. Wu and G. W. Wang, *Eur. J. Org. Chem.*, 2008, 6239–6246; (*c*) X. L. Wu and G. W. Wang, *J. Org. Chem.*, 2007, **72**, 9398–9401; (*d*) G. W. Wang and X. L. Wu, *Adv. Synth. Catal.*, 2007, **349**, 1977–1982; (*e*) S. Minakata, Y. Yoneda, Y. Oderaotoshi and M. Komatsu, *Org. Lett.*, 2006, **8**, 967–969; (*f*) X. Qi, S. H. Lee, J. Y. Kwon, Y. Kim, S. J. Kim, Y. S. Lee and J. Yoon, *J. Org. Chem.*, 2003, **68**, 9140–9143; (*g*) J. J. Xia, X. L. Wu and G. W. Wang, *ARKIVOC*, 2008, **xvi**, 22–28.

14 S. J. Zhi, H. Sun, C. Lin, G. Q. Zhang, G. Li and Y. Pan, *Sci. China Chem.*, 2010, **53**, 140–146.

15 (*a*) B. M. Trost, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5348–5355; (*b*) R. Noyori, M. Kitamura and T. Ohkuma, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5356–5362; (*c*) W. J. Tang and X. M. Zhang, *Org. Lett.*, 2002, **4**, 4159–4191; (*d*) T. V. RajanBabu, Y. Y. Yan and S. Shin, *Curr. Org. Chem.*, 2003, **7**, 1759–1773; (*e*) H. J. Drexler, J. You, S. Zhang, C. Fischer, W. Baumann, A. Spannenberg and D. Heller, *Org. Process Res. Dev.*, 2003, **7**, 355–361.

16 K. Nunami, M. Yamada, T. Fukui and K. Matsumoto, *J. Org. Chem.*, 1994, **59**, 7635–7642.

17 (*a*) N. W. Boaz, S. D. Debenham, E. B. Mackenzie and S. E. Large, *Org. Lett.*, 2002, **4**, 2421–2424; (*b*) Y. Fu, J. H. Xie, A. G. Hu, H. Zhou, L. X. Wang and Q. L. Zhou, *Chem. Commun.*, 2002, 480–481.

18 For the ORTEP diagram showing **2ab** (CCDC number 772859), please see supporting information.

19 For the ORTEP diagram showing **5** (CCDC number 772637), please see supporting information.