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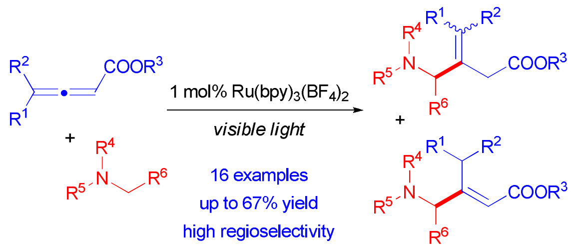

Visible-light-mediated regioselective addition of α-aminoalkyl radicals to 2,3-allenoates catalyzed by photoredox catalyst was developed. The scope and generality of the substrates were broad.

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Visible Light Photoredox Catalysis: Regioselective Radical Addition of Aminoalkyl Radicals to 2,3-Allenoates

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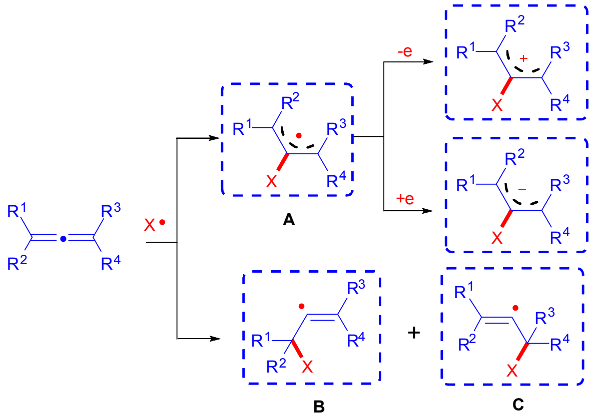
The regioselective addition of α-aminoalkyl radicals to 2,3-allenoates by visible-light-mediated electron transfer using 1 mol % of $Ru(bpy)_3(BF_4)_2$ as photocatalyst was successfully established. This photoredox protocol is a simple and effective method for the synthesis of unsaturated γ-aminobutyric ester derivatives.

Allene is a class of compound containing the unique cumulative diene structural.[1] Affected by substituent groups and chemical environment, the cumulated three-carbon atoms have different electron density distribution, which gives its distinctive reactivity. As a versatile synthon, allene has been widely used in synthetic chemistry.[2] Similar to olefin and other unsaturated hydrocarbon, allene can participate in electrophilic addition, nucleophilic addition, free radical addition reactions. In the reported radical additions of allenes, the *in situ* formed radical species can attack either the sp^2 hybridized carbon atom or the sp hybridized carbon atom, which generates a variety of isomer mixtures.[3] Due to its low regioselectivity and poor controllability, the radical reactions of allene were less examined up to date. And at the same time, the reaction conditions and structure of substrates also have a strong impact on the selectivity. In general, carbon-centered radicals tend to attack its end sp^2 hybridized carbon atoms, while heteroatom-centered radicals tend to attack the sp hybridized carbon atom.

Recently visible-light photoredox catalysis has been paid much attention due to its particular characteristics.[4] Compared with the traditional ionic and radical reactions, visible-light photoredox catalysis, which follows the "ion radical" reaction path, provides a new view for studying the reactions of allenes. According to visible light photoredox reaction path, it may proceed either by oxidative or by reductive quenching, and the *in situ* formed radicals have to lose or obtain an electron to complete the catalytic cycle.[5] Compared with vinyl radical **B** and **C**, the allylic radical **A** is more easily oxidized or reduced. However, from the stability of the radical intermediates, **A** should be more stable than **B** and **C**. Therefore, we hypothesize that radical reaction of allenes may occur in the middle sp hybridized carbon atom under visible light photoredox catalysis (Scheme 1).



Scheme 1. Possible pathways of allenes under photoredox catalysis.

Generally, tertiary amines are popular electron donors which can readily undergo single-electron oxidation, and thus have been widely used in visible light catalysis.[6-8] There are two paths for the photoredox oxidation of tertiary amine, which give the reactive intermediates electrophilic iminium ion or nucleophilic α-aminoalkyl radical according to the reaction system. The routes of addition of various nucleophiles to iminium ion, for example Strecker reaction, Mannich reaction, aza-Henry reactions, etc. have been successfully realized and extensively studied.[7] Comparatively the research of α-aminoalkyl radical is less investigated due to its easily oxidation to form the iminium ions,[9] and currently electron-deficient olefins, isocyanates, azodicarboxylates, alkynes (intramolecular reaction) function as appropriate coupling partners.[8] Recently we reported the photoredox coupling of tertiary amines with acrylate derivatives including Baylis–Hillman adducts under visible light irradiation (Scheme 2a).[10] Based on the similarity of allenoates and electron-deficient olefins, the photoredox coupling reaction with tertiary amine, mediated by visible light photoredox, was examined (Scheme 2b).

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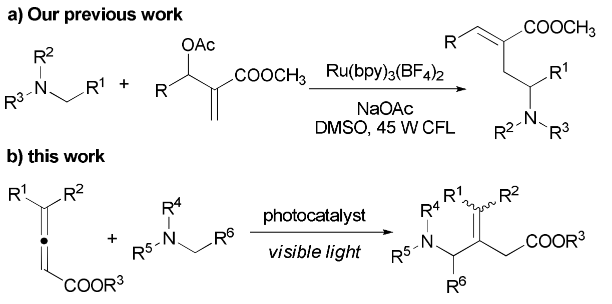
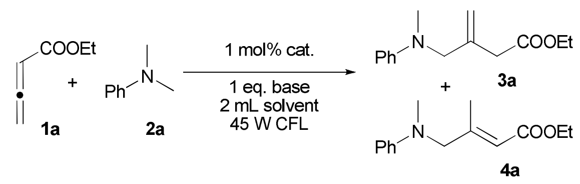


Scheme 2. Visible-light photoredox synthesis of unsaturated γ-aminobutyric ester.

Table 1. Oxidative Coupling Optimization of Ethylbuta-2,3-dienoate with *N,N*-Dimethylaniline[a]

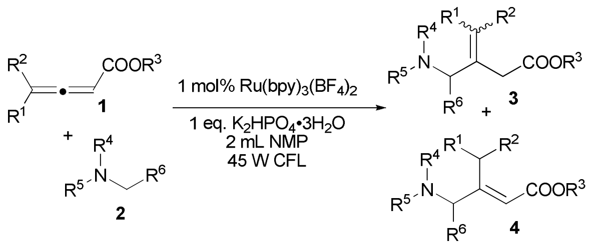


entry	Cat.	solvent	base	yield (%)[b]	**3a**:**4a**[c]
1	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	NaOAc	52	6.0:1
2[d]	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	NaOAc	0	
3	-	NMP	NaOAc	0	
4	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	-	35	6.7:1
5	Ru(bpy)$_3$Cl$_2$	NMP	NaOAc	42	5.6:1
6	Ru(Phen)$_3$(BF$_4$)$_2$	NMP	NaOAc	12	9.0:1
7	Ir(ppy)$_3$	NMP	NaOAc	trace	
8	[Ir(ppy)$_2$bpy]BF$_4$	NMP	NaOAc	46	5.6:1
9	Eosin Y	NMP	NaOAc	trace	
10	Ru(bpy)$_3$(BF$_4$)$_2$	DMSO	NaOAc	38	4.2:1
11	Ru(bpy)$_3$(BF$_4$)$_2$	MeCN	NaOAc	27	2.8:1
12	Ru(bpy)$_3$(BF$_4$)$_2$	DCM	NaOAc	31	3.0:1
13	Ru(bpy)$_3$(BF$_4$)$_2$	MeOH	K$_2$HPO$_4$•3H$_2$O	trace	
14	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	Cs$_2$CO$_3$	trace	
15	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	DABCO	trace	
16	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	2,6-lutidine	28	1.3:1
17	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	NaF	27	3.5:1
18	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	K$_2$HPO$_4$•3H$_2$O	67	5.9:1
19	Ru(bpy)$_3$(BF$_4$)$_2$	NMP	K$_2$HPO$_4$	60	6.1:1
20[e]	Ru(bpy)$_3$(BF$_4$)$_2$	NMP/H$_2$O	K$_2$HPO$_4$•3H$_2$O	54	12.8:1

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), photocatalyst (0.005 mmol), base (0.5 mmol), solvent (2 mL), 24 hrs, 45 W compact fluorescent lamp irradiation under N$_2$ and room temperature until otherwise noted; [b] Isolated yield of **3a** and **4a** based on **1a**; [c] the ratio of **3a**:**4a** was measured by GC; [d] In the dark; [e] 2 mL NMP and 2 mL H$_2$O as the solvents.

At first, the reaction of ethylbuta-2,3-dienoate (**1a**) with 1.2 equiv of *N,N*-dimethylaniline (**2a**) was carried out (Table 1). When a solution of **1a** and **2a** in the presence of 1 mol % of Ru(bpy)$_3$(BF$_4$)$_2$ and 1 equiv of NaOAc in *N*-methylpyrrolidone (NMP) was illuminated with a 45 W compact fluorescent lamp at room temperature for 24 h, ethyl 3-((methyl(phenyl)amino)methyl)but-3-enoate (**3a**) and (*E*)-ethyl 3-methyl-4-(methyl(phenyl)amino)but-2-enoate (**4a**) were obtained in 52% yield (entry 1, **3a**/**4a**=6.0/1). Next, the control experiment showed that no formation of **3a** or **4a** was observed in the absence of a photocatalyst or light (entries 2−3), and switch on-off experiment also revealed that the light was essential. Notably, without base the reaction afforded the products with diminished yield (entry 4). Examination of a range of photocatalysts showed Ru(bpy)$_3$(BF$_4$)$_2$ was the most effective catalyst (entries 5−9). Solvents affected the reaction greatly, and polar aprotic solvents facilitated the reaction (entries 10−12). The reaction was difficult to proceed in MeOH (entry 13). A survey of base demonstrated that K$_2$HPO$_4$•3H$_2$O was the best choice (entries 14−19). Curiously, the use of K$_2$HPO$_4$ gave the worse result than the one containing crystal water. However, the use of the mixture of NMP and H$_2$O as the solvent did not improve the yield (entry 20). Finally, 1 mol% of Ru(bpy)$_3$(BF$_4$)$_2$ as photocatalyst, K$_2$HPO$_4$•3H$_2$O as a base and NMP as a solvent were shown to be optimal to provide the isomer mixtures of **3a** and **4a** in 67% yield. The product of *N,N*-dimethylaniline coupling with the sp^2 hybridized carbon atom of ethylbuta-2,3-dienoate were not found in all of these reactions, indicating the high regioselectivity of the reaction.

Table 2. Scope of 2,3-Allenoates and Tertiary Amines[a]

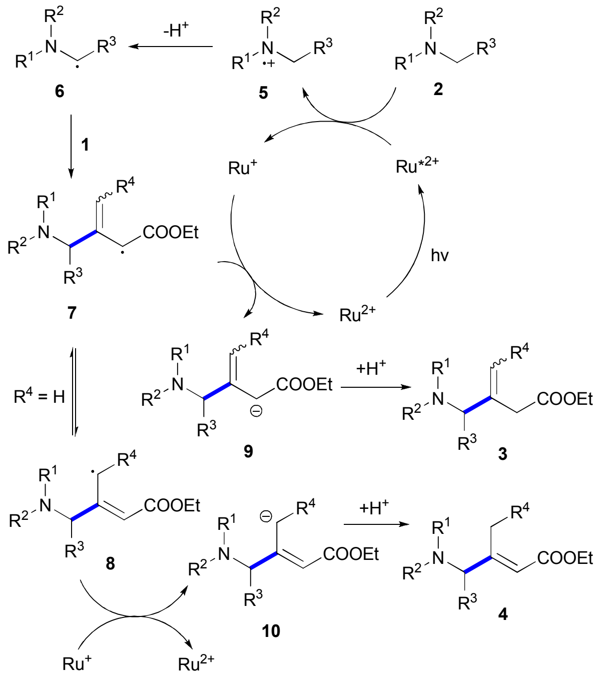


entry	R^1, R^2, R^3	R^4, R^5, R^6	yield (%)[b]
1	H, H, Et (**1a**)	Ph, Me, H (**2a**)	67 (**3a**/**4a** = 85/15)
2	Ph, H, Et (**1b**)	**2a**	52 (**3b**), *E*/*Z* = 1/1[c]
3	4-ClC$_6$H$_4$, H, Et (**1c**)	**2a**	33 (**3c**), *E*/*Z* = 1/1
4	4-OMeC$_6$H$_4$, H, Et (**1d**)	**2a**	40 (**3d**), *E*/*Z* = 1/1
5	Me, H, Et (**1e**)	**2a**	47 (**3e**), *E*/*Z* = 77/23
6	Ph, Ph, Et (**1f**)	**2a**	29 (**3f**)
7	Me, Me, Et (**1g**)	**2a**	32 (**3g**)
8	Me, Me, Me (**1h**)	**2a**	20 (**3h**)
9	**1a**	Ph, Ph, H (**2b**)	23 (**3i**/**4i** = 91/9)
10	**1a**	Ph, Et, Me (**2c**)	14 (**3j**/**4j** = 88/12)
11	**1a**	4-OMeC$_6$H$_4$, Me, H (**2d**)	38 (**3k**/**4k** = 95/5)
12	**1b**	4-MeC$_6$H$_4$, Me, H (**2e**)	41 (**3l**), *E*/*Z* = 48/52
13	**1b**	4-FC$_6$H$_4$, Me, H (**2f**)	38 (**3m**), *E*/*Z* = 51/49
14	**1b**	4-ClC$_6$H$_4$, Me, H (**2g**)	34 (**3n**), *E*/*Z* = 40/60
15	**1b**	4-BrC$_6$H$_4$, Me, H (**2h**)	38 (**3o**), *E*/*Z* = 46/54
16	**1b**	*N*-phenylpyrrolidine (**2i**)	12 (**3p**)[d]

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), photocatalyst (0.005 mmol), K$_2$HPO$_4$•3H$_2$O (0.5 mmol), NMP (2 mL), 24 hrs, 45 W compact fluorescent lamp irradiation under N$_2$ and room temperature; [b] Isolated yield based on **1**; [c] The configuration of *E/Z* was determined by NOESY spectra, please see SI; [d] Only *E* configuration product was obtained.

Other reactions of a variety of 2,3-allenoates **1** and tertiary amines **2** were investigated under the optimized reaction conditions (Table

2). When the fourth position of 2,3-allenoates with substituent groups were reacted with *N,N*-dimethylaniline, only isomer **3** was obtained and the regional isomer **4** was not found. The reactions of **1b**−**1d** bearing an aryl group at the 4-position proceeded smoothly to give the corresponding products (**3b**−**3d**) in moderate yields (entries 2−4). Ethyl penta-2,3-dienoate was also applicable to this reaction system, giving the product **3e** in 47% isolated yield (entry 5). Due to the steric effect, 4,4-disubstituted 2,3-dienoates gave the desired products in low yield (entries 6−7). The yield of methyl ester was slightly lower than the yield of ethyl ester (entry 8). On the other hand, a variety of tertiary amines **2** was examined as well. When methyldiphenylamine **2b** and *N,N*-diethylaniline **2c** reacted with ethyl buta-2,3-dienoate **1a**, it afforded the desired products **3i**/**4i** and **3j**/**4j** in low isolated yield (entries 9−10). *N,N*-Dimethylaniline with an electron-donating group on the benzene ring, afforded **3k**/**4k** and **3l** in reasonable yields (entries 11−12). The substrates with weak electron-withdrawing groups, such as F, Cl and Br, successfully afforded the desired products in moderate yields (entries 13−15). Cyclic amine *N*-phenylpyrrolidine (**2i**) was transformed into **3p** in 12% yield (entry 16). However, aromatic tertiary amines with a strong electron-withdrawing group such as 4-(dimethylamino)benzonitrile and 4-dimethylaminopyridine deter the reaction. Unfortunately, aliphatic tertiary amines could not give the desired products.



Scheme 3. Possible Mechanism.

Based on experimental results and related literatures,[9] a plausible mechanism is proposed in Scheme 3. First tertiary amine **2** is oxidized by visible light excited Ru^{*2+} to give amino radical cation **5** and Ru$^+$. In the presence of base, **5** loses a proton to afford α-aminoalkyl radical **6**, which undergoes nucleophilic radical addition to 2,3-allenoate **1** to form a new C−C bond and afford the alkyl radical **7**. When R^4 is hydrogen atom, a part of **7** can be converted into **8**. Then, a single electron transfer from the Ru$^+$ to the alkyl radical **7** and **8** completes the photoredox cycle and generates the corresponding alkyl anion **9** and **10**. Subsequent protonation of **9** leads to the product **3**, and the same with **10** to **4**.

Conclusions

In summary, we have developed a new visible light driven photocatalytic C−C coupling between tertiary amines and 2,3-allenoates. It's an efficient method for the synthesis of unsaturated γ-aminobutyric ester derivatives. Further work is in progress to broaden the synthetic applicability of the α-aminoalkyl radicals in visible-light photoredox catalysis.

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Notes and references

1 (a) N. Krause, A. S. Hashmi and Eds. Modern Allene Chemistry, Vols 1-2 Weinheim; Wiley-VCH, 2004; (b) H. F. Schuster and G. M. Coppola, Allenes in Organic Synthesis, New York: John Wiley & Sons, 1984.

2 (a) B. Alcaide, P. Almendros and T. M. del Campo, *Chem. Eur. J.*, 2010, **16**, 5836; (b) S. Ma, *Aldrichimica Acta*, 2007, **40**, 91; (c) S. Ma, *Chem. Rev.*, 2005, **105**, 2829; (d) S. Ma, *Acc. Chem. Res.*, 2009, **42**, 1679.

3 (a) L. R. Byrd and M. C. Caserio, *J. Org. Chem.*, 1972, **37**, 3881; (b) A. Ogawa, M. Imura, N. Kamada and T. Hirao, *Tetrahedron Lett.*, 2001, **42**, 2489; (c) K. Tsuchii, M. Imura, N. Kamada, T. Hirao and A. Ogawa, *J. Org. Chem.*, 2004, **69**, 6658; (d) A. P. Stefani, L. Herk and M. Szwarc, *J. Am. Chem. Soc.*, 1961, **83**, 4732; (e) Z. Ma, R. Zeng, C. Fu and S. Ma, *Tetrahedron*, 2011, **67**, 8808; (f) C. Xue, X. Jiang, C. Fu and S. Ma, *Chem. Commun.*, 2013, **49**, 5651; (g) C. Xue, C. Fu and S. Ma, *Chem. Commun.*, 2014, **50**, 15333; (h) R. Zeng, C. Fu and S. Ma, *Angew. Chem. Int. Ed.*, 2012, **51**, 3888; (i) F. Pan, C. Fu and S. Ma, *Chin. J. Org. Chem.*, 2004, **24**, 1168; (g) H. G. Meunier and P. I. Abell, *J. Phys. Chem.*, 1967, **71**, 1430.

4 (a) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77; (b) M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2008, **130**, 12886; (c) J. M. R. Narayanam, J. W. Tucker and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2009, **131**, 8756.

5 For reviews: (a) D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**, 1239176; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (c) D. A. Nicewicz and T. M. Nguyen, *ACS Catal.*, 2014, **4**, 355; (d) J. Xuan and W. J. Xiao, *Angew. Chem. Int. Ed.*, 2012, **51**, 6828; (e) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102; (f) F. Teplý, *Collect. Czech. Chem. Commun.*, 2011, **76**, 859; (g) T. P. Yoon, M. A. Ischay and J. N. Du, *Nature Chem.*, 2010, **2**, 527; (h) K. Zeitler, *Angew. Chem. Int. Ed.*, 2009, **48**, 9785; (i) F. Tan and W. J. Xiao, *Acta Chim. Sinica*, 2015, **73**, 85.

6 For reviews: (a) L. Shi and W. J. Xia, *Chem. Soc. Rev.*, 2012, **41**, 7687; (b) J. Xuan and W. J. Xiao, *Angew. Chem. Int. Ed.*, 2012, **51**, 6828; (c) J. Xie, H. M. Jin, P. Xu and C. J. Zhu, *Tetrahedron Lett.*, 2014, **55**, 36.

7 For selected recent reports *via* iminium ions as key intermediates, see: (a) A. G. Condie, J. C. González-Gómez C. R. J. and Stephenson, *J. Am. Chem. Soc.*, 2010, **132**, 1464; (b)

M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny and D. C. Fabry, *Chem. Commun.*, 2011, **47**, 2360; (c) M. Rueping, S. Q. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 8679; (d) D. P. Hari and B. König, *Org. Lett.*, 2011, **13**, 3852; (e) M. Rueping, S. Q. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 12709; (f) D. B. Freeman, L. Furst, A. G. Condie and C. R. J. Stephenson, *Org. Lett.*, 2012, **14**, 94; (g) M. Rueping, J. Zoller, D. C. Fabry, K. Poscharny, R. M. Koenigs, T. E. Weirich and J. Mayer, *Chem. Eur. J.*, 2012, **18**, 3478; (h) G. L. Zhao, C. Yang, L. Guo, H. Sun, C. Chen and W. J. Xia, *Chem. Commun.*, 2012, **48**, 2337; (i) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori and C. Vila, *Chem. Eur. J.* 2012, **18**, 5170; (j) J. Xuan, Y. Cheng, J. An, L. Q. Lu, X. X. Zhang and W. J. Xiao, *Chem. Commun.*, 2011, **47**, 8337; (k) J. Xuan, Z. J. Feng, S. W. Duan and W. J. Xiao, *RSC Adv.*, 2012, **2**, 4065; (l) D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.*, 2012, **134**, 8094; (m) C. H. Dai, F. Meschini, J. M. R. Narayanam and C. R. J. Stephenson, *J. Org. Chem.*, 2012, **77**, 4425; (n) Z. Q. Wang, M. Hu, X. C. Huang, L. B. Gong, Y. X. Xie and J. H. Li, *J. Org. Chem.*, 2012, **77**, 8705; (o) S. Q. Zhu and M. Rueping, *Chem. Commun.*, 2012, **48**, 11960; p) Y. Q. Zou, L. Q. Lu, L. Fu, N. J. Chang, J. Rong, J. R. Chen and W. J. Xiao, *Angew. Chem. Int. Ed.*, 2011, **50**, 7171; (q) M. Rueping, D. Leonori and T. Poisson, *Chem. Commun.*, 2011, **47**, 9615; (r) T. Courant and G. Masson, *Chem. Eur. J.*, 2012, **18**, 423; (s) J. H. Park, K. C. Ko, E. Kim, N. Park, J. H. Ko, D. H. Ryu, T. K. Ahn, J. Y. Lee and S. U. Son, *Org. Lett.*, 2012, **14**, 5502; (t) S. Y. Cai, X. Y. Zhao, X. B. Wang, Q. S. Liu, Z. G. Li, D. Z. Wang, *Angew. Chem. Int. Ed.*, 2012, **51**, 8050; (u) H. Jiang, C. M. Huang, J. J. Guo, C. Q. Zeng, Y. Zhang and S. Y. Yu, *Chem. Eur. J.*, 2012, **18**, 15158; (v) W.-J. Yoo, A. Tanoue and S. Kobayashi, *Chem. Asian J.*, 2012, **7**, 2764; (w) Y. Yasu, T. Koike and M. Akita, *Chem. Commun.*, 2012, **48**, 5355; (x) G. Bergonzini, C. S. Schindler, C.-J. Wallentin, E. N. Jacobsen and C. R. J. Stephenson, *Chem. Sci.*, 2014, **5**, 112; (y) C. Vila and M. Rueping, *Green Chem.*, 2013, **15**, 2056; (z) M. Rueping and C. Vila, *Org. Lett.*, 2013, **15**, 2092.

8 For selected recent reports via α-aminoalkyl radicals as key intermediates, see: (a) P. Kohls, D. Jadhav, G. Pandey and O. Reiser, *Org. Lett.*, 2012, **14**, 672; (b) Y. Miyake, K. Nakajima and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2012, **134**, 3338; (c) Y. Miyake, Y. Ashida, K. Nakajima and Y. Nishibayashi, *Chem. Commun.*, 2012, **48**, 6966; (d) X. H. Ju, D. J. Li, W. F. Li, W. Yu and F. L. Bian, *Adv. Synth. Catal.*, 2012, **354**, 3561; (e) Y. Miyake, K. Nakajima and Y. Nishibayashi, *Chem. Eur. J.*, 2012, **18**, 16473; (f) S. Q. Zhu, A. Das, L. Bui, H. J. Zhou, D. P. Curran and M. Rueping, *J. Am. Chem. Soc.*, 2013, **135**, 1823; (g) L. R. Espelt, E. M. Wiensch and T. P. Yoon, *J. Org. Chem.*, 2013, **78**, 4107; (h) A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114; (i) H. X. Zhou, P. Lu, X. Y. Gu and P. X. Li, *Org. Lett.*, 2013, **15**, 5646; (j) A. Singh, A. Arora and J. D. Weaver, *Org. Lett.*, 2013, **15**, 5390; (k) P. Zhang, T. B. Xiao, S. W. Xiong, X. C. Dong and L. Zhou, *Org. Lett.*, 2014, **16**, 3264.

9 D. D. M. Wayner, J. J. Dannenberg and D. Griller, *Chem. Phys. Lett.*, 1986, **131**, 189.

10 X. J. Dai, D. P. Cheng, B. C. Guan, W. J. Mao, X. L. Xu and X. N. Li, *J. Org. Chem.*, 2014, **79**, 7212.