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Copper-catalyzed synthesis of 1,2,4-trisubstituted pyrroles *via* cascade reactions of aryloxy-enynes with amines†

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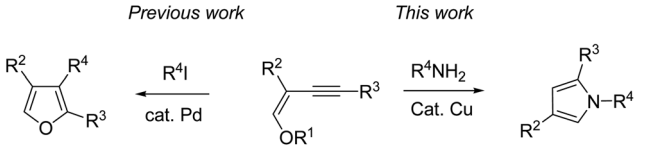
A highly efficient copper-catalyzed cascade reaction of aryloxy-enynes with amines under mild reaction conditions has been developed. This methodology offers rapid access to 1,2,4-trisubstituted pyrroles in good to excellent yields in a regioselective manner.

Substituted pyrroles are some of the most important heterocycles, being present as key structural units in many bioactive compounds,[1] natural products,[2] and functional materials.[3] Consequently, a variety of synthetic methods have been developed for the construction of pyrrole rings or its related compounds.[4] The majority of which include the classical approaches, such as Paal–Knorr synthesis,[5] the Hantzsch procedure,[6] modern transition-metal-mediated cyclizations,[7] multicomponent reactions,[8] and others.[9] However, most known procedures are effective for 2,5-di or polysubstituted pyrroles.[10] It is highly desirable to develop methodologies for pyrrole ring formation with precise substituents location from readily accessible starting materials. In particular, synthetic approaches toward 1,2,4,-trisubstituted pyrroles are quite limited,[11] although theses compounds are interesting because of their remarkable biological activities, such as synthetic histone deacetylase inhibitors.[12] In connection with our work of metal-catalyzed methodology for the preparation of heterocycles using aryloxy-enynes,[13] we envisioned that substituted pyrroles might be produced by the replacement of *O*-nucleophiles to *N*-nucleophiles (Scheme 1). Herein, we would like to report the effective synthesis of 1,2,4-trisubstituted pyrroles through the Cu-catalyzed cascade reactions of aryloxy-enyne with amines (Scheme 1). Synthesis of 1,2,4-trisubstituted pyrroles from enynals with amines has been described in the literature. However, the substrates are limited to aryl amines and expensive Ag catalyst.[11b]

The requisite (*E*)-1-aryloxy-1-en-3-ynes with an ester group on C-2 (**1**) were synthesized *via* the Sonogashira coupling of the corresponding 2-bromo-3-aryloxypropenoates and terminal alkynes.[13a] Firstly, the reaction of (*E*)-1-phenoxy-1-en-3-yne with an ethyl ester group on C-2 (**1a**) with cyclohexanamine (**2a**) was carried out using $FeCl_3 \cdot 6H_2O$ (10 mol%) as the catalyst, Cs_2CO_3 (2 equiv.) as the base in DMF at 90 °C. However, only trace amount of the desired pyrrole **3a** was detected (Table 1, entry 1). $FeCl_3$ gave similar result as that of $FeCl_3 \cdot 6H_2O$. When $PdCl_2(PPh_3)_2$ was used, **3a** was produced in 37% yield (Table 1, entry 3). Changing the catalyst to $Cu(OAc)_2$ afforded **3a** in a better yield (Table 1, entry 4). It is interesting that CuCl resulted in 54% yield of **3a** (Table 1, entry 5). Then other copper salt such as CuI in DMF was tested, satisfyingly, the desired trisubstituted pyrrole was produced in 80% yield (Table 1, entry 6). The use of other bases such as K_2CO_3 or ^{t}BuOK, gave no good results (Table 1, entries 7 and 8). Changing the solvent to toluene, THF, or DMSO, **3a** were produced in much lower yields, respectively (Table 1, entries 9–11). Increasing the catalyst loading to 20 mol% gave similar result as that of 10 mol% (Table 1, entry 12). 5 mol% of the catalyst gave only 41% yield (Table 1, entry 16). When 2.1 equiv. of **2a** was used, the yield of **3a** was decreased slightly (Table 1, entry 13). When the reaction was carried out at 70 °C, the desired product was obtained in a lower yield (Table 1, entry 17). Therefore, the optimized reaction condition was to use 10 mol% of CuI as the catalyst, 2.0 equiv. of Cs_2CO_3 as the



Scheme 1

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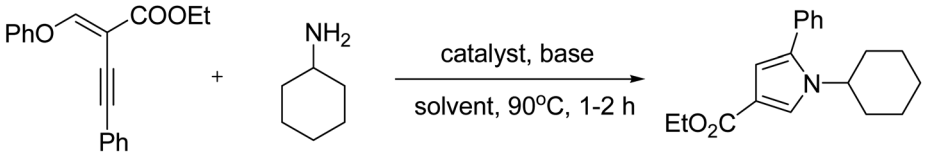
† Electronic supplementary information (ESI) available: Experimental details, spectroscopic characterization of all new compounds and X-ray crystallography of compound **3m** (ref. 14) are given. CCDC 955843. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra44595j

Table 1 Optimization of reaction conditions for the formation of **3a**



1a **2a** **3a**

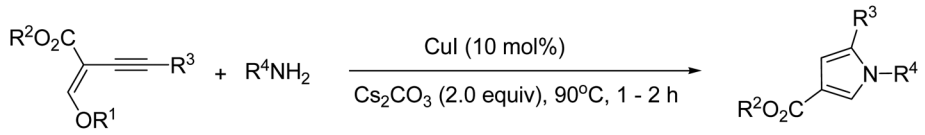
Entry	Catalyst	Base (*n* equiv.)	Solvent	Yield[a,b]
1	$FeCl_3 \cdot 6H_2O$	Cs_2CO_3 (2.0)	DMF	Trace
2	$FeCl_3$	Cs_2CO_3 (2.0)	DMF	Trace
3	$PdCl_2(PPh_3)_2$	Cs_2CO_3 (2.0)	DMF	37%
4	$Cu(OAc)_2$	Cs_2CO_3 (2.0)	DMF	45%
5	CuCl	Cs_2CO_3 (2.0)	DMF	54%
6	CuI	Cs_2CO_3 (2.0)	DMF	80%
7	CuI	K_2CO_3 (2.0)	DMF	—
8	CuI	^tBuOK (2.0)	DMF	Trace
9	CuI	Cs_2CO_3 (2.0)	Tol	26%
10	CuI	Cs_2CO_3 (2.0)	DMSO	39%
11	CuI	Cs_2CO_3 (2.0)	THF	20%
12	CuI	Cs_2CO_3 (2.0)	DMF	79%[c]
13	CuI	Cs_2CO_3 (2.0)	DMF	75%[d]
14	CuI	Cs_2CO_3 (2.0)	DMF	35%[e]
15	CuI	Cs_2CO_3 (2.0)	DMF	77%
16	CuI	Cs_2CO_3 (2.0)	DMF	41%[f]
17	CuI	Cs_2CO_3 (2.0)	DMF	55%[g]
18	—	Cs_2CO_3 (2.0)	DMF	—

[a] Unless otherwise noted, all reaction were carried out using 10 mol% of catalyst with the ratio of **1a : 2a** = 1 : 1.1. [b] Isolated yield. [c] 20 mol% of CuI was used. [d] The ratio of **1a : 2a** = 1 : 2.1. [e] The reaction was carried out under air. [f] 5 mol% of CuI was used. [g] The reaction was carried out at 70 °C.

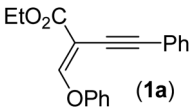
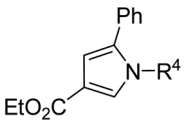
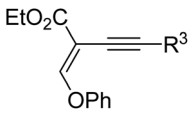
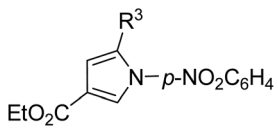
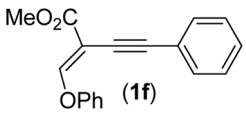
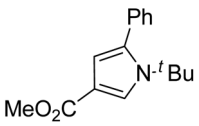
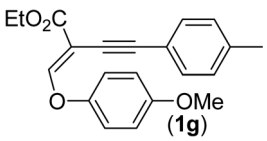
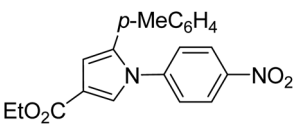
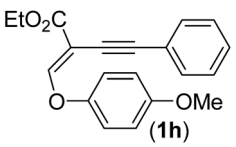
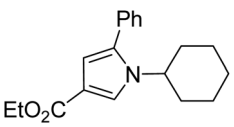
base, and DMF as the solvent at 90 °C. One of the advantages of this method to pyrrole is that the regioselective introduction of substituents on the pyrrole ring comes down to the appropriate choice of the aryloxy-enyne and amine, which allows for considerable versatility.

With the optimized reaction conditions in hand, we next examined the substrate scope of this catalytic method for the synthesis of 1,2,4-trisubstituted pyrroles using a variety of (*E*)-1-aryloxy-1-en-3-ynes and amines, the results are shown in Table 2. We first investigated the electronic effects of amines. It was found that electron-donating alkyl amines reacted with enynyl ether to give the corresponding pyrroles in good yields. For example, butylamine (**2b**) reacted with **1a** to produce **3b** in 68% yield (Table 2, entry 1). **2c** with a bulky *tert*-butyl group reacted successfully under the optimal conditions, leading to the corresponding **3c** in 72% yield (Table 2, entry 2). Benzyl amine worked nicely, producing **3d** in 78% yield (Table 2, entry 3). It is worthy to note when aryl amine such as aniline **2e** was employed to react with **1a** under the optimized reaction conditions, desired pyrrole **3e** was obtained in only 24% yield along with the formation of ethyl 5-phenylfuran-3-carboxylate (**3a′**).[13a] It was because that enynyl ether **1a** was hydrolyzed to the corresponding carbonyl group by H_2O, and then undergo an *O*-cyclization.[13a] In order to improve the yield of pyrrole, 4Å MS was added to the reaction mixture. To our delight, the corresponding pyrrole **3e** was produced in 43%, along with 48% of the corresponding furan (Table 2, entry 4). 4-Methoxyphenyl amine (**2f**) furnished **3f** in 42% yield (Table 2, entry 5). An electron-withdrawing aryl amine such as 4-cyanobenzamine (**2g**) is also compatible in the reaction to give **3g** in 68% yield (Table 2, entry 6). It is interesting when 4-nitrobenzenamine (**2h**) was reacted with **1a** in the presence of 4Å MS, the corresponding **3h** was produced in 79% yield, and no furan formation was observed (Table 2, entry 7). Then we investigated the substituent effects on the triple bond. It was found that electron-donating aryl groups such as –OMe (**1b**) reacted with 4-nitrobenzenamine (**2h**) to afford the corresponding product **3i** in 80% (Table 2, entry 8). Naphthyl substituted one (**1c**) gave high yield of **3j** (Table 2, entry 9). The substituents on the triple bond could also be alkyl groups, such as *n*-butyl (**1d**) and phenylethyl (**1e**), furnishing **3k** and **3l** in 65% and 74% yields, respectively (Table 2, entries 10 and 11). When the ester group of enynyl ether was methyl ester, the corresponding pyrrole **3m** was produced in 78% yield (Table 2, entry 12). The structure of **3m** was further confirmed by X-ray crystallographic analysis. It is noteworthy that the aryloxyl substituent of **1** can be changed to 4-methoxyphenoxyl group, such as **1g** or **1h**, it reacted with **2h** or **2a** to provide the desired **3n** or **3a** in 90 or 70% yields, respectively (Table 2, entries 13 and 14).

Table 2 Synthesis of various of 1,2,4-trisubstituted pyrroles



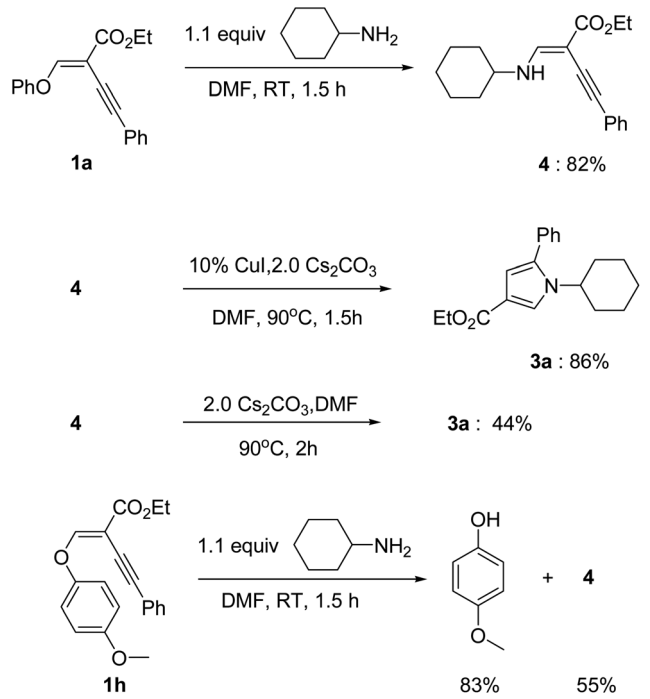
1 **2** **3**

Entry	Enynyl ether	Amine	Product		Yield[a]
		R^4NH_2			
1	**1a**	R^4 = *n*-butyl:**2b**	R^4 = *n*-butyl	**3b**	68%
2	**1a**	R^4 = *t*-butyl:**2c**	R^4 = *t*-butyl	**3c**	72%
3	**1a**	R^4 = Bn:**2d**	R^4 = Bn	**3d**	78%
4	**1a**	R^4 = Ph:**2e**	R^4 = Ph	**3e**	43%[b,e]
5	**1a**	R^4 = *p*-$MeOC_6H4$:**2f**	R^4 = *p*-$MeOC_6H_4$	**3f**	42%[c,e]
6	**1a**	R^4 = *p*-CNC_6H_4:**2g**	R^4 = *p*-CNC_6H_4	**3g**	68%[d,e]
7	**1a**	R^4 = *p*-$NO_2C_6H_4$:**2h**	R^4 = *p*-$NO_2C_6H_4$	**3h**	79%[e]
					
8	R^3 = *p*-$MeOC_6H_4$:**1b**	**2h**	R^3 = *p*-$MeOC_6H_4$	**3i**	80%[e]
9	R^3 = 1-naphthyl:**1c**	**2h**	R^3 = 1-naphthyl	**3j**	89%[e]
10	R^3 = *n*-butyl:**1d**	**2h**	R^3 = *n*-butyl	**3k**	65%[e]
11	R^3 = phenethyl:**1e**	**2h**	R^3 = phenethyl	**3l**	74%[e]
12		**2c**		**3m**	78%
13		**2h**		**3n**	90%[e]
14		**2a**		**3a**	70%

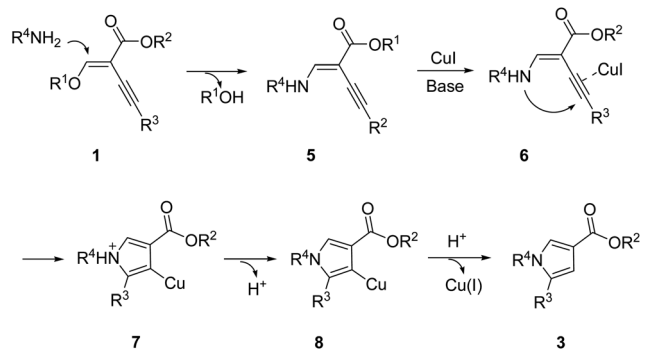
[a] Isolated yields. Unless noted, all the reactions were carried out using 10 mol% of CuI and 2.0 equiv. of Cs_2CO_3 in DMF at 90 °C. [b] Ethyl 5-phenylfuran-3-carboxylate (**3a′**) was formed in 48% yield. [c] **3a′** was formed in 50% yield. [d] **3a′** was formed in 29% yield. [e] 4Å MS was added.

In order to understand the reaction mechanism, we examined the reaction of (*E*)-ethyl 2-(phenoxymethylene)-4-phenylbut-3-ynoate (**1a**) with cyclohexanamine (**2a**) under various conditions carefully. It was found that when the reaction was carried out at room temperature in DMF, substitution reaction took place in the absence of both CuI and Cs_2CO_3 to give enynyl amine **4** in 82% yield after 1.5 h (Scheme 2, eqn (1)). The isolated **4** was subjected to the standard conditions to afford **3a** in 86% yield (Scheme 2, eqn (2)). With the addition of Cs_2CO_3 only, **3a** could also be produced in 44% yield after 2 h (Scheme 2, eqn (3)). However, in the presence of only CuI (10 mol%), **3a** could not be detected even after 8 h. These results indicated that the intramolecular cyclization would occur under basic condition, copper salts could accelerate the cyclization process, and the combination of both CuI and Cs_2CO_3 are essential for high yielding formation of the target pyrrole derivatives. In order to confirm the release of phenol derivatives during the reaction, 4-methoxyphenoxyl substituted enynyl ether **1h** was reacted with cyclohexanamine at room temperature, and 4-methoxyphenol was obtained in 83% yield (Scheme 2, eqn (4))

On the basis of the above observations and our reported work, a possible reaction mechanism is proposed in Scheme 3.



Scheme 2



Scheme 3 A proposed reaction pathway.

First, Michael addition of R^4NH_2 to the enone moiety of enynyl ether **1** with the elimination of R^1OH to give enynyl amine **5**. Then **5** is activated by the subsequent coordination of the alkynyl moiety to Cu(I) to produce **6**, which enhances the electrophilicity of the triple bond, and facilitates an intramolecular cyclization of the nitrogen onto the alkyne to give **7**. Deprotonation of **7** affords **8**. Demetalation of **8** with regeneration of the Cu(I) catalyst furnishes the desired pyrrole **3**.

In conclusion, we have shown that 1,2,4-trisubstituted pyrroles can be efficiently prepared by the Cu-catalyzed cascade reactions using aryloxy-enynes and amines. Aryl and alkyl substituents on the acetylene terminus and a variety of amines are compatible in the annulation reaction, furnishing the desired pyrroles in good to high yields. In this procedure, the regioselective introduction of substituents on the pyrrole ring comes down to the appropriate choice of the aryloxy-enyne and amine, which allows for considerable versatility.

Experimental section

A typical procedure for the Cu-catalyzed synthesis of ethyl 1-cyclohexyl-5-phenyl-1*H*-pyrrole-3-carboxylate (3a)

(*E*)-Ethyl 2-(phenoxymethylene)-4-phenylbut-3-ynoate (88 mg, 0.3 mmol) in DMF (2 mL), CuI (6 mg, 0.03 mmol), cyclohexanamine (0.038 mL, 0.33 mmol), Cs_2CO_3 (196 mg, 0.6 mmol) were added to a Schlenk tube under nitrogen. The resulting solution was stirred at 90 °C. After the reaction was complete as monitored by thin-layer chromatography, the mixture was treated with water and extracted with EA. The extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under the reduced pressure, and the residue was purified by chromatography on silica gel to afford the 1,2,4-trisubstituted pyrrole derivatives **3a** (71 mg, 80%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 1.18–1.29 (m, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.60–1.69 (m, 3H), 1.76–1.84 (m, 2H), 1.97–2.00 (m, 2H), 3.94–4.00 (m, 1H), 4.29 (q, J = 7.2 Hz, 2H), 6.55 (d, J = 1.2 Hz, 1H), 7.32–7.43 (m, 5H), 7.50 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 14.40, 25.14, 25.61, 34.71, 55.63, 59.53, 109.39, 115.63, 123.51, 127.63, 128.53, 129.32, 132.71, 134.94, 165.11; HRMS (EI) calcd for $C_{19}H_{23}NO_2$ 297.1729, found 297.1730.

Acknowledgements

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References

1 (*a*) H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264; (*b*) A. H. Lipkus, Q. Yuan, K. A. Lucas, S. A. Funk, W. F. Bartelt, R. J. Schenck and A. J. Trippe, *J. Org. Chem.*, 2008, **73**, 4443; (*c*) R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 2, pp. 119–206.

2 (*a*) C. T. Walsh, S. Garneau-Tsodikova and A. R. Howard-Jones, *Nat. Prod. Rep.*, 2006, **23**, 517; (*b*) S. Agarwal, S. Cammerer, S. Filali, W. Frohner, J. Knoll, M. P. Krahl, K. R. Reddy and H.-J. Knolker, *Curr. Med. Chem.*, 2005, **9**, 1601; (*c*) A. Furstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582; (*d*) H. Hoffmann and T. Lindel, *Synthesis*, 2003, 1753.

3 (*a*) P. Plitt, D. E. Gross, V. M. Lynch and J. L. Sessler, *Chem.–Eur. J.*, 2007, **13**, 1374; (*b*) V. M. Domingo, C. Aleman, E. Brillas and L. Julia, *J. Org. Chem.*, 2001, **66**, 4058; (*c*) P. A. Gale, *Acc. Chem. Res.*, 2006, **39**, 465; (*d*) D. W. Yoon, H. Hwang and C. H. Lee, *Angew. Chem., Int. Ed.*, 2002, **41**, 1757.

4 For reviews, see: (*a*) G. Balme, *Angew. Chem., Int. Ed.*, 2004, **43**, 6238; (*b*) R. Vicente, *Org. Biomol. Chem.*, 2011, **9**, 6469; (*c*) S. Cacchi, G. Fabrizi and A. Goggiamani, *Org. Biomol. Chem.*, 2011, **9**, 641; (*d*) K. Kruger, A. Tillack and M. Beller, *Adv. Synth. Catal.*, 2008, **350**, 2153; (*e*) L. Ackermann, *Synlett*, 2007, 507, and references cited therein.

5 (*a*) L. Knorr, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1635; (*b*) C. Paal, *Ber. Dtsch. Chem. Ges.*, 1885, **18**, 367.
6 (*a*) A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, **23**, 1474.
7 For recent selected examples, see: (*a*) W. Geng, W.-X. Zhang, W. Hao and Z. Xi, *J. Am. Chem. Soc.*, 2012, **134**, 20230; (*b*) S. Zhang, X. Sun, W.-X. Zhang and Z. Xi, *Chem.–Eur. J.*, 2009, **15**, 12608; (*c*) F. Chen, T. Shen, Y. Cui and N. Jiao, *Org. Lett.*, 2012, **14**, 4926; (*d*) D. Dhara, K. S. Gayen, S. Khamarui, P. Pandit, S. Ghosh and D. K. Maiti, *J. Org. Chem.*, 2012, **77**, 10441; (*e*) Y. Wang, X. Bi, D. Li, P. Liao, Y. Wang, J. Yang, Q. Zhang and Q. Liu, *Chem. Commun.*, 2011, **47**, 809; (*f*) B. B. Thompson and J. Montgomery, *Org. Lett.*, 2011, **13**, 3289; (*g*) S. Rakshit, F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9585; (*h*) Q. Li, A. Fan, Z. Lu, Y. Cui, W. Lin and Y. Jia, *Org. Lett.*, 2010, **12**, 4066; (*i*) X. Du, X. Xie and Y. Liu, *J. Org. Chem.*, 2010, **75**, 510; (*j*) Y. Lu, X. Fu, H. Chen, X. Du, X. Jia and Y. Liu, *Adv. Synth. Catal.*, 2009, **351**, 129; (*k*) I. Bergner, C. Wiebe, N. Meyer and T. Opatz, *J. Org. Chem.*, 2009, **74**, 8243; (*l*) Y.-F. Wang, K. K. Toh, S. Chiba and K. Narasaka, *Org. Lett.*, 2008, **10**, 5019; (*m*) X. Yuan, X. Xu, X. Zhou, J. Yuan, L. Mai and Y. Li, *J. Org. Chem.*, 2007, **72**, 1510; (*n*) J. T. Binder and S. F. Kirsch, *Org. Lett.*, 2006, **8**, 2151; (*o*) B. Gabriele, L. Veltri, P. Plastina, R. Mancuso, M. V. Vetere and V. Maltese, *J. Org. Chem.*, 2013, **78**, 4919; (*p*) S. Kamijo, C. Kanazawa and Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 9260.
8 (*a*) S. Lamande-Langle, M. Abarbri, J. Thibonnet, A. Duchene and J.-L. Parrain, *Chem. Commun.*, 2010, **46**, 5157; (*b*) R. Dhawan and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2004, **126**, 468; (*c*) X. Wang, X.-P. Xu, S.-Y. Wang, W. Zhou and S.-J. Ji, *Org. Lett.*, 2013, **15**, 4246.
9 (*a*) Z.-H. Guan, L. Li, Z.-H. Ren, J. Li and M.-N. Zhao, *Green Chem.*, 2011, **13**, 1664; (*b*) M. Rueping and A. Parra, *Org. Lett.*, 2010, **12**, 5281; (*c*) I. Bergner and T. Opatz, *J. Org. Chem.*, 2007, **72**, 7083; (*d*) Y. Lu, X. Fu, H. Chen, X. Du, X. Jia and Y. Liu, *Adv. Synth. Catal.*, 2009, **351**, 129; (*e*) A. Aponick, C.-Y. Li, J. Malinge and E. F. Marques, *Org. Lett.*, 2009, **11**, 4624.
10 A. V. Kel'in, A. W. Sromek and V. Gevorgyan, *J. Am. Chem. Soc.*, 2001, **123**, 2074.
11 (*a*) M. G. Banwell, B. L. Flynn, D. C. R. Hockless, R. W. Longmore and A. D. Rae, *Aust. J. Chem.*, 1999, **52**, 755; (*b*) W.-L. Chen, J. Li, Y.-H. Zhu, L.-T. Ye, W. Hu and W.-M. Mo, *ARKIVOC*, 2011, 381; (*c*) A. S. Demir, A. C. Igdir and B. Gunay, *Tetrahedron: Asymmetry*, 2005, **16**, 3170.
12 A. Mai, S. Massa, I. Cerbara, S. Valente, R. Ragno, P. Bottoni, R. Scatena, P. Loidl and G. Brosch, *J. Med. Chem.*, 2004, **47**, 1098.
13 (*a*) E. Li, W. Yao, X. Xie, C. Wang, Y. Shao and Y. Li, *Org. Biomol. Chem.*, 2012, **10**, 2960; (*b*) E. Li, X. Cheng, C. Wang, Y. Shao and Y. Li, *J. Org. Chem.*, 2012, **77**, 7744.
14 CCDC 955843 (**3m**) contains the supplementary crystallographic data for this paper.

