Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7309

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COMMUNICATION

Copper(I)-catalyzed synthesis of 1,3-enynes *via* coupling between vinyl halides and alkynes or domino coupling of vinyl halides†

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Received 20th July 2011, Accepted 31st August 2011
DOI: 10.1039/c1ob06210g

1,3-Enynes were easily prepared from coupling between vinyl halides and alkynes or domino coupling of vinyl halides in the presence of copper iodide. It is noteworthy that the double-bond geometry of the vinyl halides was retained during the reaction. This ligand-free protocol is potentially useful and practical.

The 1,3-enyne is a core structure of various natural products or designed pharmaceutical molecules.[1] Successful examples of these include terbinafine (**A**) which is used in the treatment of superficial fungal infections,[2] oxamflatin (**B**) which is a novel antitumor compound that inhibits mammalian histone deacetylase,[3] and 17-hydroxy-17-pentafluoroethylestra-4,9(10)-dien-11-ethynylphenyl derivative (**C**) which is used as progesterone receptor antagonists (Fig. 1).[4] In addition, 1,3-enynes are important precursors to polysubstituted benzenes and conjugated dienes.[5]

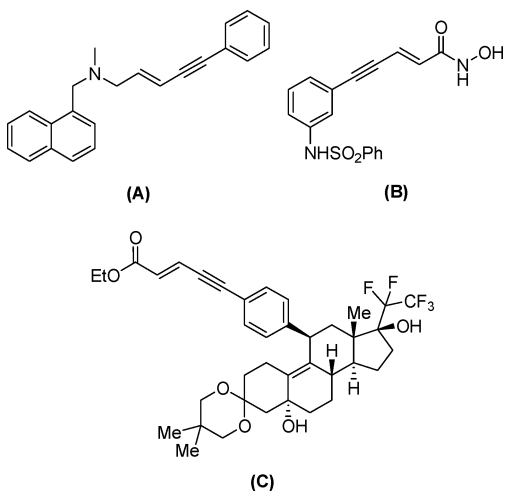
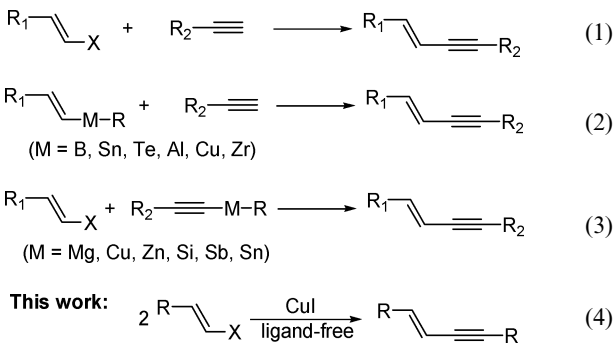


Fig. 1 Examples of compounds containing the 1,3-enyne moiety.

Traditionally, the 1,3-enynes were prepared *via* Pd/Cu-catalyzed Sonogashira coupling between terminal alkyne and vinyl halide, which is certainly considered as the most straightforward way [eqn (1)].[6] In the past several years, some modified protocols have been developed using iron or copper catalysts.[7] On the other hand, conjugated enynes could also be obtained by metal-catalyzed couplings between a terminal alkyne and an organometallic alkene (B, Sn, Te, Al, Cu, Zr) [eqn (2)].[8] The alternative way is by coupling between an alkene and an alkynylmetal (Mg, Cu, Zn, Si, Sb, Sn) [eqn (3)].[9] However, these organometallic reagents are not only toxic, but are also difficult to prepare. In this paper, it is the first time that we report a new approach to synthesizing symmetrical 1,3-enynes just by domino coupling of vinyl halides in the presence of CuI under ligand-free conditions [eqn (4)]. Furthermore, this methodology could be applied to the coupling between terminal alkyne and vinyl halide to prepare unsymmetrical 1,3-enynes.



Initially, we examined the domino coupling of (*E*)-β-bromostyrene as the model reaction to screen the reaction conditions and the results are depicted in Table 1. It can be seen that only 10 mol% of CuI could catalyze the coupling to afford the desired (*E*)-1,4-diphenylbut-1-en-3-yne in 54% yield (Table 1, entry 1). Under the same conditions, the control experiment showed that the reaction could not occur without using copper salt (Table 1, entry 2). Screening various bases including organic bases and inorganic bases (Table 2, entries 3–6), K_3PO_4 was proved the best (Table 1, entry 5). DMSO showed higher efficiency as the reaction medium than all other employed solvents, such as DMF, PEG-400 and NMP (Table 1, entries 7–9). Other copper sources gave inferior results (Table 1, entries 10–14). Varying the amount of CuI did not afford higher yields of desired product (Table 1, entries 15–16). When the temperature was increased to 135 °C, the corresponding 1,3-enyne was obtained in a yield of 82% (Table 1, entry 17).

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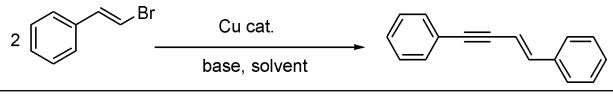
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1ob06210g

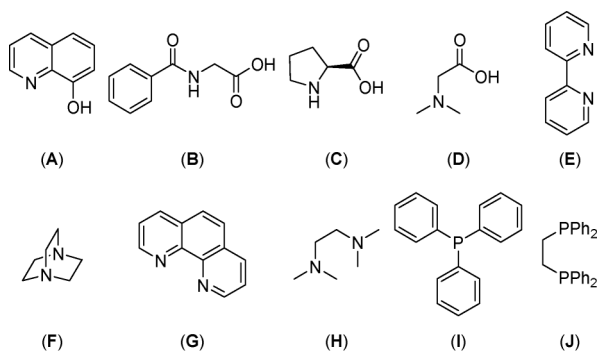
Table 1 Screening conditions for domino coupling of (*E*)-β-bromostyrene[a]



Entry	Cu cat. (mol%)	Base	Solvent	Yield (%)[b]
1	CuI (10)	Cs_2CO_3	DMSO	54
2	—	Cs_2CO_3	DMSO	NR
3	CuI (10)	K_2CO_3	DMSO	trace
4	CuI (10)	Et_3N	DMSO	trace
5	CuI (10)	K_3PO_4	DMSO	78
6	CuI (10)	^tBuOK	DMSO	48
7	CuI (10)	K_3PO_4	DMF	51
8	CuI (10)	K_3PO_4	PEG-400	34
9	CuI (10)	K_3PO_4	NMP	45
10	CuBr (10)	K_3PO_4	DMSO	74
11	Cu_2O (10)	K_3PO_4	DMSO	71
12	CuCl (10)	K_3PO_4	DMSO	77
13	Cu (10)	K_3PO_4	DMSO	<20
14	$Cu(OAc)_2$ (10)	K_3PO_4	DMSO	trace
15	CuI (5)	K_3PO_4	DMSO	42
16	CuI (20)	K_3PO_4	DMSO	75
17[c]	CuI (10)	K_3PO_4	DMSO	82

[a] Reaction conditions: (*E*)-β-bromostyrene (0.8 mmol), base (0.8 mmol), solvent (2 mL), 110 °C, Ar, 24 h. [b] Isolated yield (based on (*E*)-β-bromostyrene). [c] 135 °C.

In order to improve the results, various commonly-used ligands (**A–J**) were investigated in the domino coupling of (*E*)-β-bromostyrene. It can be seen from Fig. 2 that some N,N-ligands (**E**, **F**, **H**) could give good results and other ligands afforded low



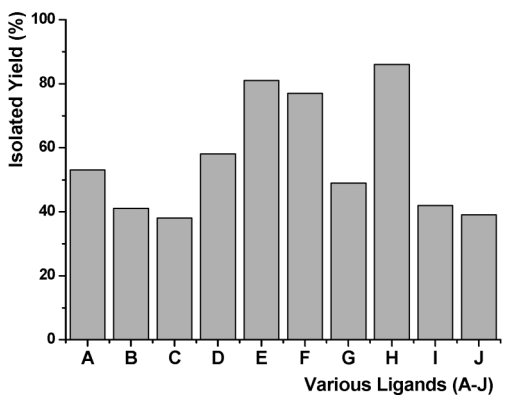
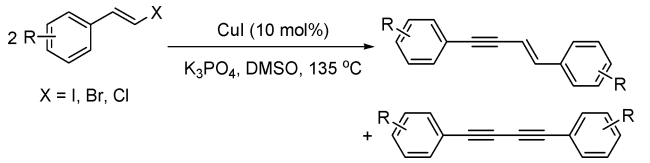
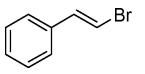
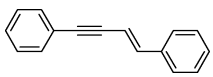
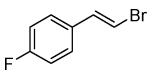
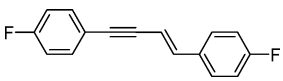
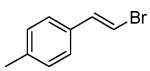
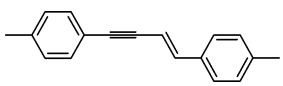
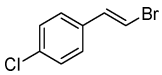
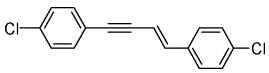
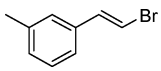
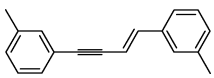
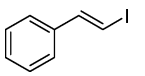
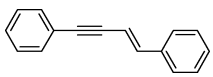
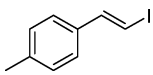
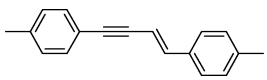
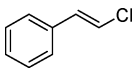
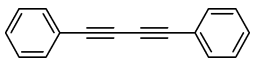
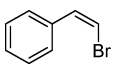
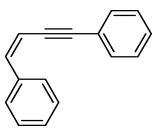
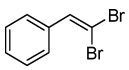
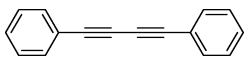
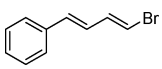
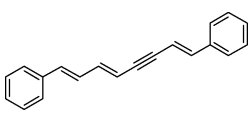


Fig. 2 The relationship between ligands and catalytic effect: [Reaction conditions: CuI (10 mol%), ligand (20 mol%), (*E*)-β-bromostyrene (0.8 mmol), K_3PO_4 (0.8 mmol), DMSO (2 mL), 110 °C, Ar, 24 h].

Table 2 Domino coupling of various (*E*)-vinyl halides in the presence of CuI[a]



Entry	Vinyl halide	Product	Yield (%)[b]
1			82
2			55
3			69
4			70
5			55
6			45
7			52
8			38
9			25
10			<5
11			36

[a] Reaction conditions: Vinyl halide (0.8 mmol), CuI (0.04 mmol), K_3PO_4 (0.8 mmol), DMSO (2 mL), 135 °C, Ar, 24 h. [b] Isolated yield based on half of vinyl halide (average of two runs).

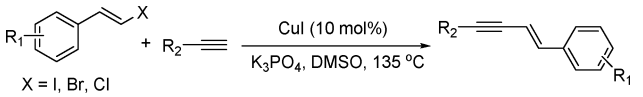
yields of desired product. Compared with the result from using only CuI as the catalyst, we did not acquire a much better result. Thus, in view of the cost of catalytic reaction, the best protocol for the following experiments was determined to be ligand-free conditions.

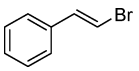
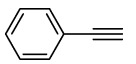
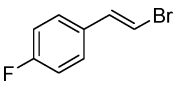
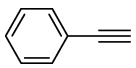
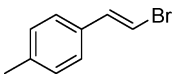
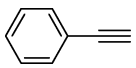
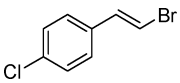
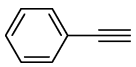
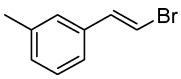
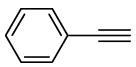
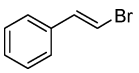
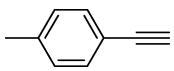
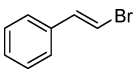
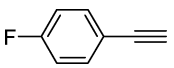
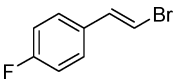
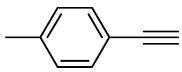
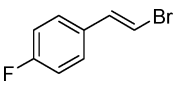
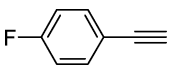
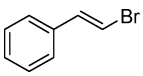
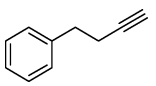
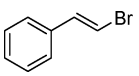
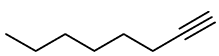
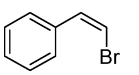
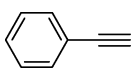
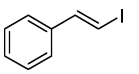
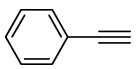
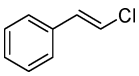
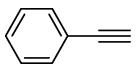
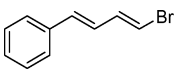
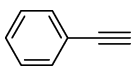
We next aimed to investigate the analogous sequence of alternative (*E*)-vinyl halides[10] and the domino coupling yields are listed in Table 2. Using electron-rich or electron-deficient

vinyl bromides, moderate yields of desired products were obtained (55–82%) (Table 2, entries 1–5). Subsequently, (*E*)-β-iodostyrene with higher activity was employed into the reaction. However, to our surprise, the expected enyne product was acquired with 45% yield (Table 2, entry 6). TLC indicated that a large amount of byproduct was obtained from homocoupling of phenylacetylene. Under the same conditions, a slightly higher yield was obtained when electron-rich vinyl iodide was used (Table 2, entry 7). Using (*E*)-β-chlorostyrene as the substrate, the desired enyne product was not obtained, but the homocoupling product was produced in 38% yield (Table 2, entry 8). In addition, (*Z*)-β-bromostyrene[11] was also employed into the domino coupling reaction and the corresponding product was obtained in low yield (Table 2, entry 9), which was possibly ascribed to the case that the more stable (*E*)-isomer was more easily generated than the less stable (*Z*)-isomer of the enyne product. Furthermore, coupling of 1-(2,2-dibromovinyl)benzene afforded a low amount of homocoupling product (Table 2, entry 10). The domino coupling of conjugated vinyl bromide, 1-((1*E*,3*E*)-4-bromobuta-1,3-dienyl)benzene, was examined using our methodology. The desired (1*E*,3*E*,7*E*)-1,8-diphenylocta-1,3,7-trien-5-yne was obtained in 36% yield (Table 2, entry 11). It is noteworthy that the double-bond geometry of the vinyl halides was retained during the reaction.

Since symmetrical 1,3-enynes were obtained, the question was raised: how can we get the unsymmetrical 1,3-enynes? As we know, the direct synthesis was *via* coupling between vinyl halides and alkynes.[7] Actually, in the past several years, some efficient catalytic systems have been developed for such coupling reactions. For example, Bao and co-workers found that just 15 mol% of CuI could catalyze the coupling of (*E*)-β-bromostyrene and phenylacetylene with 88% yield in the presence of 30 mol% of 1,10-phenanthroline as the ligand;[7b] Li and Xie *et al.* reported a convenient iron-catalyzed cross-coupling of terminal alkynes with vinyl iodides with moderate yields using 1,10-phenanthroline as the ligand. However, their protocol is not suitable for the reaction of vinyl bromides.[7c] Thus, based on this research background, the optimized protocol was applied to such couplings and the related results are illustrated in Table 3. It was found that the coupling of (*E*)-β-bromostyrene and phenylacetylene afforded the desired product with quantitative yield (Table 3, entry 1). Subsequently, various vinyl bromides with substituents were employed as the substrates and moderate to good yields of corresponding products were obtained (Table 3, entries 2–5). Generally, terminal alkynes with an electron-donating group showed higher reactivity than those with electron-withdrawing groups (Table 3, entries 6–9). The couplings of aliphatic alkynes were also investigated and the corresponding products were obtained with considerably lower yields (Table 3, entries 10–11). In addition, the coupling of (*Z*)-β-bromostyrene and phenylacetylene afforded the (*Z*)-isomer of product in 27% yield (Table 3, entry 12). The coupling of vinyl iodide with phenylacetylene resulted in 20% yield of desired product (Table 3, entry 13). However, the corresponding product was not observed when vinyl chloride was employed (Table 3, entry 14). Perhaps it is attributed to the competing reaction that vinyl halides could generate alkynes *in situ*. Another experiment was carried out by cross-coupling of 1-((1*E*,3*E*)-4-bromobuta-1,3-dienyl)benzene and phenylacetylene. It can be seen that the corresponding (1*E*,3*E*)-1,6-diphenylhexa-1,3-dien-5-yne was acquired in 42% yield (Table 3, entry 15). Thus, these fluorescent

Table 3 CuI-catalyzed coupling between (*E*)-vinyl halide and alkyne to prepare unsymmetrical 1,3-enynes[a]



Entry	Vinyl halide	Alkyne	Yield (%)[b]
1			>99
2			81
3			68
4			41
5			67
6			99
7			76
8			76
9			62
10			42
11			trace
12			27
13[c]			20
14[c]			trace
15			42

[a] Reaction conditions: Vinyl halide (0.4 mmol), terminal alkyne (0.5 mmol), CuI (0.04 mmol), K_3PO_4 (0.8 mmol), DMSO (2 mL), 135 °C, Ar, 24 h. [b] Isolated yield based on vinyl halide (average of two runs). [c] Homocoupling of phenylacetylene was obtained.

enynes may find some uses in the emerging field of functional materials in the future.

To further highlight the synthetic utility of our new protocol, the CuI-catalyzed decarboxylative coupling of (*E*)-β-bromostyrene and phenylpropiolic acid[12] was performed in the absence of any ligand. The desired conjugated 1,3-enynes was obtained in 89% yield, which is shown in Scheme 1. As far as we know, this is also the first example of copper-catalyzed decarboxylative coupling of (*E*)-β-bromostyrene and phenylpropiolic acid in the absence of ligand.

Scheme 1 CuI-catalyzed decarboxylative coupling between (*E*)-β-bromostyrene and phenylpropiolic acid.

In summary, we have developed an effective way to prepare conjugated 1,3-enynes by copper-catalyzed domino coupling of vinyl halides or coupling between various vinyl halides and terminal alkynes and the corresponding target products were obtained in moderate to good yields. It is noteworthy that the double-bond geometry of the vinyl halides was retained during the reaction. Thus, this ligand-free protocol is potentially useful in the synthesis of some biologically active molecules. Further investigations in this direction are in progress.

Acknowledgements

We are grateful to the grants from Natural Science Foundation of China (20802046), International S&T Cooperation Program of Jiangsu Province (BZ2010048) and the Key Laboratory of Organic Synthesis of Jiangsu Province for financial support. This project was also funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions. We thank Dr Marc Creus from University of Basel, Switzerland for helpful discussion.

References

1 (*a*) N. El-Jaber, A. Estévez-Braun, A. G. Ravelo, O. Muñoz-Muñoz, A. Rodríguez-Afonso and J. R. Murguia, *J. Nat. Prod.*, 2003, **66**, 722–724; (*b*) A. Fontana, G. d'Ippolito, L. D'Souza, E. Mollo, P. S. Parameswaram and G. Cimino, *J. Nat. Prod.*, 2001, **64**, 131–133; (*c*) A. Rudi, M. Schleyer and Y. Kashman, *J. Nat. Prod.*, 2000, **63**, 1434–1436; (*d*) T. F. Spande, P. Jain, H. M. Garraffo, L. K. Pannell, H. J. C. Yeh, J. W. Daly, S. Fukumoto, K. Imamura, T. Tokuyama, J. A. Torres, R. R. Snelling and T. H. Jones, *J. Nat. Prod.*, 1999, **62**, 5–21; (*e*) D. Ma and F. Liu, *Chem. Commun.*, 2004, 1934–1935; (*f*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131.

2 S. L. Iverson and J. P. Uetrecht, *Chem. Res. Toxicol.*, 2001, **14**, 175–181.

3 N. Zein, A. M. Sinha, W. J. McGahren and G. A. Ellestad, *Science*, 1988, **240**, 1198–1201.

4 Y. B. Kim, K.-H. Lee, K. Sugita, M. Yoshida and S. Horinouchi, *Oncogene*, 1999, **18**, 2461–2470.

5 (*a*) G. Zweifel and N. L. Polston, *J. Am. Chem. Soc.*, 1970, **92**, 4068–4071; (*b*) J. F. Normant and A. Alexakis, *Synthesis*, 1981, 841–870; (*c*) S. Saito, M. M. Salter, V. Gevorgyan, N. Tsuboya, K. Tando and Y. Yamamoto, *J. Am. Chem. Soc.*, 1996, **118**, 3970–3971; (*d*) R. Hara, Y. Liu, W.-H. Sun and T. Takahashi, *Tetrahedron Lett.*, 1997, **38**, 4103–4106.

6 (*a*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467–4470; (*b*) M. Alami, F. Ferri and G. Linstrumelle, *Tetrahedron Lett.*, 1993, **34**, 6403–6406; (*c*) U. Halbes, P. Bertus and P. Pale, *Tetrahedron Lett.*, 2001, **42**, 8641–8644; (*d*) A. Mori, T. Shimada, T. Kondo and A. Sekiguchi, *Synlett*, 2001, 649–651; (*e*) T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato and I. Ryu, *Org. Lett.*, 2002, **4**, 1691–1694; (*f*) J. P. Genet and M. Savignac, *J. Organomet. Chem.*, 1999, **576**, 305–317; (*g*) M. Feuerstein, L. Chahen, H. Doucet and M. Santelli, *Tetrahedron*, 2006, **62**, 112–120.

7 (*a*) C. G. Bates, P. Saejueng and D. Venkataraman, *Org. Lett.*, 2004, **6**, 1441–1444; (*b*) Y. Liu, J. Yang and W. Bao, *Eur. J. Org. Chem.*, 2009, 5317–5320; (*c*) X. Xie, X. Xu, H. Li, X. Xu, J. Yang and Y. Li, *Adv. Synth. Catal.*, 2009, **351**, 1263–1267; (*d*) K. Okuro, M. Furuune, M. Enna, M. Miura and M. Nomura, *J. Org. Chem.*, 1993, **58**, 4716–4721; (*e*) K. Okuro, M. Furuune, M. Miura and M. Nomura, *J. Org. Chem.*, 1993, **58**, 7606–7607; (*f*) L.-X. Shao and M. Shi, *Tetrahedron*, 2007, **63**, 11938–11942.

8 (*a*) M. Hoshi, H. Nakayabu and K. Shirakawa, *Synthesis*, 2005, 1991–2007; (*b*) S.-K. Kang, W.-Y. Kim and X. Jiao, *Synthesis*, 1998, 1252–1254; (*c*) C. C. Silveira, A. L. Braga, A. S. Vieira and G. Zeni, *J. Org. Chem.*, 2003, **68**, 662–665; (*d*) A. Alexakis, G. Cahiez and J. F. Normant, *Synthesis*, 1979, 826–830; (*e*) P. J. Stang and T. Kitamura, *J. Am. Chem. Soc.*, 1987, **109**, 7561–7563; (*f*) E. Negishi, N. Okukado, A. O. King, D. E. Vanhorn and B. I. Spiegel, *J. Am. Chem. Soc.*, 1978, **100**, 2254–2256; (*g*) N. Miyaura, K. Yamada, H. Suginome and A. Suzuki, *J. Am. Chem. Soc.*, 1985, **107**, 972–980; (*h*) P. J. Stang and T. Kitamura, *J. Am. Chem. Soc.*, 1987, **109**, 7561–7563; (*i*) P. Ramiandrasoa, B. Brehon, A. Thivet, M. Alami and G. Cahiez, *Tetrahedron Lett.*, 1997, **38**, 2447–2450.

9 (*a*) U. Halbes, P. Bertus and P. Pale, *Tetrahedron Lett.*, 2001, **42**, 8641–8644; (*b*) J. A. Marshall, H. R. Chobanian and M. M. Yanik, *Org. Lett.*, 2001, **3**, 4107–4110; (*c*) N. Kakusawa, K. Yamaguchi and J. Kurita, *J. Organomet. Chem.*, 2005, **690**, 2956–2966; (*d*) Y. Masuda, M. Murata, K. Sato and S. Watanabe, *Chem. Commun.*, 1998, 807–808; (*e*) H. P. Dang and G. Linstrumelle, *Tetrahedron Lett.*, 1978, 191–194; (*f*) Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, 1988, **53**, 918–920; (*g*) D. A. Siesel and S. W. Staley, *Tetrahedron Lett.*, 1993, **34**, 3679–3682; (*h*) J. K. Stille and J. H. Simpson, *J. Am. Chem. Soc.*, 1987, **109**(9), 2138–2152; (*i*) W. J. Scott, G. T. Crisp and J. K. Stille, *J. Am. Chem. Soc.*, 1984, **106**, 4630–4632; (*j*) E. I. Negishi, M. X. Qian, F. X. Zeng, L. Anastasia and D. Babinski, *Org. Lett.*, 2003, **5**, 1597–1600; (*k*) E. C. Stracker and G. Zweifel, *Tetrahedron Lett.*, 1991, **32**, 3329–3332.

10 S. Chowdhury and S. Roy, *J. Org. Chem.*, 1997, **62**, 199–200.

11 (*a*) C. Kuang, H. Senboku and M. Tokuda, *Tetrahedron Lett.*, 2001, **42**, 3893–3896; (*b*) C. Kuang, Q. Yang, H. Senboku and M. Tokuda, *Tetrahedron*, 2005, **61**, 4043–4052.

12 (*a*) J. Moon, M. Jeong, H. Nam, J. Ju, J. H. Moon, H. M. Jung and S. Lee, *Org. Lett.*, 2008, **10**, 945–948; (*b*) J. Moon, M. Jang and S. Lee, *J. Org. Chem.*, 2009, **74**, 1403–1406; (*c*) H. Kim and P. H. Lee, *Adv. Synth. Catal.*, 2009, **351**, 2827–2832; (*d*) W.-W. Zhang, X.-G. Zhang and J.-H. Li, *J. Org. Chem.*, 2010, **75**, 5259–5264; (*e*) K. Park, G. Bae, J. Moon, J. Choe, K. H. Song and S. Lee, *J. Org. Chem.*, 2010, **75**, 6244–6251.

