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Copper-catalyzed synthesis of internal alkynes *via* domino coupling between 1,1-dihalo-1-alkenes and arylboronic acids†

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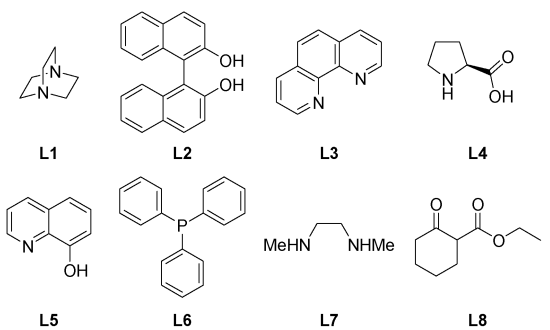
We have developed the practical copper-catalyzed formation of various internal alkynes *via* domino couplings between 1,1-dihalo-1-alkenes and arylboronic acids in the presence of low-cost 8-hydroxylquinoline as the ligand.

It is well known that structural motifs with carbon–carbon triple bonds have prevailed in many bioactive compounds, natural products, pharmaceuticals, and functional materials.[1] Since the late 20th century, the Sonogashira reaction has been proved to be an effective approach for the synthesis of various alkynes.[2] The typical Sonogashira coupling is performed in the presence of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ together with CuI as the cocatalyst and larger amount of amines as the solvents or cosolvents.[3] In view of the high-cost and toxicity of Pd catalysts, chemists have paid more attention to the cheaper metals. In the past ten years, many efficient protocols have been developed based on copper or iron catalysts.[4] Thus, Sonogashira couplings can potentially be applied in industrial applications because of the reduced cost. Although the question of a low-cost catalyst has been solved, easily available resources of raw materials should also be considered. It is known that various types of terminal alkynes are usually volatile liquids with bad smells that are not easily prepared or stored. Thus, some chemists[5a–h] and our group[5i–j] have found that stable alkynyl carboxylic acids could be successfully employed as alternative sources of alkynes for the decarboxylative coupling reaction with aryl halides. However, these alkynyl carboxylic acids were not yet readily available.

Recently, *gem*-dihaloolefins have been widely used in organic syntheses owing to their utility as synthetic intermediates.[6] They can be easily prepared from corresponding aldehydes and ketones using CBr_4/PPh_3[7] or the ylide CCl_2PPh_3.[8] So far, it is easy to believe that the internal alkynes could possibly be prepared by coupling between *gem*-dihaloolefins and some nucleophiles. Shen and Wang described the preparation of trisubstituted alkenes and internal alkynes *via* the Stille reaction of 1,1-dibromo-1-alkenes in the presence of a Pd catalyst.[9] Chelucci *et al.* disclosed a Pd-based protocol for the one-pot synthesis of internal alkynes from the Suzuki–Miyaura coupling of 1,1-dibromo-1-alkenes with arylboronic acids or borate esters followed by dehydrobromination of the intermediate coupled products.[10] However, Schmidt and Rahimi have just found that a cyclobutene-1,2-bis(imidazolium) salt is an efficient catalyst precursor for the Pd-catalyzed tandem reaction of 1,1-dibromo-1-alkenes with arylboronic acids.[11] Recently, Rao and co-workers have found that 0.09 equiv of $Pd(PPh_3)_4$ could successfully catalyze the domino couplings between 1,1-dibromo-1-alkenes and triarylbismuths.[12] Although great progress has been made in the past few decades, toxic and high-cost Pd-catalysts will undoubtedly limit their application at industrial scales. Herein, from the cost perspective, we report a copper-catalyzed synthesis of internal alkynes *via* the one-step domino couplings between 1,1-dihalo-1-alkenes and various arylboronic acids.

We started our investigation by treating 1,1-dibromo-1-alkene with 4-methoxyphenylboronic acid. The efficiency of a series of readily available ligands was initially studied (**L1–L8**, Scheme 1), including 1,4-diazabicyclo[2.2.2]octane (**L1**), *rac*-binol (**L2**), 1,10-phenanthroline (**L3**), L-proline (**L4**), 8-hydroxylquinoline (**L5**), triphenylphosphine (**L6**), N^1,N^2-dimethylethane-1,2-diamine (**L7**) and ethyl 2-oxocyclohexanecarboxylate (**L8**). As shown in Fig. 1, it was clear to see that **L5** afforded a better yield of the desired



Scheme 1 Various ligands evaluated in this study.

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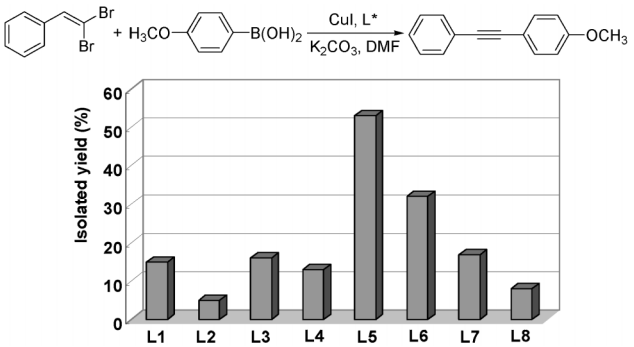
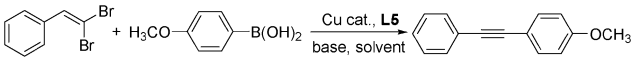


Fig. 1 The relationship between ligand and the catalytic effect.

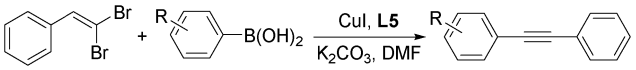
Table 1 Screening of the catalytic conditions in the domino coupling between phenylboronic acid and 1,1-dibromo-2-phenylethene[a]

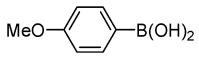
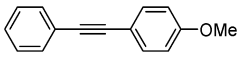
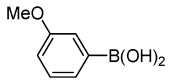
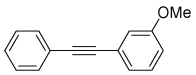
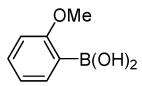
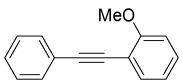
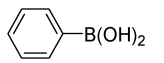
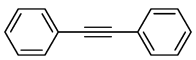
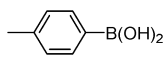
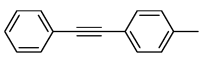
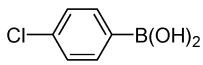
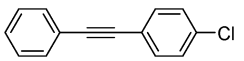
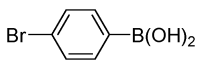
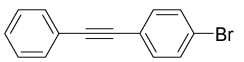
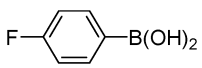
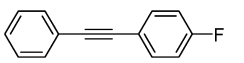
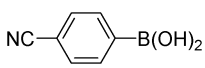
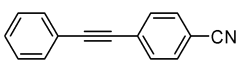
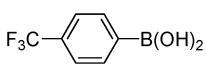
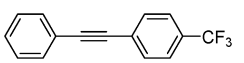
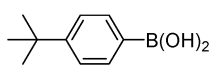
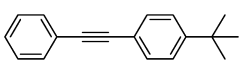
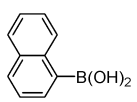
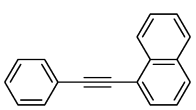
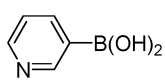
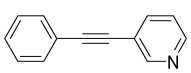


Entry	Cu cat. (mol%)	Solvent	Base	T (°C)/t (h)	Yield[b] (%)
1	CuI (15)	DMF	K_2CO_3	110/18	53
2	CuI (15)	PEG400	K_2CO_3	110/18	28
3	CuI (15)	H_2O	K_2CO_3	110/18	NR
4	CuI (15)	toluene	K_2CO_3	110/18	–
5	CuI (15)	DMSO	K_2CO_3	110/18	38
6	CuI (15)	CH_3CN	K_2CO_3	110/18	–
7	CuI (15)	DMAc	K_2CO_3	110/18	50
8	CuI (15)	DMF	^tBuOK	110/18	12
9	CuI (15)	DMF	K_3PO_4	110/18	9
10	CuI (15)	DMF	KOH	110/18	13
11	CuI (15)	DMF	Et_3N	110/18	NR
12	CuI (15)	DMF	Na_2CO_3	110/18	NR
13	CuI (15)	DMF	Cs_2CO_3	110/18	46
14	Cu (15)	DMF	K_2CO_3	110/18	39
15	CuO (15)	DMF	K_2CO_3	110/18	–
16	$Cu(OAc)_2$ (15)	DMF	K_2CO_3	110/18	36
17	CuBr (15)	DMF	K_2CO_3	110/18	27
18	Cu_2O (15)	DMF	K_2CO_3	110/18	42
19	CuI (15)	DMF	K_2CO_3	90/18	29
20	CuI (15)	DMF	K_2CO_3	100/18	37
21	CuI (15)	DMF	K_2CO_3	120/18	43
22	CuI (15)	DMF	K_2CO_3	130/18	26
23[c]	CuI (10)	DMF	K_2CO_3	110/18	38
24[d]	CuI (10)	DMF	K_2CO_3	110/18	48
25[e]	CuI (15)	DMF	K_2CO_3	110/18	34
26[f]	CuI (15)	DMF	K_2CO_3	110/18	58
27[f,g]	CuI (15)	DMF	K_2CO_3	110/18	trace
28[f,h]	CuI (15)	DMF	K_2CO_3	110/18	10
29[f,i]	CuI (15)	DMF	K_2CO_3	110/18	58
30[f,j]	CuI (15)	DMF	K_2CO_3	110/18	42
31[f,k]	CuI (15)	DMF	K_2CO_3	110/18	28
32[f]	–	DMF	K_2CO_3	110/48	NR
33[f]	CuI (15)	DMF	K_2CO_3	110/24	61
34[f]	CuI (15)	DMF	K_2CO_3	110/48	52

[a] Catalytic conditions: 1,1-dibromo-2-phenylethene (0.3 mmol), phenylboronic acid (0.4 mmol), catalyst (15 mol%), ligand (30 mol%), additive (30 mol%), base (2 equiv), solvent (2 mL), 110 °C, 18h, in Ar. [b] Isolated yield based on 1,1-dibromo-1-alkene. [c] **L5** (10 mol%). [d] **L5** (20 mol%). [e] 1,1-Dibromo-1-alkene (0.4 mmol), phenylboronic acid (0.3 mmol). [f] 1,1-Dibromo-1-alkene (0.3 mmol), phenylboronic acid (0.6 mmol). [g] Iodine as the additive. [h] NaI as the additive. [i] TBAB as the additive. [j] LiCl as the additive. [k] Ligand-free.

Table 2 Copper-catalyzed domino couplings between various arylboronic acids and 1,1-dibromo-2-phenylethene [a]

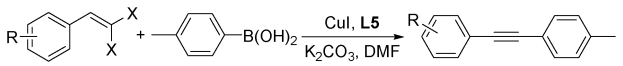


Entry	$ArB(OH)_2$	Product	Yield[b] (%)
1			61
2			52
3			42
4			20
5			73
6			56
7			73
8			60
9			63
10			46
11			51
12			34
13			17

[a] Reaction conditions: 1,1-dibromo-2-phenylethene (0.3 mmol), arylboronic acid (0.6 mmol), CuI (15 mol%), **L5** (30 mol%), K_2CO_3 (2 equiv), DMF (2 mL), 110 °C, 24 h, in Ar. [b] Isolated yield based on 1,1-dibromo-2-phenylethene (average of two runs).

product, giving a result of 53% (Table 1, entry 1). Then, after a series of solvents was tested using this readily available ligand, it was found that DMF is superior to other solvents for the formation of the expected product, though DMAc was also a solvent candidate, giving a result of 50% (Table 1, entry 7). At the same time, TLC detection showed that the use of either a common weak organic base (such as triethylamine) or strong inorganic bases

Table 3 Copper-catalyzed domino couplings between various 1,1-dihalo-1-alkenes and 4-methylphenylboronic acid[a]



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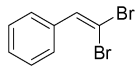
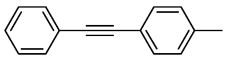
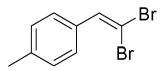
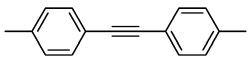
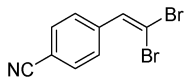
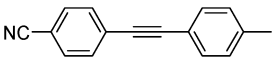
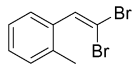
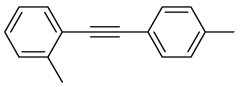
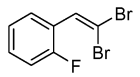
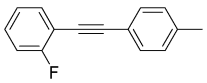
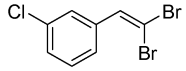
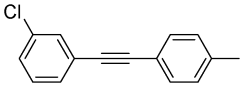
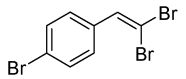
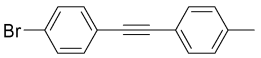
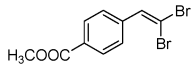
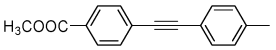
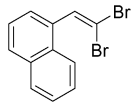
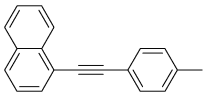
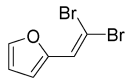
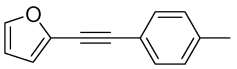
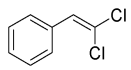
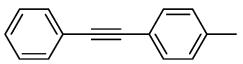
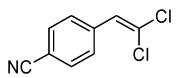
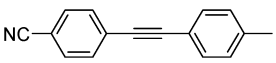
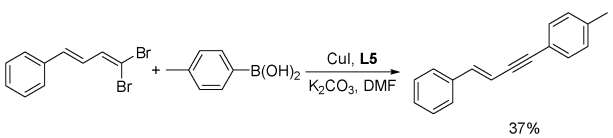
1			73
2			33
3			82
4			43
5			53
6			64
7			59
8			60
9			82
10			65
11[c]			13
12			80

[a] Reaction conditions: 1,1-dibromo-1-alkene (0.3 mmol), 4-methylphenylboronic acid (0.6 mmol), CuI (15 mol%), **L5** (30 mol%), K_2CO_3 (2 equiv), DMF (2 mL), 110 °C, 24 h, in Ar. [b] Isolated yield based on 1,1-dibromo-1-alkene (average of two runs). [c] 48 h.

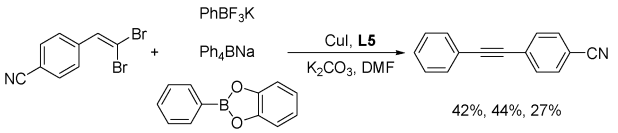
(such as ^{t}BuOK and KOH) were unfavorable for the reaction (Table 1, entries 8, 10–11). Another interesting aspect of the reaction is the source of copper. The use of copper powder and $Cu(OAc)_2$ both lead to lower catalytic efficiency. When CuO was employed in the reaction, no desired product was detected (Table 1, entry 15). It can be seen that the Cu(I) salt was the ideal catalyst, especially CuI, which exhibited higher a efficiency than any other Cu(I) salts. As we all know, copper-catalyzed Suzuki reactions usually need higher reaction temperatures.[13] In this study, 110 °C was favorable for the catalytic reaction after screening different temperatures (Table 1, entries 19–22). The effect of the amount of copper salt and the ligand was also tested. It was indicated that the catalyst system containing 15 mol% of CuI and 30 mol% of ligand was optimal (58% yield) (Table 1, entry 26). In order to improve the yield, some additives were employed, such as iodine, TBAB, NaI and LiCl. However, we never acheieved better results (Table 1, entries 27–30). In addition, the control experiment in the absence of ligand showed low catalytic efficiency, only giving a result of 28% (Table 1, entry 31). As expected, in the absence of CuI, no product was achieved (Table 1, entry 32). Then, the reaction times were screened (Table 1, entries 33–34) and 24 h was the optimal. Based on the above results, the optimal reaction conditions proved to be with **L5** as the ligand, CuI as the copper source, and DMF as the solvent at 110 °C for 24 h.

With the optimized protocol in hand, we then set out to investigate the scope and limitations of this domino coupling reaction. The results are shown in Table 2. Various arylboronic acids were tested under our standard conditions, and most of the substrates could achieve moderate yields. We found that the reactions of 1,1-dibromo-1-alkenes with 4-, 3- and 2-methoxyphenylboronic acids gave the cross-coupling products in decreased yields from 61% to 42% (Table 2, entries 1–3). The coupling of phenylboronic acid and α-naphthylboronic acid afforded the corresponding products in low yield (20% and 34%, respectively) (Table 2, entries 4 and 12). Other substituted phenylboronic acids can proceed smoothly to give the desired coupling products in moderate to good yields (Table 2, entries 5–11). To our disappointment, 3-pyridylbronic acid was not a suitable substrate for the copper-catalyzed domino coupling reaction (17%, Table 2, entry 13).

We next applied our methodology to the domino coupling between 4-methyl phenylboronic acid and various 1,1-dihalo-1-alkenes (Table 3). We can see that 1,1-dibromo-1-alkenes bearing either electron-donating or electron-withdrawing groups reacted well with 4-methylphenylboronic acid to provide the desired products in yields ranging from 33% to 82% (Table 3, entries 1–9). We were delighted to observe that heteroaryl *gem*-dibromoalkene was suitable for the domino coupling reaction under the standard conditions (Table 3, entry 10), as we know that C–Br bond cleavage usually takes place in preference to C–Cl bond cleavage. The corresponding product of 1,1-dichloro-1-alkene was obtained in poor yield (Table 3, entry 11). Interestingly, an excellent catalytic



Scheme 2 Synthesis of *trans*-1-phenyl-4-tolyl-but-3-ene-1-yne.



Scheme 3 Copper-catalyzed couplings between 4-cyano-1,1-dibromo-1-alkene and various phenylboronic acid derivatives.

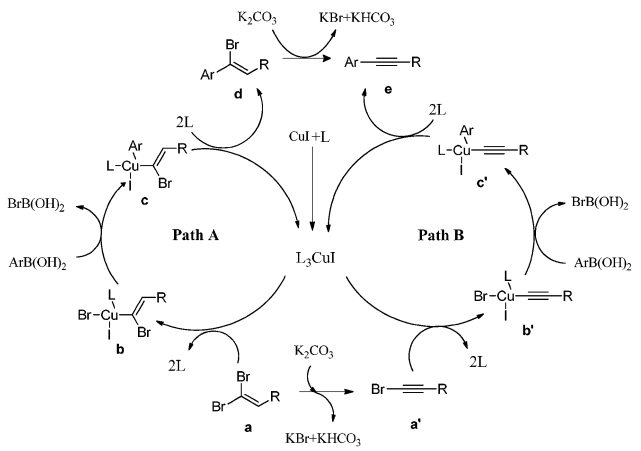
performance was observed with the cyano-substituted *gem*-dichloroalkene (Table 3, entry 12).

Enynes have been proven to have versatile uses, they are not only present in abundant natural products but are also intermediates for the manufacture of potential pharmaceuticals and chemicals.[14] *trans*-1-Phenyl-4-tolyl-but-3-ene-1-yne can be readily synthesized using our protocol (Scheme 2).

Meanwhile, a wide range of arylboronic reagents, including potassium tetrafluoroborate, sodium tetraphenylborate and 2-phenylbenzo[*d*][1,3,2]dioxaborole, have been successfully coupled with 4-cyano-1,1-dibromo-1-alkene under the optimized conditions, as presented in Scheme 3.

A possible mechanism is proposed in Scheme 4.[15] Initially, copper iodide is coordinated with 8-hydroxylquinoline to form tetracoordinated copper complex (L_3CuI). Afterwards, the reaction might go through two paths. On the one hand, L_3CuI could react directly with 1,1-dibromo-1-alkene *via* intermolecular oxidative addition to afford intermediate **b** in *Path A*. Then, intermediate **c** was easily generated in the presence of $ArB(OH)_2$. Subsequently, reductive elimination of intermediate **c** gave intermediate **d** and liberated L_3CuI to go on for another circle. Finally the coupling product **e** was afforded by the elimination of **d** in the basic condition. On the other hand, 1,1-dibromo-1-alkene might undergo elimination in the presence of potassium carbonate to create 1-bromo-2-phenylacetylene (**a**′) firstly. Then it goes through *Path B* in a similar way to *Path A* to form the final product (**e**).

In summary, we have successfully accomplished the copper-catalyzed synthesis of internal alkynes *via* the domino couplings between various 1,1-dihalo-1-alkenes and arylboronic acids in a single step. Our methodology is efficient for a wide substrate scope. It is noteworthy that our protocol avoided the use of high-cost and toxic palladium catalysts or any organoreagents, which is of benefit when considering possible large-scale synthesis or industrial application. It can be seen that this is a practical approach for preparing various substituted diarylalkynes. Efforts are underway to extend this methodology to other types of 1,1-dihalo-1-alkenes and aryl reagents.



Scheme 4 Proposed reaction mechanism

Acknowledgements

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References

1 R. Chinchilla and C. Najera, *Chem. Rev.*, 2007, **107**, 874–922.
2 K. Sonogashira, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and L. Fleming, Pergamon Press, Elmsford, NY, 1991, **vol. 3**, pp. 521–549.
3 (*a*) H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834–871; (*b*) H. Plenio, *Angew. Chem., Int. Ed.*, 2008, **47**, 6954–6956.
4 (*a*) J. Mao, G. Xie, M. Wu, J. Guo and S. Ji, *Adv. Synth. Catal.*, 2008, **350**, 2477–2482; (*b*) X. Meng, C. Li, B. Han, T. Wang and B. Chen, *Tetrahedron*, 2010, **66**, 4029–4031; (*c*) J. Bonnamour, M. Piedrafita and C. Bolm, *Adv. Synth. Catal.*, 2010, **352**, 1577–1581; (*d*) M. Taillefer, *US Pat.*, 60/818, 334, 2006, (*WO* 2008/004088 A3); (*e*) M. Taillefer, N. Xia and A. Ouali, *Angew. Chem., Int. Ed.*, 2007, **46**, 934–936; (*f*) E. Shirakawa, D. Ikeda, S. Yamaguchi and T. Hayashi, *Chem. Commun.*, 2008, 1214–1216; (*g*) E. Shirakawa, T. Yamagami, T. Kimura, S. Yamaguchi and T. Hayashi, *J. Am. Chem. Soc.*, 2005, **127**, 17164–17165; (*h*) X.-F. Wu and C. Darcel, *Eur. J. Org. Chem.*, 2009, 4753–4756; (*i*) D. Guo, H. Huang, Y. Zhou, J. Wu, H. Jiang and H. Liu, *Green Chem.*, 2010, **12**, 276–281; (*j*) V. H. Jadhav, D. K. Dumbre, V. B. Phapale, H. B. Borate and R. D.Wakharkar, *Catal. Commun.*, 2007, **8**, 65–68; (*k*) H. Huang, H. Jiang, K. Chen and H. Liu, *J. Org. Chem.*, 2008, **73**, 9061–9064; (*l*) Z. Wang, H. Fu, Y. Jiang and Y. Zhao, *Synlett*, 2008, 2540–2546; (*m*) X. Ku, H. Huang, H. Jiang and H. Liu, *J. Comb. Chem.*, 2009, **11**, 338–340; (*n*) S. Li, W. Jia and N. Jiao, *Adv. Synth. Catal.*, 2009, **351**, 569–575; (*o*) C. M. Rao Volla and P. Vogel, *Tetrahedron Lett.*, 2008, **49**, 5961–5964.
5 (*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; (*f*) Y. Kim, A. Park, K. Park and S. Lee, *Tetrahedron Lett.*, 2011, **52**, 1766–1769; (*g*) A. Park, K. Pak, Y. Kim and S. Lee, *Org. Lett.*, 2011, **13**, 944–947; (*h*) K. Park, G. Bae, A. Park, Y. Kim, J. Choe, K. H. Song and S. Lee, *Tetrahedron Lett.*, 2011, **52**, 576–580; (*i*) T. Li, X. Qu, Y. Zhu, P. Sun, H. Yang, Y. Shan, H. Zhang, D. Liu, X. Zhang

and J. Mao, *Adv. Synth. Catal.*, 2011, **353**, 2731–2738; (*j*) X. Qu, T. Li, P. Sun, Y. Zhu, H. Yang and J. Mao, *Org. Biomol. Chem.*, 2011, **9**, 6938–6942.

6 For reviews of *gem*-dihaloolefins, see:(*a*) *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-I. Negishi, Wiley-Interscience, New York, 2002, p. 650; (*b*) B. Xu and S. Ma, *Chin. J. Org. Chem.*, 2001, **21**, 252–262.

7 (*a*) F. Ramiraz, N. B. Desai and N. McKelvie, *J. Am. Chem. Soc.*, 1962, **84**, 1745–1747; (*b*) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, **13**, 3769–3772.

8 (*a*) A. J. Speziale, G. J. Marco and K. W. Ratts, *J. Am. Chem. Soc.*, 1960, **82**, 1260–1261; (*b*) A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, 1962, **84**, 854–859; (*c*) A. J. Speziale, K. W. Ratts and D. E. Bissing, *Organic Synthesis*, Wiley, New York, 1973, **vol. 5**, p. 361.

9 W. Shen and L. Wang, *J. Org. Chem.*, 1999, **64**, 8873–8879.

10 G. Chelucci, F. Capitta, S. Baldino and G. A. Pinna, *Tetrahedron Lett.*, 2007, **48**, 6514–6517.

11 A. Rahimi and A. Schmidt, *Synthesis*, 2010, **15**, 2621–2625.

12 M. L. N. Rao, D. N. Jadhav and P. Dasgupta, *Org. Lett.*, 2010, **12**, 2048–2051.

13 A. Corma, C. González-Arellano, M. Iglesias and F. Sánchez, *Angew. Chem., Int. Ed.*, 2007, **46**, 7820–7822.

14 S. P. Bew, G. M. M. El-Taeb, S. Jones, D. W. Knight and W.-F. Tan, *Eur. J. Org. Chem.*, 2007, 5759–5770.

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