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Efficient copper(I)-catalyzed, microwave-assisted, one-pot synthesis of 3,4-diaryl isoquinolines

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Abstract An efficient copper-catalyzed, microwave-assisted, one-pot reaction has been developed for synthesis of 3,4-diaryl isoquinolines. The reaction was performed in two steps via a CuI/2,2′-biimidazole-catalyzed tandem process from *N*-*tert*-butyl-*o*-iodobenzaldimine and a terminal aryl alkyne, followed by addition of an aryl iodide. A variety of 3,4-diaryl isoquinolines have been obtained in moderate to good yields.

Keywords Isoquinolines · Copper-catalyzed · One-pot synthesis · Microwave irradiation

Introduction

The isoquinoline nucleus frequently occurs in natural products and pharmaceutically active compounds with remarkable biological activity, for example antifertility [1], antitumor [2], anti-HIV [3, 4], analgesic [5], anti-inflammatory [6], among others. As a consequence of their substantial biological importance, much attention has recently been devoted to the synthesis of isoquinoline derivatives. Some valuable approaches to isoquinolines have been developed via transition metal-catalyzed synthesis, including use of palladium [7–10], nickel [11], cobalt [12], and copper [13]; palladium-catalyzed processes, in particular, have received much attention. Unfortunately, palladium-catalyzed methodology is difficult to apply

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because of high cost and the difficulty of removing of palladium. To the best of our knowledge, copper-catalyzed, one-pot synthetic strategies to obtain isoquinolines are still scarce.

It is noteworthy that microwave irradiation (MWI) is a widely applied and powerful tool in organic synthesis; its advantages, including enormous acceleration of the rate of reaction, and improved yields and selectivity, have been well demonstrated [14–16]. As a continuation of our long-term interest in developing new methods for synthesis of functionalized heterocyclic compounds [17–19], we describe herein a copper(I)-catalyzed, one-pot, microwave-assisted procedure for synthesis of 3,4-diaryl isoquinolines.

Experimental

General procedures

All microwave reactions were conducted in sealed, oven-dried microwave vials. An LWMC-201 microwave reactor was used for all experiments; the conditions used are described below. Unless otherwise indicated, all reactions were conducted under a dry nitrogen atmosphere. The chemicals were obtained from commercial sources and used as received unless otherwise noted. Melting points (mp) were obtained on a Büchi B-540 melting-point apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data were recorded on a DPX-400 instrument with $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are given in ppm and spin–spin coupling constants, *J*, are given in Hz. Mass spectra (MS) were recorded on an HP5989A mass spectrometer.

Synthesis of *N*-*tert*-butyl-*o*-iodobenzaldimine (**1**) [8]

tert-Butylamine (25.8 mmol) was added to a solution of *o*-iodobenzaldehyde (2.00 g, 8.6 mmol) in CH_2Cl_2 (30 mL). The resulting mixture was stirred under a nitrogen atmosphere at room temperature for 12 h. After the *o*-iodobenzaldehyde had been consumed completely (monitored by TLC), the solution was concentrated under reduced pressure, and the resulting residue was extracted with ether. The organic phases were combined, dried with Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure and *N*-*tert*-butyl-*o*-iodobenzaldimine was afforded in 87 % yield as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.30 (s, 9H), 7.02–7.06 (m, 1H), 7.28–7.35 (m, 1H), 7.78–7.89 (m, 2H), 8.37 (s, 1H). ESI–MS: $[M + 1]^+$ *m*/*z* 288.1.

General procedure for copper-catalyzed one-pot synthesis of isoquinolines **(4)**

In an oven-dried 5-mL microwave vial, *N*-*tert*-butyl-*o*-iodobenzaldimine (0.14 g, 0.5 mmol) was dissolved in freshly distilled dioxane (3 mL), then CuI (9.5 mg, 0.05 mmol, 10 mol%), 2,2′-biimidazole (13.4 mg, 0.1 mmol, 20 mol%), Cs_2CO_3 (0.49 g, 1.5 mmol), and aryl alkyne (0.55 mmol) were added. The vial was purged

with nitrogen, sealed, and placed in the microwave reactor for 20 min at 550 W. An aryl iodide (0.55 mmol) in dry dioxane (1 mL) was added to the vial and the resulting mixture was heated in the microwave reactor (550 W) for 20 min. After cooling, the reaction mixture was diluted with diethyl ether and washed with brine (10 mL). The aqueous phase was extracted with diethyl ether (2 × 5 mL). The organic phases were combined and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel with ethyl acetate–hexanes (1:8 to 1:2) as eluent. The desired products **4** were afforded.

*3,4-Diphenylisoquinoline (**4a**)*

White solid, mp 166–168 °C (lit. [7] 168–169 °C), yield 56 %; ^{1}H NMR ($CDCl_3$) δ: 7.12–7.18 (m, 3H), 7.21–7.26 (m, 2H), 7.29–7.37 (m, 5H), 7.56–7.62 (m, 2H), 7.68 (dd, J = 4.8 and 4.2 Hz, 1H), 8.06 (dd, J = 6.0 and 4.2 Hz, 1H), 9.36 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 125.2, 126.7, 126.9, 127.0, 127.3, 127.4, 127.5, 128.4, 130.0, 130.3, 130.6, 131.3, 135.6, 137.3, 140.5, 150.6, 151.8. ESI–MS: $[M + 1]^+$ m/z 282.1.

*3-Phenyl-4-p-tolylisoquinoline (**4b**)*

White solid, mp 126–128 °C (lit. [7] 129 °C), yield 51 %; ^{1}H NMR ($CDCl_3$) δ: 2.35 (s, 3H), 7.12–7.25 (m, 7H), 7.34–7.36 (m, 2H), 7.57–7.61 (m, 2H), 7.65–7.69 (m, 1H), 8.03–8.05 (m, 1H), 9.35 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.7, 126.1, 126.9, 127.1, 127.3, 127.5, 127.6, 128.8, 130.3, 130.7, 130.9, 131.4, 134.5, 136.1, 137.2, 140.4, 150.7, 151.9. ESI–MS: $[M + 1]^+$ m/z 296.2.

*4-(4-Methoxyphenyl)-3-phenylisoquinoline (**4c**)*

White solid, mp 143–145 °C (lit. [10] 141–142 °C), yield 57 %; ^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H), 7.00 (d, J = 7.2 Hz, 2H), 7.13–7.25 (m, 5H), 7.36 (d, J = 7.2 Hz, 2H), 7.58–7.62 (m, 2H), 7.68–7.70 (m, 1H), 8.01–8.03 (m, 1H), 9.34 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 55.1, 114.2, 126.1, 127.0, 127.3, 127.5, 127.8, 128.5, 129.3, 130.3, 130.5, 131.1, 133.0, 136.5, 140.5, 150.9, 151.8, 159.2. ESI–MS: $[M + 1]^+$ m/z 312.1.

*4-(4-Nitrophenyl)-3-phenylisoquinoline (**4d**)*

Yellow white solid, mp 134–136 °C, (lit. [10] 133–134 °C), yield 63 %; ^{1}H NMR ($CDCl_3$) δ: 7.21–7.25 (m, 3H), 7.29–7.32 (m, 2H), 7.39–7.45 (m, 2H), 7.52–7.55 (m, 1H), 7.63–7.68 (m, 2H), 8.05–8.09 (m, 1H), 8.21–8.24 (m, 2H), 9.40 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 125.1, 125.8, 127.0, 127.5, 127.9, 128.3, 128.5, 128.7, 130.5, 131.3, 131.9, 133.2, 140.5, 145.8, 147.0, 150.6, 152.0. ESI–MS: $[M + 1]^+$ m/z 327.2.

*3-(4-Methoxyphenyl)-4-p-tolylisoquinoline (**4e**)*

White solid, mp 156–158 °C, yield 65 %; ^{1}H NMR ($CDCl_3$) δ: 2.33 (s, 3H), 3.84 (s, 3H), 7.02 (d, $J = 7.2$ Hz, 2H), 7.13–7.25 (m, 4H), 7.35–7.37 (m, 2H), 7.59–7.63 (m, 2H), 7.66–7.70 (m, 1H), 8.02–8.05 (m, 1H), 9.35 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.8, 55.2, 114.3, 126.2, 127.0, 127.2, 127.5, 127.7, 128.5, 129.1, 130.0, 130.2, 130.6, 131.0, 133.2, 140.4, 150.8, 151.7, 159.1. ESI–MS: $[M + 1]^+$ *m*/*z* 326.3.

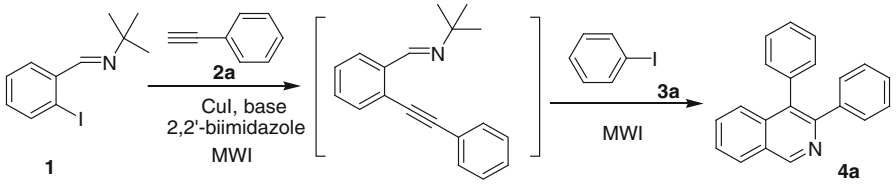
*3,4-Bis(4-methoxyphenyl)isoquinoline (**4f**)*

White solid, mp 149–151 °C, yield 62 %; ^{1}H NMR ($CDCl_3$) δ: 3.84 (s, 6H), 7.01 (d, $J = 7.2$ Hz, 2H), 7.08 (d, $J = 7.2$ Hz, 2H), 7.33–7.37 (m, 2H), 7.58–7.63 (m, 3H), 7.64–7.71 (m, 2H), 8.02–8.06 (m, 1H), 9.34 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 55.1, 114.2, 114.3, 126.1, 126.8, 127.2, 127.6, 127.9, 128.4, 128.6, 129.1, 130.5, 131.0, 140.5, 150.7, 151.6, 159.1, 160.2. ESI–MS: $[M + 1]^+$ *m*/*z* 342.1.

*3-(4-Methoxyphenyl)-4-(4-nitrophenyl)isoquinoline (**4g**)*

Yellow white solid, mp 179–181 °C, (lit. [10] 181–182 °C), yield 71 %; ^{1}H NMR ($CDCl_3$) δ: 3.81 (s, 3H), 6.99 (d, $J = 7.2$ Hz, 2H), 7.26–7.32 (m, 2H), 7.48–7.54 (m,

Table 1 Optimization of copper-catalyzed one-pot synthesis of isoquinolines



Entry	Catalyst/L	Amount of catalyst (L)	Solvent	Base	MWI	Yield (%)[a]
1	CuI/L	10 (20) mol%	Toluene	Cs_2CO_3	550 W, 20 min	25
2	CuI/L	10 (20) mol%	DMF	Cs_2CO_3	550 W, 20 min	34
3	CuI/L	10 (20) mol%	Dioxane	Cs_2CO_3	550 W, 20 min	56
4	CuI/L	10 (20) mol%	THF	Cs_2CO_3	550 W, 20 min	22
5	CuI/L	10 (20) mol%	Dioxane	K_2CO_3	550 W, 20 min	37
6	CuI/L	10 (20) mol%	Dioxane	Cs_2CO_3	600 W, 20 min	52
7	CuI/L	10 (20) mol%	Dioxane	Cs_2CO_3	450 W, 20 min	39
8	$Cu(OAc)_2$/L	10 (20) mol%	Dioxane	Cs_2CO_3	550 W, 20 min	7
9	CuCl/L	10 (20) mol%	Dioxane	Cs_2CO_3	550 W, 20 min	15
10	CuI/L	5 (10) mol%	Dioxane	Cs_2CO_3	550 W, 20 min	31
11	CuI/L	20 (40) mol%	Dioxane	Cs_2CO_3	550 W, 20 min	58

Reaction conditions: after mixing of **1** (1.0 equiv), **2a** (1.1 equiv), CuI (10 mol%), 2,2′-biimidazole (20 mol%), and base (3.0 equiv), the mixture was microwaved in microwave-resistant vials for 20 min, then **3a** (1.1 equiv) was added and the mixture was again treated with microwaves for 20 min

[a] Isolated yields

3H), 7.65–7.70 (m, 2H), 8.04–8.06 (m, 1H), 8.21–8.25 (m, 2H), 9.37 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 55.2, 114.2, 124.6, 125.1, 126.9, 127.2, 128.0, 128.4, 131.0, 131.5, 132.5, 134.6, 145.4, 147.0, 150.8, 152.7, 159.2. ESI–MS: $[M + 1]^+$ *m/z* 357.1.

*4-(4-(4-Methoxyphenyl)isoquinolin-3-yl)benzonitrile (**4h**)*

White solid, mp 136–138 °C, yield 33 %; ^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H), 7.02 (d, $J = 7.2$ Hz, 2H), 7.36–7.39 (m, 2H), 7.58–7.61 (m, 3H), 7.65–7.70 (m, 3H), 7.78–7.80 (m, 1H), 8.06–8.09 (m, 1H), 9.38 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 55.4, 111.5, 114.2, 117.6, 126.3, 126.9, 127.3, 128.2, 128.3, 128.6, 128.7, 129.2, 130.7, 131.2, 140.6, 146.2, 150.8, 151.9, 159.2. ESI–MS: $[M + 1]^+$ *m/z* 337.2.

*4-(4-(4-Nitrophenyl)isoquinolin-3-yl)benzonitrile (**4i**)*

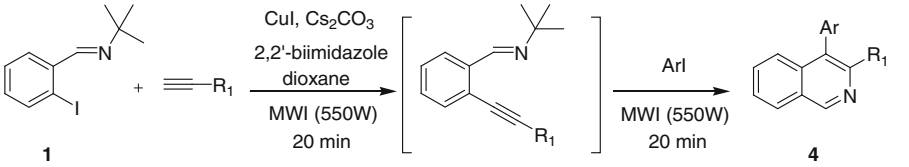
Yellow white solid, mp 152–153 °C, yield 36 %; ^{1}H NMR ($CDCl_3$) δ: 7.38–7.44 (m, 2H), 7.53–7.56 (m, 1H), 7.62–7.70 (m, 5H), 7.78–7.81 (m, 1H), 8.09–8.11 (m, 1H), 8.22–8.26 (m, 2H), 9.43 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 111.5, 117.7, 125.7, 126.4, 127.1, 127.4, 128.3, 128.6, 128.9, 129.0, 129.4, 131.5, 132.2, 141.8, 147.1, 152.6, 154.8, 159.3. ESI–MS: $[M + 1]^+$ *m/z* 352.1.

Results and discussion

N-tert-butyl-*o*-iodobenzaldimine (**1**), phenylacetylene (**2a**), and iodobenzene (**3a**) were used as the starting materials to develop a procedure for one-pot, microwave-assisted synthesis of isoquinoline **4a**. Initially, one-pot, three-component reactions in the presence of CuI–2,2′-biimidazole (L) and Cs_2CO_3 in dioxane under different reaction conditions with MWI were investigated; LC–MS analysis revealed the desired products were obtained in low yields (<5 %). After more tests, we found that better yields could be achieved by stepwise MWI. Thus, the one-pot, two-step procedure for synthesis of isoquinolines was developed. A study of the effect of different solvents (toluene, DMF, dioxane, and THF) on the reactions was performed and dioxane seemed to be the best solvent for the processes (Table 1, entries 1–4). Comparison of the efficiency of different bases in the reaction revealed Cs_2CO_3 was more effective than K_2CO_3 (Table 1, entries 3 and 5). Different levels of irradiation were also investigated. It was observed that microwave power at 550 W gave better results (Table 1, entries 3, 6 and 7). A brief study of several copper compounds as catalyst was conducted. CuI furnished acceptable results, whereas $Cu(OAc)_2$ and CuCl performed poorly in the reactions (Table 1, entries 3, 8, and 9). In an effort to determine the optimum amount of CuI (L) we found that 10 (20) mol% was the best choice. When the amount of CuI (L) was decreased to 5 (10) mol%, the yield was dramatically reduced. It should be noted that no significant effect on reactivity was observed when the amount of CuI (L) was raised from 10 (20) to 20 (40) mol% whereas product yield improved slightly from 56 to 58 % (Table 1, entries 3, 10, and 11).

Encouraged by these results, we started to investigate the scope of this one-pot synthesis under the optimized conditions (CuI (10 mol%), 2,2′-biimidazole

Table 2 Copper-catalyzed one-pot synthesis of isoquinolines **4** under microwave irradiation



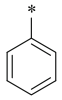
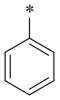
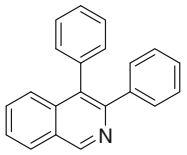
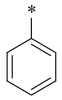
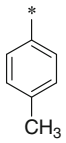
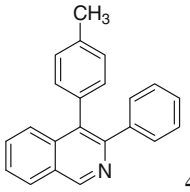
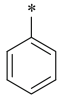
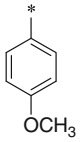
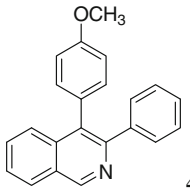
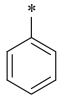
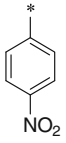
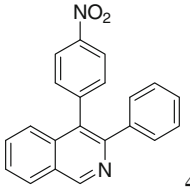
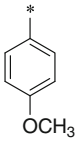
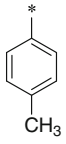
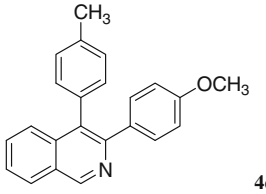
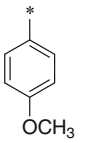
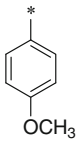
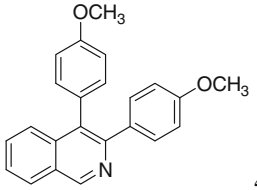
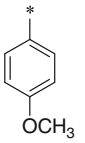
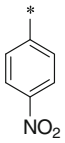
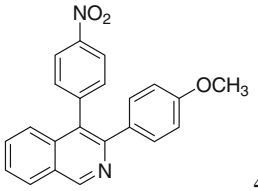
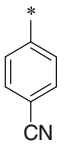
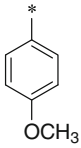
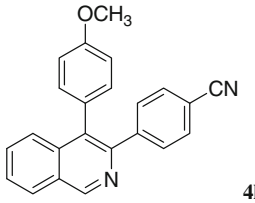
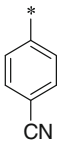
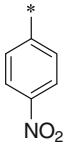
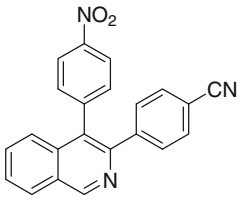
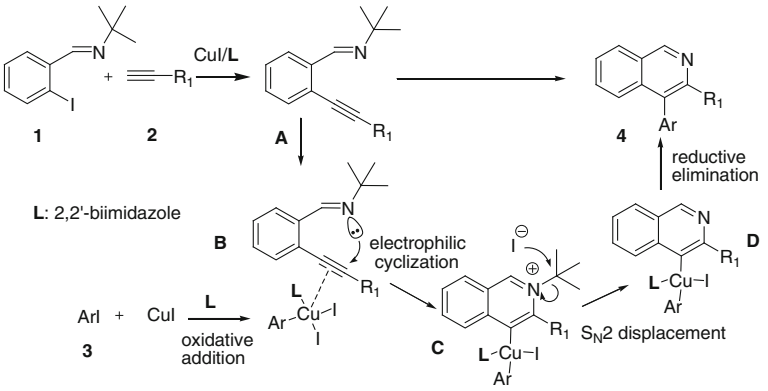
Entry	R_1	Ar	Product	Yield (%)[a]
1			 **4a**	56
2			 **4b**	51
3			 **4c**	57
4			 **4d**	63
5			 **4e**	65

Table 2 continued

Entry	R_1	Ar	Product	Yield (%)[a]
6			 **4f**	62
7			 **4g**	71
8			 **4h**	33
9			 **4i**	36

[a] Isolated yields after column chromatography

(20 mol%), Cs_2CO_3 (3.0 equiv), dioxane, MWI 550 W, 20 min). The 3,4-diaryl isoquinolines were characterized by electrospray LC–MS, and ^{1}H NMR and ^{13}C NMR spectroscopy. The results are summarized in Table 2. These results show that yields of the isoquinolines depended on the nature of substituents on the aryl acetylenes. When aryl acetylenes bearing electron-donating groups were used, the corresponding isoquinoline derivatives were obtained in moderate to good yields (Table 2, entries 5, 6, and 7). When the strongly electron-withdrawing cyano group was present on the aryl acetylene, yields decreased drastically, and isoquinolines **4h** and **4i** were isolated in 33 and 36 % yields, respectively (Table 2, entries 8 and 9). When different aryl iodides were used, no significant electronic effect was observed. When the reaction was conducted using aryl iodides with electron-withdrawing



Scheme 1 A proposed mechanism for the copper-catalyzed synthesis of 3,4-diaryl isoquinolines

groups, good results were obtained (Table 2, entries 4 and 7). Surprisingly, aryl iodides bearing electron-donating groups were well tolerated and afforded the desired isoquinolines in satisfactory yields (Table 2, entries 2, 3, 5, and 6). These results can be rationalized as a consequence of the high nucleophilicity of the *tert*-butylimine moiety.

Mechanistically, we believe that the overall process involves two steps (Scheme 1). First, CuI/2,2′-biimidazole can catalyze the coupling of *N*-*tert*-butyl-*o*-iodobenzaldimine (**1**) with aryl alkynes (**2**) to form *N*-*tert*-butyl-*o*-(1-alkynyl)benzaldimine (**A**). Oxidative addition of aryl iodide (**3**) to CuI with 2,2′-biimidazole affords an electrophilic species, which activates the alkyne triple bond of (**A**) by coordination to form a π-copper complex (**B**), which subsequently undergoes electrophilic cyclization leading to (**C**), *tert*-butyl group removal via S_N2 displacement leading to (**D**), and reductive elimination affording the corresponding 3,4-diaryl isoquinoline (**4**).

Conclusions

In summary, we have developed an experimentally simple procedure for synthesis of 3,4-diaryl isoquinolines. The most important aspect of the method was use of a copper-catalyzed system. Although product yields were sometimes restricted if the aryl acetylenes bore electron-withdrawing groups, the inexpensive CuI, the convenient availability of the ligand, and experimental ease are still attractive for isoquinoline preparation in many cases.

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References

1. R.S. Gupta, V.P. Dixit, M.P. Dobhal, Fitoterapia **61**, 67 (1990)

2. M. Zheng, Y. Yang, M. Zhao, X. Zhang, J. Wu, G. Chen, L. Peng, Y. Wang, S. Peng, Eur. J. Med. Chem. **46**, 1672 (2011)
3. J.F. Miller, K.S. Gudmundsson, L.D. Richardson, S. Jenkinson, A. Spaltenstein, M. Thomson, P. Wheelan, Bioorg. Med. Chem. Lett. **20**, 3026 (2010)
4. M. He, D. Yuan, W. Lin, R. Pang, X. Yu, M. Yang, Bioorg. Med. Chem. Lett. **15**, 3978 (2005)
5. X. Zhang, W. Ye, S. Zhao, C.T. Che, Phytochemistry **65**, 929 (2004)
6. D.S. Bae, Y.H. Kim, C.H. Pan, C.W. Nho, J. Samdan, J. Yansan, J.K. Lee, BMB. Rep. **45**, 108 (2012)
7. F. Yang, J. Zhang, Y. Wu, Tetrahedron **67**, 2969 (2011)
8. K.R. Roesch, H.M. Zhang, R.C. Larock, J. Org. Chem. **66**, 8042 (2001)
9. T. Konno, J. Chae, T. Miyabe, T. Ishihara, J. Org. Chem. **70**, 10172 (2005)
10. G. Dai, R.C. Larock, Org. Lett. **3**, 4035 (2001)
11. R.P. Korivi, C.H. Cheng, Org. Lett. **7**, 5179 (2005)
12. C.C. Liu, R.P. Korivi, C.H. Cheng, Chem. Eur. J. **14**, 9503 (2008)
13. X. Yu, J. Wu, J. Comb. Chem. **11**, 895 (2009)
14. C.O. Kappe, Chem. Soc. Rev. **37**, 1127 (2008)
15. V. Polshettiwar, R.S. Varma, Chem. Soc. Rev. **37**, 1546 (2008)
16. D. Dallinger, C.O. Kappe, Chem. Rev. **107**, 2563 (2007)
17. Z. Hu, S.D. Li, P.Z. Hong, Arkivoc **2010**, 171 (2010)
18. Z. Hu, W. Ye, H. Zou, Y. Yu, Synth. Commun. **40**, 222 (2010)
19. Z. Hu, S.D. Li, P.Z. Hong, Z. Wu, Arkivoc **2011**, 147 (2011)