Facile synthesis of 4,4'-bis-sydnones

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Abstract
An efficient method is developed for direct dehydrogenative C–C coupling of 3-arylsydnones in the presence of palladium(II) acetate catalyst under oxygen. The reaction proceeds efficiently and leads to the formation of bis-sydnones in high yields

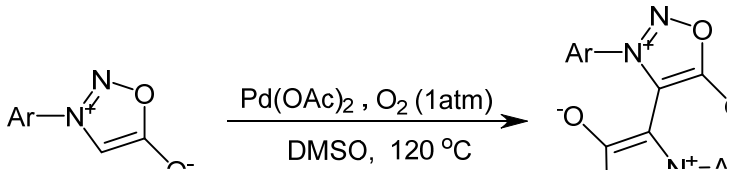
Keywords: 3-Arylsydnones, palladium(II) acetate, C–H bond activation, 4,4'-bis-sydnones

Introduction

Sydnones, unique, dipolar, and five-membered heterocycles, [1] are of interest because of their diverse biological activities, such as antimicrobial,[2] anti-inflammatory,[3] antitumor,[4] antimalarial,[5] analgesic, and antipyretic.[6] These compounds are also known for their potential applications in therapeutic agents,[7-8] liquid crystals,[9-10] and electrolytic solvents.[11] Previous research on the synthesis of bis-sydnone focused on the use of 4-halosydnone or mercuric chloride derivatives of sydnone as starting materials,[12-13] which often need to be synthesized. These methods leads generally to low yields. Specifically, the multi-step synthesis of bis-(3-phenylsydnone) which involved the use of butyllithium to form unstable lithiosydnone species and the addition of copper (I) bromide or copper (II) chloride under harsh condition (−78 °C) resulted in low yield (25%) products.[14] Recently, a series of new synthetic methods for the direct functionalization of 3-arylsydnones have been developed.[15-17] However, there is still no literature reporting the preparation of bis-sydnones. Therefore, it is desirable to develop a convenient and practical synthetic route for the synthesis of them.

C–H bond activation catalyzed by transition metals and C–C bond formation, which features high atom economy and bond formation efficiency, have attracted much attention in recent years.[18-21] Direct cross-dehydrogenative coupling of C–H bonds, which avoids pre-functionalization of the substrates has been successfully used to construct organic molecules.[22-23]

In this paper, we report a novel method for the synthesis of bis-sydnones (**2**) via direct cross-dehydrogenative coupling of 3-arylsydnones (**1**) in the presence of Pd (II) catalyst under oxygen (Scheme 1).

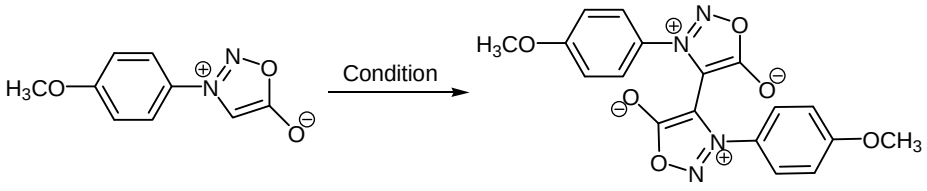


Scheme 1. Synthesis of bis-sydnones (**2**).

Results and Discussion

To establish the optimal reaction conditions, we selected 3-(4-methoxyphenyl)sydnone (**1a**) as the model substrate. A mixture of **1a** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), and $Cu(OAc)_2$ (0.6 mmol) was mixed with 2 mL of DMSO in a sealed tube and stirred in an oil bath at 120 °C. After 16 h, product **2a** was obtained in 93% yield (Table 1, entry 1). The effects of different catalysts and oxidants in different solvents at various reaction temperatures on the formation of **2a** were investigated. Table 1 shows that using toluene, 1,2-dichloroethane (DCE), 1,4-dioxane, *N*,*N*-dimethylformamide (DMF), and acetonitrile as solvents, instead of DMSO, the yield of **2a** (Table 1, entries 2–6) was decreased. Thus, DMSO was determined to be the best solvent. Oxidant screening showed that an improved chemical yield could be obtained by using O_2 (1 atm) as the oxidant, whereas other oxidants, such as $K_2S_2O_8$, Ag_2CO_3, AgOAc, and benzoquinone were less effective (Table 1, entries 8–12). When no oxidant was used in the reaction, the yield decreased to 63% (Table 1, entry 7). Therefore, O_2 (1 atm) was chosen as the ideal oxidant. The effect of various dosage of $Pd(OAc)_2$ was further investigated. When the dosage of $Pd(OAc)_2$ was reduced to 0.05 and 0.02 eq., the yield was decreased (Table 1, entries 13–14). Different reaction temperatures were also examined. When the reaction temperature was decreased, the yield dropped dramatically (Table 1, entries 15–17). The effects of different catalysts on **2a** formation were also evaluated. **2a** was not obtained when no catalyst was used in the reaction or when the catalyst $Pd(OAc)_2$ was changed to CuI and $FeCl_3$ (Table 1, entries 18–21). Considering these findings, we established the optimal reaction conditions as follows: 0.1 eq. $Pd(OAc)_2$ catalyst, DMSO solvent, 120 °C reaction temperature, and 16 h reaction time under O_2 (1 atm) atmosphere (Table 1, entry 12).

Table 1. Screening for optimal reaction conditions[a]



1a **2a**

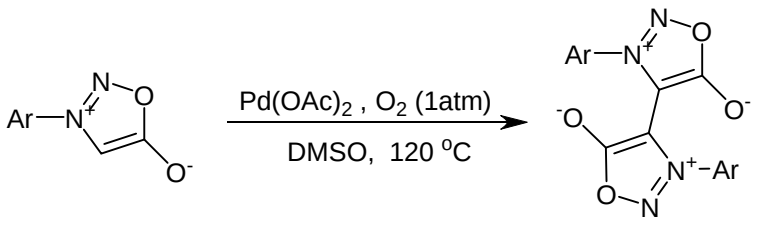
Entry	Catalyst(0.1 eq.)	Oxidant(2 eq.)	Solvent	T (^{o}C)	Yield of **2a** (%)[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$	DMSO	120	93
2	$Pd(OAc)_2$	$Cu(OAc)_2$	toluene	120	33
3	$Pd(OAc)_2$	$Cu(OAc)_2$	DCE	120	26
4	$Pd(OAc)_2$	$Cu(OAc)_2$	1,4-dioxane	120	55
5	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	120	12
6	$Pd(OAc)_2$	$Cu(OAc)_2$	acetonitrile	120	37
7	$Pd(OAc)_2$	none	DMSO	120	63
8	$Pd(OAc)_2$	$K_2S_2O_8$	DMSO	120	74
9	$Pd(OAc)_2$	Ag_2CO_3	DMSO	120	71
10	$Pd(OAc)_2$	AgOAc	DMSO	120	68
11	$Pd(OAc)_2$	Benzoquinone	DMSO	120	26
12	**$Pd(OAc)_2$**	**O_2（1atm）**	**DMSO**	**120**	**95**
13	$Pd(OAc)_2$ (0.05)	O_2 (1atm)	DMSO	120	52
14	$Pd(OAc)_2$ (0.02)	O_2 (1atm)	DMSO	120	40
15	$Pd(OAc)_2$	O_2 (1atm)	DMSO	90	80
16	$Pd(OAc)_2$	O_2 (1atm)	DMSO	60	61
17	$Pd(OAc)_2$	O_2 (1atm)	DMSO	25	16
18	none	O_2 (1atm)	DMSO	120	0
19	none	none	DMSO	120	0
20	CuI (0.2)	none	DMSO	120	0
21	$FeCl_3$ (0.3)	none	DMSO	120	0

[a] Reaction conditions: 1.0 eq. of **1a** , 0.1 eq. of catalyst, 2 eq. of oxidant in 2mL solvent were stirred for 16h. [b] Isolated yield.

A variety of 3-arylsydnone (**1**) substrates were also investigated under the optimized conditions. Table 2 shows that bis-sydnones (**2**) were efficiently generated with moderate to

good yields. The reaction proceeded efficiently when the aryl group of 3-arylsydnone (**1**) is a phenyl that carries an electron-donating group such as methoxy (**1a**) or methyl (**1b** and **1c**), less so with an electron-withdrawing substituent such as halogen (**1e**–**1h**). The presence of an electron-donating group in the phenyl group of 3-arylsydnone (**1a-c**) increased the reaction yield compared with **1d** (Table 2, entries 1–3). In contrast, the presence of one or two electron-withdrawing substituents in the phenyl group (**1e**–**1h**) generated relatively low yields of product 2 (Table 2, entries 5–8). Furthermore, higher yields were obtained when the substrates contained an electron-donating substituent at the para position than that at the meta position. This finding could be attributed to the ability of the electron-donating group at the para position to exert a stronger electron-donating inductive effect than the group at the meta position (Table 2, entries 2,3). This behavior was contrary to that of substrates (**1**) containing electron-withdrawing groups (Table 2, entries 6,7). We have also tested the reactivity of 3-(4-nitrophenyl)sydnone under the optimal conditions, but the desired product 3,3'-bis(4-nitrophenyl)-4,4'-bis-sydnone (**2i)** was not found (Table 2, entry 9). It appears that the strong electron-withdrawing inductive effect of the nitro group greatly reduced its reactivity.

Table 2. 3-Arylsydnones **1**: scope in dimerization reaction (Scheme 1)[a]

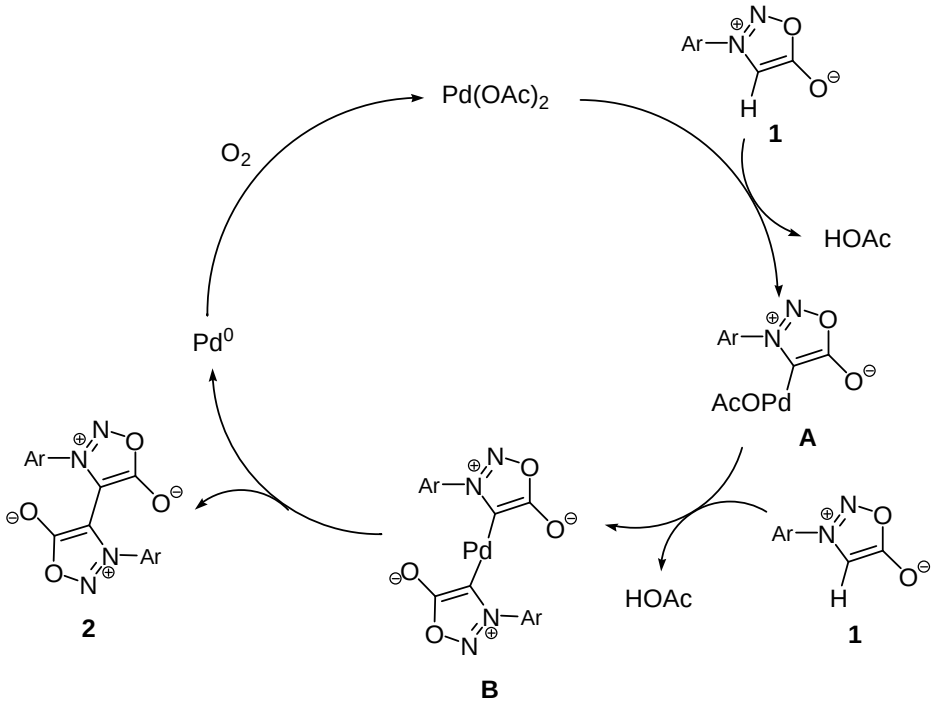


1 **2**

Entry	Sydnone **1** Ar group	Bis-sydnone **2**	Yield[b] of **2**
1	**1a**; 4-$MeOC_6H_4$	**2a**	95
2	**1b**; 4-MeC_6H_4	**2b**	81
3	**1c**; 3-MeC_6H_4	**2c**	75
4	**1d**; Ph	**2d**	66
5	**1e**; 4-FC_6H_4	**2e**	52
6	**1f**; 4-ClC_6H_4	**2f**	30
7	**1g**; 3-ClC_6H_4	**2g**	47
8	**1h**; 3-Cl-4-FC_6H_3	**2h**	33
9	**1i**; 4-$O_2NC_6H_4$	**2i**	0

[a] Reaction conditions: 1.0 eq. of **1** and 0.1 eq. of $Pd(OAc)_2$ in 2mL DMSO were stirred at 120°C for 16h under O_2(1atm) atmosphere. [b] Isolated yield.

A plausible reaction mechanism for the synthesis of bis-sydnones (**2**) is shown in Scheme 2. The initial electronic attack of Pd (II) on 3-arylsydnone (**1**) and the subsequent deprotonation form species **A**.[24-25] The resulting species **A** reacted with another 3-arylsydnone molecule to generate the corresponding intermediate **B**.[26] The intermediate was then subjected to reductive elimination to synthesize the product **2** and generate Pd^0. Finally, Pd(II) was regenerated through the oxidation of Pd^0.



Scheme 2. Possible mechanism for the formation of **2.**

Conclusions

In summary, we synthesized bis-sydnones in moderate to high yields through direct cross-dehydrogenative coupling of 3-arylsydnones catalyzed by Pd under oxygen. It was convenient, efficient, and environment friendly and considered an atom- and step-economical process.

Experimental Section

General. All commercially available reagents and solvent were obtained from the commercial providers and used without further purification. Melting points were recorded using a WRS-2A melting point apparatus. IR spectra were obtained on a Nexus FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Varian 400 MHz spectrometer. Chemical

shifts were reported relative to internal tetramethylsilane (0.00 ppm) for ^{1}H and $CDCl_3$ (77.0 ppm) for ^{13}C. High-resolution mass spectra were obtained on a Finnigan-NAT GC/MS/DS 8430 spectrometer. 3-Arylsydnones **1** were prepared according to literature procedures.[27-29]

General procedure for the synthesis of 2. A mixture of 3-arylsydnone (0.3 mmol) and $Pd(OAc)_2$ (0.03 mmol) in dimethyl sulfoxide (DMSO, 2 mL) was placed in a tube. The tube was equipped with a balloon filled with O_2 (1 atm). The mixture was stirred in an oil bath at 120 °C for 16 h. After the reaction was completed (as monitored by TLC), the mixture was cooled to room temperature. The reaction mixture was then added with 30 mL of water and extracted with EtOAc three times (20 mL of each extraction). The combined organic layers were washed with saturated brine, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified through flash column chromatography (petroleum ether/ethyl acetate = 2:1, v/v) to yield bis-sydnones (**2**).

3,3'-Bis(4-methoxyphenyl)-4,4'-bis-sydnone (**2a**). Yellow solid; yield 95%; mp 194.4-195.1°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H), 3.86 (s, 3H), 7.00 (dd, *J* 9.2, 2.0 Hz, 4H), 7.41(dd, *J* 9.2, 2.4 Hz, 4H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 55.8 (2C), 93.2 (2C), 115.3 (4C), 125.2 (4C), 126.1 (2C), 126.7 (2C), 166.6 (2C). IR (KBr): 3077, 2926, 2857, 1757, 1598, 1506, 1447, 1405, 1254, 1175, 832 cm^{-1}.HR-MS(ESI): *m/z* calcd for $C_{18}H_{14}N_4NaO_6$: 405.0805 $[M+Na]^+$; found: 405.0801.

3,3'-Di-*p*-tolyl-4,4'-bis-sydnone (**2b**). Tan solid; yield 81%; mp 189.9-190.6°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 2.44 (s, 3H), 7.33 (d, *J* 9.2 Hz, 4H), 7.41 (d, *J* 8.4 Hz, 4H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 21.5 (2C), 93.2 (2C), 123.5 (4C), 130.8 (4C), 131.2 (2C), 143.8 (2C), 166.4 (2C). IR (KBr): 3070, 2925, 2860, 1751, 1606, 1503, 1434, 1282, 1183, 818 cm^{-1}. HR-MS(ESI): *m/z* calcd for $C_{18}H_{14}N_4NaO_4$: 373.0907 $[M+Na]^+$; found: 373.0902.

3,3'-Di-*m*-tolyl-4,4'-bis-sydnone (**2c**). Tan solid; yield 75%; mp 172.0-172.9°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 6H), 7.22 (d, *J* 7.2 Hz, 2H), 7.25 (s, 2H), 7.38-7.48 (m, 4H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 21.3 (2C), 93.1 (2C), 120.7 (2C), 124.3 (2C), 130.0 (2C), 133.6 (2C), 133.6 (2C),141.0 (2C), 166.3 (2C). IR (KBr): 3069, 2925, 2860, 1749, 1622, 1466, 1388, 1292, 1183, 791 cm^{-1}. HR-MS(ESI): *m/z* calcd for $C_{18}H_{14}N_4NaO_4$: 373.0907 $[M+Na]^+$; found: 373.0903.

3,3'-Diphenyl-4,4'-bis-sydnone (**2d**). Tan solid; yield 66%; mp 181.4-182.5°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* 8.0 Hz, 4H), 7.57 (t, *J* 7.8 Hz, 4H), 7.67 (d, *J* 7.4 Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 93.2 (2C), 123.8 (4C), 130.3 (4C), 132.9 (2C), 133.6 (2C), 166.3 (2C). IR (KBr): 3099, 1750, 1645, 1481, 1412, 1276, 1089, 721 cm^{-1}. HR-MS(ESI): *m/z* calcd for $C_{16}H_{10}N_4NaO_4$: 345.0594 $[M+Na]^+$; found: 345.0590.

3,3'-Bis-(4-fluorophenyl)-4,4'-bis-sydnone (**2e**). Tan solid; yield 52%; mp 207.7-208.9°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.32 (m, 4H), 7.52-7.60 (m, 4H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 93.3 (2C), 117.7 (d, *J* 23.6 Hz, 4C), 126.3 (d, *J* 9.4 Hz, 4C), 129.6 (2C), 164.8 (d, *J* 249.2 Hz, 2C), 166.1 (2C). IR (KBr): 3086, 1768, 1598, 1504, 1408, 1234, 1096, 842 cm^{-1}. HR-MS(ESI): *m/z* calcd for $C_{16}H_8F_2N_4NaO_4$: 381.0406 $[M+Na]^+$; found: 381.0403.

3,3'-Bis-(4-chlorophenyl)-4,4'-bis-sydnone (**2f**). Tan solid; yield 30%; mp 213.8-214.4°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (d, *J* 8.8 Hz, 4H), 7.56 (d, *J* 8.4 Hz, 4H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 93.1 (2C), 125.2 (4C), 130.7 (4C), 131.9 (2C), 139.7 (2C), 166.0 (2C). IR (KBr): 3062, 1757, 1646, 1465, 1278, 1085, 757 cm^{-1}. HR-MS(ESI): *m/z* calcd for $C_{16}H_8{}^{35}Cl_2N_4NaO_4$: 412.9815 $[M+Na]^+$; found: 412.9810

3,3'-Bis-(3-chlorophenyl)-4,4'-bis-sydnone (**2g**). Light yellow solid; yield 47%; mp 105.6-106.9°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.52(m, 4H), 7.55 (t, *J* 8.2 Hz, 2H), 7.67 (d, *J* 8.0 Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 90.7 (2C), 105.0 (2C), 122.1 (2C), 124.2 (2C), 131.5 (2C), 133.3 (2C), 136.4 (2C), 162.0 (2C). IR (KBr): 3080, 1799, 1589, 1461, 1295, 1085, 785 725 cm^{-1}. HR-MS(ESI): *m/z* calcd for $C_{16}H_8{}^{35}Cl_2N_4NaO_4$: 412.9815 $[M+Na]^+$; found: 412.9811

3,3'-Bis-(3-chloro-4-fluorophenyl)-4,4'-bis-sydnone (**2h**). Yellow solid; yield 33%; mp 119.8-120.7°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (t, *J* 8.2 Hz, 2H), 7.53-7.61 (m, 2H), 7.65-7.72 (m, 2H). ^{13}C NMR (100MHz, $CDCl_3$): δ = 93.3 (2C), 118.6 (d, *J* 23.2 Hz, 2C),124.0 (2C), 124.2 (d, *J* 8.4 Hz, 2C), 126.8 (2C), 129.7 (d, *J* 3.1 Hz, 2C), 160.7 (d, *J* 257.4 Hz, 2C), 165.7 (2C). IR (KBr): 3090, 1800, 1639, 1496, 1265, 1074, 712 cm^{-1}. HR-MS(ESI): *m/z* calcd for $C_{16}H_6{}^{35}Cl_2{}^{19}F_2N_4NaO_4$: 448.9626 $[M+Na]^+$; found: 448.9622

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References

1. Browne, D. L.; Harrity J. P. A. *Tetrahedron* **2010**, *66*, 553. http://dx.doi.org/10.1016/j.tet.2009.10.085
2. Kavali, J. R.; Badami, B. V. *Farmaco* **2000**, *55*, 406. http://dx.doi.org/10.1016/S0014-827X(00)00061-6
3. Hill, J. B.; Ray, R. E.; Wagner, H.; Aspinall, R. L. *J. Med. Chem.* **1975**, *18*, 50. http://dx.doi.org/10.1021/jm00235a011
4. Kier, L. B.; Roche, E. B. *J. Pharm. Sci.* **1967**, *56*, 149. http://dx.doi.org/10.1002/jps.2600560202
5. McCaustland, D. J.; Burton, W. H.; Cheng, C. C. *J. Heterocycl. Chem.* **1971**, *8*, 89. http://dx.doi.org/10.1002/jhet.5570080117
6. Satyanarayana, K.; Rao, M. N. A. *J. Pharm. Sci.* **1995**, *84*, 263. http://dx.doi.org/10.1002/jps.2600840228

7. Dunkley, C. S.; Thomas, C. J. Bioorg. *Med. Chem. Lett*. **2003**, *13*, 2899. http://dx.doi.org/10.1016/S0960-894X(03)00487-6
8. Moustafa, M. A.; Gineinah, M. M.; Nasr, M. N.; Bayoumi, W. A. H. *Arch. Pharm*. (Weinheim) **2004**, *337*, 164. http://dx.doi.org/10.1002/ardp.200300814
9. Geoffroy, I.; Carre, B.; Lemordant, D. *ITE Lett. Batter., New Technol. Med.* **2000**, *1*, 20.
10. Chan, W. L.; Zhang, W. H.; Szeto, Y. S. *Mater. Lett.* **2000**, *42*, 280. http://dx.doi.org/10.1016/S0167-577X(99)00196-2
11. Sasaki, Y.; Hirobomi, O.; Handa, M. *Nippon Kagaku Kaishi* **1993**, 1217. http://dx.doi.org/10.1246/nikkashi.1993.1217
12. Tien, H. J.; Yeh, M. Y. *J. Chin. Chem. Soc.* **1977**, 24, 123. http://dx.doi.org/10.1002/jccs.197700020
13. Tien, H. J.; Lee, Y. K. *J. Chin. Chem. Soc* **1988**, 35, 63. http://dx.doi.org/10.1002/jccs.198800010
14. Kalinin, V. N.; Min, S. F. *J. Organomet. Chem*. **1988**, *352*, C34. http://dx.doi.org/10.1016/0022-328X(88)83049-3
15. Wu, C.; Li, P.; Fang, Y.; Zhao, J.; Xue, W.; Li, Y.;Larock, R. C.; Shi, F. *Tetrahedron Lett.* **2011**, 52, 3797. http://dx.doi.org/10.1016/j.tetlet.2011.05.058
16. Brown, A. W.; Harrity, J. P. A. *J. Org. Chem.* **2015**, 80, 2467. http://dx.doi.org/10.1021/acs.joc.5b00143
17. Yang, Y.; Kuang, C. *Eur. J. Org. Chem.* **2014**, 7810. http://dx.doi.org/10.1002/ejoc.201403211
18. Chen, X.; Engle, K. M.; Wang, D.; Yu, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. http://dx.doi.org/10.1002/anie.200806273
19. Sun, C.; Li, B.; Shi, Z. *Chem. Commun*. **2010**, *46*, 677. http://dx.doi.org/10.1039/b908581e
20. Fan, M.; Ma, D. *Angew. Chem. Int. Ed*. **2013**, *52*, 12152. http://dx.doi.org/10.1002/anie.201306583
21. Baumann, C. G.; Ornellas, S. D.; Reeds, J. P.; Storr, T. E.; Williams, T. J.; Fairlamb, I. J. S. *Tetrahedron* **2014**, *70*, 6174. http://dx.doi.org/10.1016/j.tet.2014.06.002
22. Li, C. *Acc. Chem. Res*. **2008**, *42*, 335. http://dx.doi.org/10.1021/ar800164n
23. Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. *Angew. Chem. Int. Ed*. **2011**, *50*, 1.
24. Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc*. **2008**, *130*, 3708. http://dx.doi.org/10.1021/ja710221c
25. Lu, Z.; Luo, F.; Wang, L.; Zhu, G. *J. Org. Chem*. **2013**, *78*, 10894. http://dx.doi.org/10.1021/jo4018793

26. Liang, P.; Xiong, H.; Guo, H.; Yin, G. *Catal. Commun*. **2010**, *11*, 560. http://dx.doi.org/10.1016/j.catcom.2009.12.019
27. Rai, N. S.; Kalluraya, B.; Lingappa, B.; Shenoy, S.; Puranic, V. G. *Eur. J. Med. Chem*. **2008**, *43*, 1715. http://dx.doi.org/10.1016/j.ejmech.2007.08.002
28. Asundaria, S. T.; Patel, N. S.; Patel, K. C. *Org. Commun*. **2010**, *3*, 30.
29. Fang, Y.; Wu, C.; Larock, R. C.; Shi, F. *J. Org. Chem*. **2011**, *76*, 8840. http://dx.doi.org/10.1021/jo201605v

