Organic LETTERS

Letter

pubs.acs.org/OrgLett

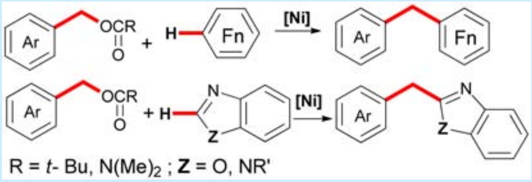
Nickel-Catalyzed Direct C−H/C−O Cross Couplings Generating Fluorobenzenes and Heteroarenes

Jing Xiao, Tieqiao Chen,* and Li-Biao Han*

State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

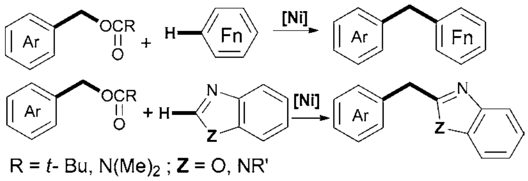
Ⓢ *Supporting Information*

ABSTRACT: The Ni-catalyzed direct C−H/C−O cross couplings of benzylic alcohol derivatives with fluorobenzenes and heteroarenes are disclosed. This transformation provides a straightforward and efficient method for the synthesis of these valuable heteroatom-containing compounds.



Because of the unique properties of fluoroaryl and heteroaryl compounds in pharmaceutical and material science,[1] the development of an efficient method for their preparation has attracted much attention. Inspired by Itami's and related works on transition metal-catalyzed C−H/C−O cross couplings for the construction of C−C bonds,[2,3] we envision that if these reactions can take place successfully with the commercially available fluorobenzenes and heteroarenes, access to these valuable heteroatom-containing aryl compounds would be more practical than the classical procedures.[4−6] Herein, we report a Ni-catalyzed C−H/C−O cross coupling of benzylic alcohol derivatives with polyfluoroarenes and heteroarenes, leading to the generation of a variety of heteroatom-containing diarylmethanes from the readily available alcohol derivatives and the hydrocarbons in good to excellent yields (Scheme 1).

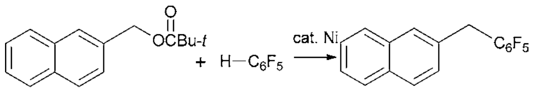
Scheme 1. Generation of Fluorobenzenes and Heteroarenes via Ni-Catalyzed Direct C−H/C−O Cross Couplings



These compounds are important in pharmaceutical chemistry and organic synthesis.[7] They are also frequently found as key subunits in supramolecules.[8] Although Friedel−Crafts alkylation of arenes is a well-established method for the preparation of diarylmethanes, it only works well with electron-rich arenes and the control of the regioselectivity is also difficult.[5] Recently, transition metal-catalyzed cross coupling is emerging as a powerful approach to prepare these compounds;[6] however, these transformations usually require the use of organometallic reagents,[9] and(or) organohalides[10] and organoborides.[11]

We began this work by examining the reactivity of 2-naphthylmethyl pivalate **1a** with pentafluorobenzene **2a**, and the results obtained are compiled in Table 1. After an extensive screening, we found that under a mild condition the

Table 1. Ni-Catalyzed Cross Coupling of 2-Naphthylmethyl Pivalate with Pentafluorobenzene[a]



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

entry	ligand	base (equiv)	temp (°C)	solvent	yield[b] (%)
1	Et_3P	*t*-BuONa (2.0)	80 °C	toluene	28%
2	PCy_3	*t*-BuONa (2.0)	80 °C	toluene	50%
3	Ph_3P	*t*-BuONa (2.0)	80 °C	toluene	58%
4	dppe	*t*-BuONa (2.0)	80 °C	toluene	23%
5	dppp	*t*-BuONa (2.0)	80 °C	toluene	54%
6	dppb	*t*-BuONa (2.0)	80 °C	toluene	90%
7	dpph	*t*-BuONa (2.0)	80 °C	toluene	79%
8	dppf	*t*-BuONa (2.0)	80 °C	toluene	75%
9	dppb	*t*-BuONa (1.5)	80 °C	toluene	91%
10	dppb	*t*-BuONa (1.0)	80 °C	toluene	82%
11	**dppb**	***t*-BuONa (1.5)**	**60 °C**	**toluene**	**99%**
12	dppb	*t*-BuONa (1.5)	40 °C	toluene	48%
13	dppb	*t*-BuONa (1.5)	60 °C	hexane	45%
14	dppb	*t*-BuONa (1.5)	60 °C	THF	8%
15	dppb	*t*-BuONa (1.5)	60 °C	dioxane	22%
16	dppb	*t*-BuONa (1.5)	60 °C	DMF	trace
17	dppb	K_3PO_4 (1.5)	60 °C	toluene	trace
18	dppb	Cs_2CO_3 (1.5)	60 °C	toluene	trace

[a] Conditions: a mixture of **1a** (0.1 mmol), **2a** (0.12 mmol), $Ni(COD)_2$ (0.01 mmol), a phosphine ligand (P/Ni = 2:1), and a base in the solvent (1.5 mL) was stirred at the temperature indicated for 18 h. [b] GC yield using tridecane as an internal standard.

Received: December 15, 2014
Published: February 10, 2015

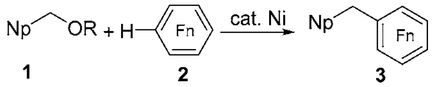
ACS Publications © 2015 American Chemical Society

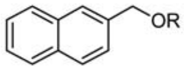
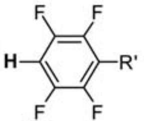
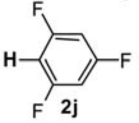
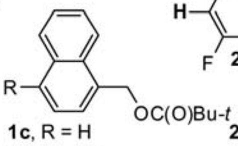
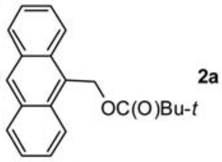
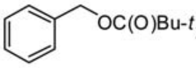
Ni(COD)$_2$/phosphine ligand, in the presence of a base, could mediate the coupling of **2a** with **1a** via C−H/C−O cross coupling affording **3a**. As to the phosphine investigated, dppb (Ph$_2$P(CH$_2$)$_4$PPh$_2$) gave the highest yield of the product, followed by a decreasing order in catalytic activity of dpph (79% yield, Ph$_2$P(CH$_2$)$_6$PPh$_2$), dppf (75% yield), Ph$_3$P (58% yield), dppp (54% yield), PCy$_3$ (50% yield), Et$_3$P (28% yield), and dppe (23% yield) (entries 1−8). Thus, catalyzed by Ni(COD)$_2$/dppb (10 mol %), the cross coupling of **1a** with **2a** took place readily at 80 °C in toluene in the presence of 2.0 equiv of *t*-BuONa, producing the corresponding product **3a** in 90% GC yield (entry 6). Further optimization of the conditions revealed that a nearly quantitative yield of **3a** was generated when the reaction was conducted at 60 °C with 1.5 equiv of *t*-BuONa (entry 11). However, upon further lowering the reaction temperature to 40 °C, only 48% yield of **3a** was produced (entry 12). This C−H/C−O coupling could also proceed in hexane, but poorly takes place in THF, dioxane, and DMF (entries 13−16). As to the base, K$_3$PO$_4$ and Cs$_2$CO$_3$ only produced a trace amount of the coupling product under similar conditions (entries 17 and 18).

This Ni-catalyzed C−H/C−O coupling reaction could be applied to other substrates to produce the corresponding substituted fluorobenzenes. As shown in Table 2, pivalate **1a** and carbamate **1b** coupled with pentafluorobenzene **2a** to yield the corresponding fluorobenzene **3a** in 95% and 70% yields, respectively (entries 1 and 2). Worth noting is that a variety of fluorobenzenes with either an electron-withdrawing or electron-donating group, all could be coupled readily to the corresponding diarylmethanes efficiently (entries 3−10). Thus, 1,2,4,5-tetrafluorobenzene **2b** served as a good substrate in this reaction to produce **3b** in 73% yield (entry 3). Moderate to high yields of the diarylmethanes were obtained from tetrafluorobenzenes **2** bearing CH$_2$OPiv, OMe, OPiv, and amido groups (entries 5−8). Tetrafluorobenzene **2i** bearing an electron-withdrawing CF$_3$ group also coupled with **1a** smoothly to give the corresponding product **3i** in 92% yield (entry 10). A trifluorobenzene **2j** could also be used as the substrate, albeit the yield of the coupling product **3j** was low (entry 11). 1-Naphthylmethyl pivalates also coupled efficiently with **2a** to generate the corresponding diarylmethanes in high yields (entries 12−15). 9-Anthracenylmethyl pivalate **1g** produced 20% yield of **3o** under similar conditions (entry 16). However, only a trace of product was detected when **1h** was used as substrate (entry 17). It should be noted that 1,2-di(naphthalen-2-yl)ethane and reduced benzylic pivalates were detected as byproduct in the catalytic system by GC and GC−MS.

As demonstrated in Scheme 2, this Ni-catalyzed C−H/C−O cross coupling has the potential for the preparation of high molecule-weight compounds containing fluorobenzene units, which are of-interest functional materials. Thus, under standard conditions, compound **3b**, synthesized by the coupling of **1a** with **2b** (entry 3, Table 2), could further couple with pivalate **1a** to produce a linear dibenzylated product **3q** in 75% yield. However, two fluorobenzenes were successfully introduced in one pot by the cross coupling of **1i** with **2b** to give a linear fluoroarylated product **3r** in 57% yield. Similarly, further coupling reaction of **3r** with benzylic alcohol derivatives would produce higher molecule weight fluorobenzene-containing linear products via the Ni-catalyzed C−H/C−O cross coupling. These materials have potential applications as liquid crystal materials.[12]

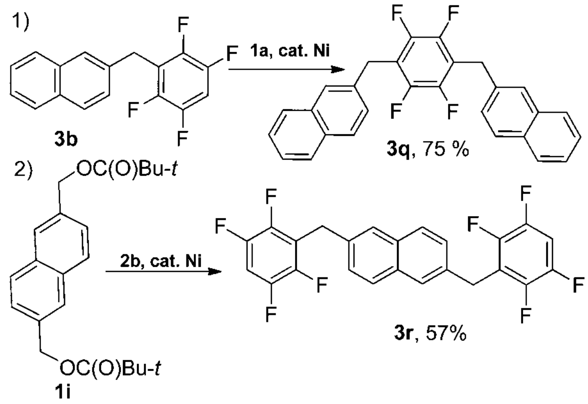
Table 2. Ni-Catalyzed Cross Coupling of Benzylic Alcohol Derivatives with Fluorobenzenes[a]



entry	substrate 1	substrate 2	product 3	yield[b]
				
1	**1b**, R = CONMe$_2$	**2a**, R' = F	**3a**	70%
2	**1a**, R = COBu-*t*	**2a**, R' = F	**3a**	95%
3[c]		**2b**, R' = H	**3b**	73%
4[c]		**2c**, R' = Me	**3c**	58%
5[d,e]		**2d**, R' = CH$_2$OPiv	**3d**	62%
6[c]		**2e**, R' = OMe	**3e**	96%
7[e,f]		**2f**, R' = OPiv	**3f**	63%
8[d,f]		**2g**, R' = NHPiv	**3g**	60%
9[c]		**2h**, R' = NMe$_2$	**3h**	37%
10[c,g]		**2i**, R' = CF$_3$	**3i**	92%
11[f,h]		 **2j**	**3j**	19%
				
12	**1c**, R = H	**2a**	**3k**	96%
13[c]	**1d**, R = Me	**2a**	**3l**	89%
14[c,d]	**1e**, R = OMe	**2a**	**3m**	93%
15[c]	**1f**, R = F	**2a**	**3n**	87%
16[h]	**1g** 	**2a**	**3o**	20%
17	**1h** 	**2a**	**3p**	trace

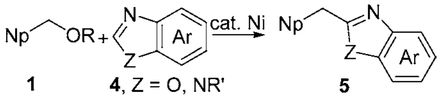
[a] Conditions: **1** (0.1 mmol), **2** (0.12 mmol), Ni(COD)$_2$ (10 mol %), dppb (10 mol %), *t*-BuONa (0.15 mmol), toluene (1.5 mL), 60 °C, 18 h. [b] Isolated yield. [c] 80 °C. [d] Ni(COD)$_2$ (20 mol %), dppb (20 mol %). [e] 100 °C. [f] 120 °C. [g] **2i** (0.15 mmol), *t*-BuONa (0.2 mmol). [h] Ni(COD)$_2$ (20 mol %), PEt$_3$ (40 mol %).

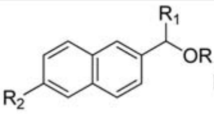
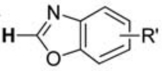
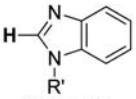
Scheme 2. Synthesis of Linear Molecules via Ni-Catalyzed C−H/C−O Coupling



To our delight, this C−H/C−O coupling method could also be used for the preparation of heteroarenes. As shown in Table 3, we found that by switching the ligand dppb to PEt$_3$, the

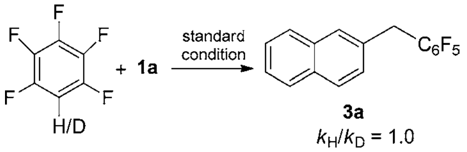
Table 3. Ni-Catalyzed Cross Coupling of Benzylic Alcohol Derivatives with Heteroarenes[a]



entry	substrate 1	substrate 2	product 5	yield[b]
				
1[c]	**1a**	**4a**, R' = H	**5a**	60%
2	**1b**	**4a**, R' = H	**5a**	77%
3	**1a**	**4b**, R' = 5-Me	**5b**	58%
4	**1a**	**4c**, R' = 6-Me	**5c**	66%
5	**1a**	**4d**, R' = 5-*t*-Bu	**5d**	61%
6	**1a**	**4e**, R' = 5-Ph	**5e**	56%
7	**1a**	**4f**, R' = 5-Cl	**5f**	45%
8	**1a**	**4g**, R' = 5-NO_2	**5g**	n.d.
9[d]	R= *i*-PrOC(O) **1j** R_1 = Me R_2 = OMe	**4a**, R' = H	**5h**	31%
10	**1h**	**4a**, R' = H	**5i**	n.d.
				
11[e]	**1a**	**4i**, R' = Me	**5j**	83%
12[e]	**1a**	**4j**, R' = Ph	**5k**	59%

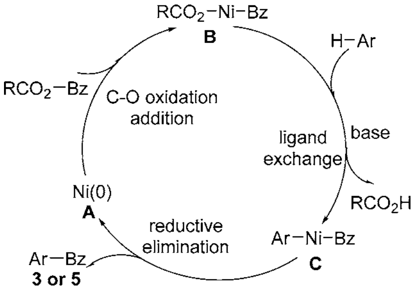
[a]Conditions: **1** (0.1 mmol), **4** (0.12 mmol), Ni(COD)$_2$ (20 mol %), PEt$_3$ (40 mol %), *t*-BuONa (1.5 equiv), toluene (1.5 mL), 120 °C, 18 h. [b]Isolated yields. [c]140 °C. [d]100 °C, 1.5 equiv of KOAc was added. [e]2.0 equiv of K$_3$PO$_4$ was added.

Scheme 3. Kinetic Isotope Effect Experiment



k_H/k_D = 1.0

Scheme 4. Proposed Mechanism; Ligands Are Omitted for Clarity



coupling of heteroarenes with the benzylic alcohol derivatives took place efficiently via a similar Ni-catalyzed C−H/C−O cross coupling, readily yielding the corresponding heteroarenes **5** (Table 3). For example, both pivalate **1a** and carbamate **1b** successfully coupled with benzoxazole **4a** to give the desired diarylmethanes **5a** in 60% and 77% yields, respectively (entries 1 and 2). Other benzoxazole analogues bearing electron-donating groups also coupled with **1a** and were converted to the corresponding diarylmethanes **5** in moderate yields under similar reaction conditions (entries 3−6). Surprisingly, compound **5f** having a chloro atom could also be obtained in 45% yield from the chloro substituted benzoxazole **4f** (entry 7). However, a benzoxazole analogue with a strong electron-withdrawing NO$_2$ group did not give the expected coupling product under similar conditions (entry 8). Notably, secondary carbonate **1j** also coupled with **4a** to give **5h** in 31% yield (entry 9). When **1h** was used, no cross coupling product was detected (entry 10). In addition to these benzoxazoles, the valuable benzoimidazolyl groups were also successfully benzylated to produce the corresponding diarylmethanes **5** in good yields (entries 11 and 12).

To gain insight into the reaction mechanism, kinetic isotope effect (KIE) experiments were performed, and a kinetic isotope effect (k_H/k_D = 1.0) was obtained, indicating that C−H functionalization perhaps is not the rate-determining step in the reaction (Scheme 3).

The mechanism is not fully understood. On the basis of the above experiments and the previous investigations,[3a,b,13] we propose a catalytic cycle as shown in Scheme 4. First, Ni(0) oxidatively adds to the C−O bonds to generate complex **B**, which subsequently undergoes ligand exchange with a C−H bond by the aid of a base to yield **C**. Reductive elimination of **C** produces the corresponding diarylmethanes and regenerates Ni(0) complex **A**.

In summary, we have successfully developed a C−H/C−O cross coupling of benzylic alcohol derivatives with fluorobenzenes and heteroarenes in the presence of a nickel catalyst. This reaction provided a direct and efficient protocol to synthesize a wide range of heteroatom-containing diarylmethanes under mild reaction conditions, which are important molecular skeletons in pharmaceutical and material science.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General procedure, spectra data of products, and copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chentieqiao@hnu.edu.cn.
*E-mail: libiao-han@aist.go.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSFC 21373080 and 21403062 and the Fundamental Research Funds for the Central Universities (Hunan University) for financial support.

■ REFERENCES

(1) (a) Meyer, E. A.; Castellano, R. K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1210. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (e) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem.—Eur. J.* **2011**, *17*, 10113.

(2) For reviews, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299. (b) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19. (c) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.*

2010, *43*, 1486. (d) Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081. (e) Tobisu, M.; Chatani, N. *Top. Organomet. Chem.* **2013**, *44*, 35. (f) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346.

(3) Recent examples of C−H/C−O cross coupling, see: (a) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. (b) Takise, R.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6791. (c) Tabuchi, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014**, *79*, 5401. (d) Matsubara, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2010**, *132*, 6880. (e) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360. (f) Tollefson, E. J.; Dawson, D. D.; Osborne, C. A.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 14951. (g) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083. (h) Zarate, C.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 2236. (i) Correa, A.; León, T.; Martin, R. *J. Am. Chem. Soc.* **2014**, *136*, 1062. (j) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303.

(4) (a) Gong, S. W.; He, H. F.; Zhao, C. Q.; Liu, L. J.; Cui, Q. X. *Synth. Commun.* **2012**, *42*, 574. (b) Zuidema, D. R.; Williams, S. L.; Wert, K. J.; Bosma, K. J.; Smith, A. L.; Mebane, R. C. *Synth. Commun.* **2011**, *41*, 2927. (c) Prakash, G. K. S.; Mathew, T.; Marinez, E. R.; Esteves, P. M.; Rasul, G.; Olah, G. A. *J. Org. Chem.* **2006**, *71*, 3952. (d) Ishimoto, K.; Mitoma, Y.; Nagashima, S.; Tashiro, H.; Prakash, G. K. S.; Olah, G. A.; Tashiro, M. *Chem. Commun.* **2003**, 514.

(5) (a) Anand, C.; Srinivasu, P.; Alam, S.; Balasubramanian, V. V.; Sawant, D. P.; Palanichamy, M.; Murugesan, V.; Vinu, A. *Microporous Mesoporous Mater.* **2008**, *111*, 72. (b) Esquivias, J.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629. (c) Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006**, *62*, 6731. (d) Prakash, G. K. S.; Panja, C.; Shakhmin, A.; Shah, E.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2009**, *74*, 8659. (e) Thirupathi, P.; Kim, S. S. *J. Org. Chem.* **2010**, *75*, 5240. (f) Thirupathi, P.; Neupane, L. N.; Lee, K. H. *Tetrahedron* **2011**, *67*, 7301.

(6) For reviews, see: (a) Liégault, B.; Renaud, J. L.; Bruneau, C. *Chem. Soc. Rev.* **2008**, *37*, 290. (b) Mondal, S.; Panda, G. *RSC Adv.* **2014**, *4*, 28317.

(7) (a) Long, Y. Q.; Jiang, X. H.; Dayam, R.; Sachez, T.; Shoemaker, R.; Sei, S.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 2561. (b) Hsin, L. W.; Dersch, C. M.; Baumann, M. H.; Stafford, D.; Glowa, G. R.; Rothman, R. B.; Jacobon, A. E.; Rice, K. C. *J. Med. Chem.* **2002**, *45*, 1321. (c) Preethi, M. E. L.; Sivakumar, T.; Palanichami, M. *Catal. Commun.* **2010**, *11*, 876. (d) DeHaan, F. P.; Chan, W. H.; Chang, J.; Cheng, T. B.; Chiriboga, D. A.; Irving, M. M.; Kaufman, C. R.; Kim, G. Y.; Kumar, A. *J. Am. Chem. Soc.* **1990**, *112*, 356.

(8) (a) Brotin, T.; Dutasta, J.-P. *Chem. Rev.* **2009**, *109*, 88. (b) Kim, J. S.; Quang, D. T. *Chem. Rev.* **2007**, *107*, 3780. (c) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931. (d) Conn, M. M.; J, R., Jr. *Chem. Rev.* **1997**, *97*, 1647.

(9) (a) Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 4121. (b) Schade, M. A.; Metzger, A.; Hug, S.; Knochel, P. *Chem. Commun.* **2008**, 3046. (c) Dohle, W.; Lindsay, D. M.; Knochel, P. *Org. Lett.* **2001**, *3*, 2871. (d) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107. (e) Nichele, T. Z.; Monteiro, A. L. *Tetrahedron Lett.* **2007**, *48*, 7472. (f) Rottländer, M.; Knockel, P. *Tetrahedron Lett.* **1997**, *38*, 1749.

(10) (a) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (b) Duplais, C.; Krasovskiy, A.; Wattenberg, A.; Lipshutz, B. H. *Chem. Commun.* **2010**, *46*, 562. (c) Sarca, V. D.; Laali, K. K. *Green Chem.* **2006**, *8*, 615. (d) Bedford, R. B.; Huwea, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600. (e) Srimani, D.; Bej, A.; Sarkar, A. *J. Org. Chem.* **2010**, *75*, 4296.

(11) (a) Yu, J. Y.; Kuwano, R. *Org. Lett.* **2008**, *10*, 973. (b) Bej, A.; Srimani, D.; Sarkar, A. *Green Chem.* **2012**, *14*, 661. (b) Zhang, Y.; Feng, M. T.; Lu, J. M. *Org. Biomol. Chem.* **2013**, *11*, 2266. (c) Inés, B.; SanMartin, R.; Moure, M. J.; Domínguez, E. *Adv. Synth. Catal.* **2009**, *351*, 2124. (d) Inés, B.; Moreno, I.; SanMartin, R.; Domínguez, E. *J. Org. Chem.* **2008**, *73*, 8448. (e) Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Tetrahedron Lett.* **2004**, *45*, 6959.

(12) Junge, M.; Beyer, A.; Patwal, U.; Kirsch, P.; Beck, S.; Van Oosten, C. L.; Schlosser, F. F. R. Patent EP0090373, June 19, 2014.

(13) Lu, Q.; Yu, H.; Fu, Y. *J. Am. Chem. Soc.* **2014**, *136*, 8252.