

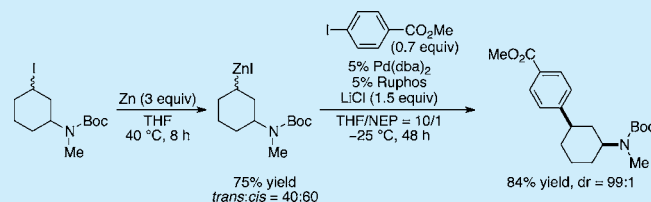
Diastereoconvergent Negishi Cross-Coupling Using Functionalized Cyclohexylzinc Reagents

Kohei Moriya and Paul Knochel*

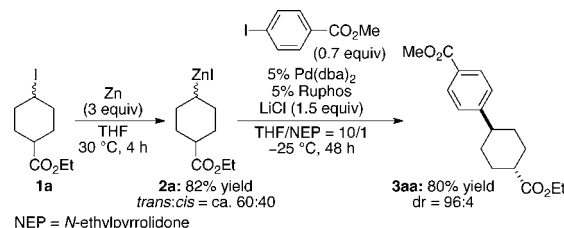
Department Chemie, Ludwig-Maximilian-Universität München, Butenandtstrasse 5-13, 81377, München, Germany

Supporting Information

ABSTRACT: Highly diastereoselective Pd-catalyzed cross-coupling reactions of functionalized 2-, 3-, and 4-substituted cyclohexylzinc reagents with aryl, heteroaryl, and alkenyl iodides have been performed under mild conditions. The use of Ruphos (2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl) as a ligand as well as LiCl and *N*-ethylpyrrolidone (NEP) as additives leads to especially high diastereoselectivities and displays good functional group tolerance. The stereoselectivity can be explained by assuming that the intermediate palladium moiety occupies an equatorial position of the cyclohexyl ring.



Scheme 1. Pd-Catalyzed Diastereoconvergent Cross-Couplings of a Functionalized Cyclohexylzinc Reagent



The performance of diastereoselective cross-coupling reactions on C_{sp^3} centers¹ is an important synthetic task for an efficient setup of multiple stereocenters. Several diastereoselective Pd-catalyzed reactions on cyclic systems have been reported so far,² and other transition metals such as Ni,³ Fe,⁴ and Co⁵ have also been used.⁶ We have also reported that cyclohexylzinc reagents with alkyl substituents at positions 2, 3, and 4 undergo Pd-catalyzed C_{sp^2} and C_{sp^3} coupling reactions in a diastereoconvergent way.^{2a,7} High diastereoselectivities were usually obtained in these systems; however, the presence of functional groups in the ring substituents complicated such cross-couplings (lower yields and diastereoselectivities). Herein, we report an improved cross-coupling procedure allowing the use of various functionalized cyclohexylzinc reagents. Such Pd-catalyzed Negishi cross-coupling reactions with various aryl, heteroaryl, and alkenyl iodides proceed in very high stereoselectivities and good yields.

Thus, ethyl 4-iodocyclohexylcarboxylate **1a** was treated with commercially available zinc dust (3 equiv) in THF to produce the corresponding cyclohexylzinc reagent **2a** (30 °C, 4 h; 82% yield).⁸ The presence of an acidic proton at the α -position to the ester group did not hamper the zinc insertion, and the resulting zinc reagent **2a** proved to be stable for several weeks without significant decomposition at 25 °C.⁹ ¹H NMR and ¹³C NMR spectroscopy of this zinc reagent **2a** in THF-*d*₈ indicated that a *trans/cis* mixture of ca. 60:40 was produced (Scheme 1).

The cross-couplings of this zinc reagent (1.0 equiv) with methyl 4-iodobenzoate¹⁰ (0.7 equiv) in the presence of various Pd-catalysts were examined. Preliminary experiments showed that the ligands of Buchwald¹¹ were the most promising. Thus, the use of SPhos (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl)^{11b} led to a moderate yield (41% yield) and diastereoselectivity (dr = 85:15) at -25 °C¹² (Table 1, entry 1). The addition of *N*-ethylpyrrolidone (NEP, 10 vol %) improved the yield as well as the diastereoselectivity (65% yield; dr = 92:8; entry 2).¹³ Further addition of LiCl (1.5 equiv)

increased the yield to 76% (entry 3).¹⁴ The best results were obtained by replacing SPhos with Ruphos (2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl),^{11c} and the thermodynamically favored *trans*-product **3aa** was obtained in 80% isolated yield¹⁵ with a *trans/cis* ratio of 96:4 (entry 4).

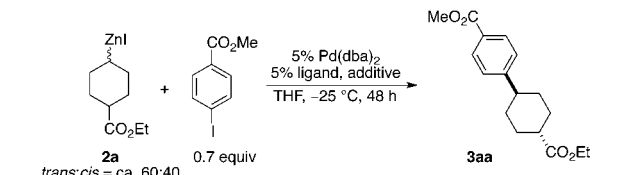
This cross-coupling procedure using the cyclohexylzinc reagent **2a** was extended to various aryl iodides (Table 2, entries 1–8). Sensitive functional groups such as a ketone (entry 2), an aldehyde (entry 3), a nitro group (entry 4), and a cyano group (entry 5) were tolerated under the reaction conditions.

In addition to electron-poor aryl iodides, an electron-rich aryl iodide can also be used (entry 6). Moreover, *meta*- or *ortho*-substituted aryl and heterocyclic iodides gave equally high diastereoselectivities (entries 7–9). Furthermore, the 3-substituted cyclohexylzinc reagent **2b** produced the thermodynamically favored *cis*-cross-coupling products (entries 10–13). An aromatic chloride substituent (entry 12) and an enone group (entry 13) are both compatible with the cross-coupling conditions.

Received: December 18, 2013

Published: January 15, 2014

Table 1. Effect of Ligands and Additives



entry	ligand ^a	additive ^b	yield ^c	dr ^d
1	SPhos	—	41%	85:15
2	SPhos	NEP (10 vol %)	65%	92:8
3	SPhos	NEP (10 vol %) LiCl (1.5 equiv)	76%	92:8
4	RuPhos	NEP (10 vol %) LiCl (1.5 equiv)	80%	96:4

^aSPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl; Ruphos = 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl. ^bNEP = *N*-ethylpyrrolidone. ^cIsolated yield of the *trans*-diastereomer. ^ddr (*trans*/*cis*) determined by capillary GC and ¹H NMR analysis.

Table 2. Scope of Pd-Catalyzed Diastereoconvergent Cross-Couplings of Substituted Cyclohexylzinc Reagents with Aryl Iodides

entry	zinc reagent	major product	yield ^a , dr ^b
1			80%, 96:4
2	2a	3ab : R = CO ₂ Me	72%, 94:6
3		3ac : R = COMe	73%, 96:4
4		3ad : R = NO ₂	74%, 96:4
5		3ae : R = CN	70%, 94:6
6		3af : R = OMe	74%, 97:3
7			68%, 93:7
8 ^c			72%, 97:3
9 ^d			69%, 97:3
10			80%, 95:5
11		3bd : R = NO ₂	74%, 97:3
12		3bj : R = Cl	79%, 94:6
13 ^d			78%, 96:4

^aIsolated yield of the major diastereomer. ^bdr (major/minor) determined by capillary GC and ¹H NMR analysis. ^cThis reaction was performed at −10 °C for 144 h. ^dThis reaction was performed at −10 °C for 48 h.

Cyclohexylzinc reagents bearing other functional groups were subjected to the cross-coupling reaction (Scheme 2 and Table 3). Thus, the 4-amino substituted cyclohexylzinc reagent **2c** prepared from the corresponding cyclohexyl iodide **1c** (30 °C, 20 h; 84% yield) underwent a smooth cross-coupling with methyl 4-iodobenzoate affording the *trans*-1,4-disubstituted cyclohexane **3ca** in 78% yield and excellent diastereoselectivity

Scheme 2. Diastereoconvergent Cross-Couplings of Cyclohexylzinc Reagents with a Nitrogen Functional Group

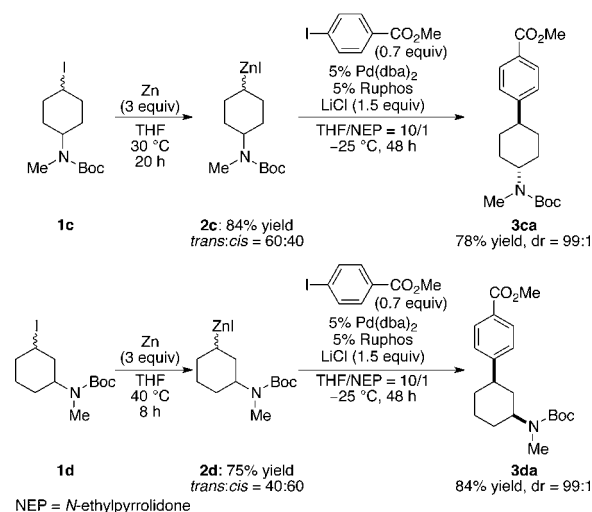


Table 3. Scope of Pd-Catalyzed Diastereoconvergent Cross-Couplings of Substituted Cyclohexylzinc Reagents with Aryl Iodides

entry	zinc reagent	major product	yield ^a , dr ^b
1			76%, 99:1
2			76%, 99:1
3			75%, 97:3
4			70%, 98:2
5			59%, 88:12

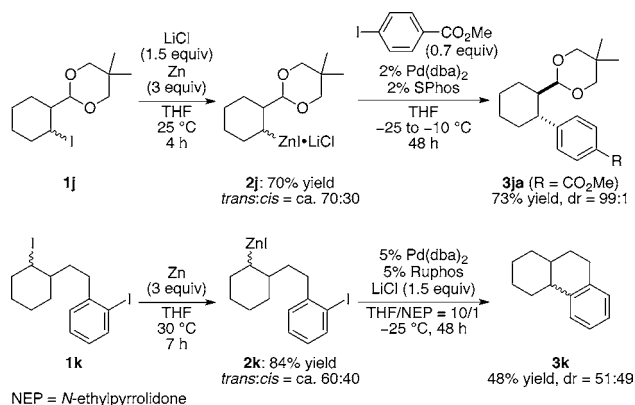
^aIsolated yield of the *trans*-diastereomer. ^bdr (*trans*/*cis*) determined by capillary GC and ¹H NMR analysis.

(dr = 99:1). Similarly, in the case of the 3-amino substituted cyclohexylzinc reagent **2d** prepared from the corresponding cyclohexyl iodide **1d** (40 °C, 8 h; 75% yield) the *cis*-1,3-disubstituted cyclohexane **3da** was obtained in 84% yield and excellent diastereoselectivity (dr = 99:1). Also, cyclohexylzinc reagents with nitrogen-containing functional groups such as an amide (**2e**, entry 1, Table 3) or a benzylamine substituent (**2f**, entry 2) underwent the cross-couplings with excellent diastereoselectivity (dr = 99:1). In the case of cyclohexylzinc reagents bearing an OTBS group (**2g**, entry 3) or TBS group (**2h**, entry 4), the cross-coupling reaction proceeded well, leading to the expected products **3ga** and **3ha** in 70–75% yield and dr = >97:3. A cyclohexylzinc reagent bearing a terminal

alkynyl group⁹ was readily prepared and led to the cross-coupling product **3ia** in 59% yield with modest diastereoselectivity (dr = 88:12). The reduced selectivity may be a consequence of the lower bulkiness of the alkynyl group.¹⁶

Furthermore, cross-coupling reactions using 2-substituted cyclohexylzinc reagents¹⁷ were examined (Scheme 3). Thus,

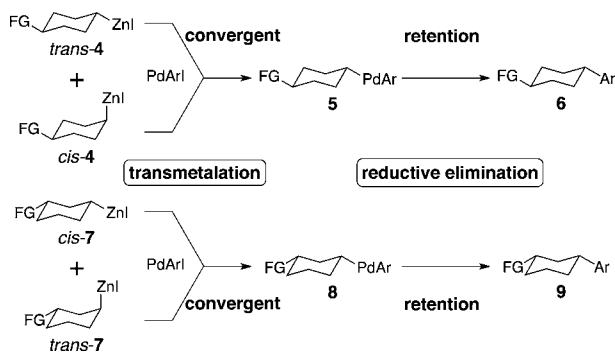
Scheme 3. Diastereoconvergent Cross-Coupling Reaction of 1,2-Substituted Cyclohexylzinc Reagents



cyclohexylzinc reagent **2j** (*trans/cis* = ca. 70:30)¹⁸ was treated with methyl 4-iodobenzoate under similar conditions to form the cross-coupling product **3ja** in excellent diastereoselectivity. However, this behavior is not general and may be complicated, especially in ring closure reactions. We have prepared the diiodide **1k** by standard methods.¹⁹ Its treatment with zinc dust in THF selectively provided the alkylzinc derivative **2k** (30 °C, 7 h; 84% yield) as a mixture of diastereomers. The addition of a Pd-catalyst led to a ring closure reaction, furnishing the tricyclic product **3k** in 48% yield as a 1:1 mixture of diastereomers.

A tentative mechanism²⁰ can be suggested for explaining the observed diastereoselectivity in this cross-coupling reaction (Scheme 4). In the case of 4-substituted cyclohexylzinc

Scheme 4. Tentative Mechanism for the Diastereoconvergent Cross-Couplings



reagents the *trans*-reagent *trans*-4 is converted to the thermodynamically favored *trans*-palladium intermediate **5** via retentive transmetalation.²¹ On the other hand, the *cis*-reagent *cis*-4 is converted to the same palladium intermediate **5** via inversive transmetalation.²² The introduction of a palladium moiety in the axial position was highly disfavored²³ due to the repulsive interactions of the bulky phosphine ligands on the palladium center with the cyclohexyl ring, which was confirmed by DFT calculations.^{2a} Thus, the thermodynamically favored

trans-cross-coupling product **6** will be obtained through the usual retentive reductive elimination.^{2g,21,22,24} Again we propose that the mixture of *cis*- and *trans*-cyclohexylzinc reagents **7** are converted in a convergent way to the thermodynamically more stable *cis*-Pd-intermediate **8** bearing the PdAr group in an equatorial position. The *cis*-cross-coupling product **9** will be formed via retentive reductive elimination.^{2g,21,22,24}

In summary, we have developed stereoconvergent cross-coupling reactions of various functionalized cyclohexylzinc reagents, which can be prepared by direct insertion of zinc dust to the corresponding cyclohexyl iodides. The stereoselectivity is excellent for a 3- or 4-substituted cyclohexyl ring system and is also applicable for some 2-substituted zinc reagents. Our method provides a range of 1,2-, 1,3-, and 1,4-substituted cyclohexane derivatives stereoselectively. Further extensions are currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization of the compounds, and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Paul.Knochel@cup.uni-muenchen.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The research leading to these results has received funding from Forschungsgemeinschaft (SFB749, B2). We also thank BASF SE (Ludwigshafen), and Rockwood Lithium GmbH (Hoechst) for the generous gift of chemicals. We thank Dr. Tobias Thaler and Dr. Stephanie Seel (LMU, München, 2010) for their valuable discussions. K.M. thanks DAAD for a scholarship.

■ REFERENCES

- (1) Recent reviews of C_{sp^3} cross-couplings: (a) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (b) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (d) Wasa, M.; Engle, K. M.; Yu, J. -Q. *Isr. J. Chem.* **2010**, *50*, 605.
- (2) (a) Thaler, T.; Haag, B.; Gavryushin, A.; Schober, K.; Hartmann, E.; Gschwind, R. M.; Zipse, H.; Mayer, P.; Knochel, P. *Nat. Chem.* **2010**, *2*, 125. (b) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774. (c) Thaler, T.; Guo, L. -N.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 2174. (d) Bercot, E. A.; Caille, S.; Bostick, T. M.; Ranganathan, K.; Jensen, R.; Faul, M. M. *Org. Lett.* **2008**, *10*, 5251. (e) Mycka, R. J.; Duez, S.; Bernhardt, S.; Heppelkausen, J.; Knochel, P.; Fleming, F. F. *J. Org. Chem.* **2012**, *77*, 7671. (f) Boudier, A.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 687. (g) Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923. (h) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (i) Trost, B. M.; Silverman, S. M.; Stambuli, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 19483.
- (3) (a) Garcia, P. M. P.; Franco, T. D.; Orsino, A.; Ren, P.; Hu, X. *Org. Lett.* **2012**, *14*, 4286. (b) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788. (c) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510. (d) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 12177. (e) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360. (f) Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S.

- J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 879. (g) Melzig, L.; Gavryushin, A.; Knochel, P. *Org. Lett.* **2007**, *9*, 5529.
- (4) (a) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (b) Hatakeyama, T.; Kondo, Y.; Fujiwara, Y.; Takaya, H.; Ito, S.; Nakamura, E.; Nakamura, M. *Chem. Commun.* **2009**, 1216. (c) Kawamura, S.; Kawabata, T.; Ishizuka, K.; Nakamura, M. *Chem. Commun.* **2012**, 48, 9376. (d) Steib, A. K.; Thaler, T.; Komeyama, K.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 3303. (e) Bensoussan, C.; Rival, N.; Hanquet, G.; Colobert, F.; Reymond, S.; Cossy, J. *Tetrahedron* **2013**, *69*, 7759.
- (5) (a) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem.—Eur. J.* **2004**, *10*, 5640. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886. (c) Nicolas, L.; Angibaud, P.; Stanfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11101.
- (6) Other metal catalyzed conditions: (a) Yasuda, S.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 287. (b) Someya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2010**, *66*, 5993. (c) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.
- (7) Enantioconvergent cross-couplings: (a) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946. (b) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154.
- (8) (a) Knochel, P.; Millot, N.; Rodriguez, A. L.; Tucker, C. E. *Org. React.* **2001**, *58*, 417. (b) Knochel, P.; Leuser, H.; Gong, L. -Z.; Perrone, S.; Kneisel, F. F. In *Handbook of Functionalized Organometallics*, Knochel, P., Eds.; Wiley-VCH: Weinheim, 2005; pp 215–333.
- (9) Knoess, H. P.; Furlong, M. T.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 5974.
- (10) These cross-couplings became much slower under our conditions if an aryl bromide is used (for example, 4-bromoanisole instead of 4-iodoanisole).
- (11) (a) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (c) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
- (12) Usually higher reaction temperatures led to lower diastereoselectivity. However, in some cases (Table 2, entries 8, 9, 13) the performance of the coupling reactions at $-10\text{ }^{\circ}\text{C}$ improved the yields without significant loss of diastereoselectivity compared to $-25\text{ }^{\circ}\text{C}$.
- (13) Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2005**, *7*, 4871.
- (14) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.
- (15) Homocoupling byproducts (biphenyls) were also produced in these cross-couplings in small amounts (6–10% NMR yield).
- (16) The A value of a terminal alkyne ($A = 0.41$) is smaller than that of other substituents such as CO_2Me ($A = 1.31$). Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344.
- (17) (a) Majid, T. N.; Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 5069. (b) Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Chem.—Eur. J.* **2000**, *6*, 2748. (c) Hupe, E.; Knochel, P. *Org. Lett.* **2001**, *3*, 127.
- (18) Seel, S. *Stereoselective Preparation and Stereochemical Behaviour of Organozinc and Organolithium Reagents*. Ph.D. Thesis, Ludwig-Maximilian-Universität München, 2012.
- (19) See Supporting Information.
- (20) We have found no evidence that *cis*- and *trans*-cyclohexylzinc reagents isomerize under our cross-coupling conditions.
- (21) (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (b) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894. (c) Falck, J. R.; Patel, P. K.; Bandyopadhyay, A. *J. Am. Chem. Soc.* **2007**, *129*, 790. (d) Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607. (e) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458.
- (22) $\text{S}_{\text{E}}2$ mechanism: (a) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666. (b) Ohmura, T.; Awano, T.; Sugimoto, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (c) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108. (d) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793.
- (23) Munro-Leighton, C.; Adduci, L. L.; Becker, J. J.; Gagné, M. R. *Organometallics* **2011**, *30*, 2646.
- (24) (a) Still, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508. (b) Labadie, J. W.; Still, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129. (c) Milstein, D.; Still, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981. (d) Krizkova, P. M.; Hammerschmidt, F. *Eur. J. Org. Chem.* **2013**, 5143.