Organic LETTERS

Letter

pubs.acs.org/OrgLett

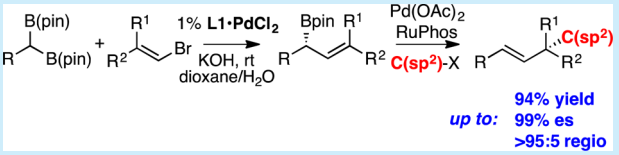
Modular, Catalytic Enantioselective Construction of Quaternary Carbon Stereocenters by Sequential Cross-Coupling Reactions

Bowman Potter, Emma K. Edelstein, and James P. Morken*

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Supporting Information

ABSTRACT: The catalytic Suzuki–Miyaura cross-coupling with chiral γ,γ-disubstituted allylboronates in the presence of RuPhos ligand occurs with high regioselectivity and enantiospecificity, furnishing nonracemic compounds with quaternary centers. Mechanistic experiments suggest that the reaction occurs by transmetalation with allyl migration, followed by rapid reductive elimination.

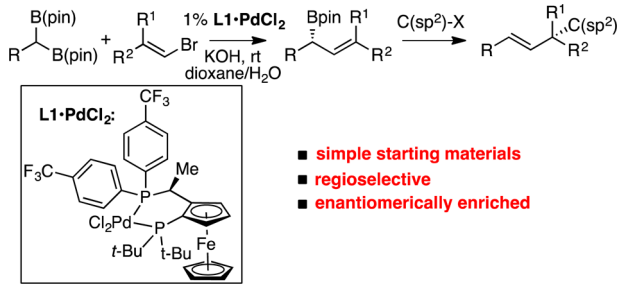


The selective and efficient construction of quaternary carbon stereocenters remains a challenging task for asymmetric catalysis.[1] While several advances have been charted, one method that has not been broadly employed for this undertaking is the Suzuki–Miyaura cross-coupling reaction.[2] A lack of advances in this area can plausibly be traced to the expectation that such catalytic reactions would require the intermediacy of highly hindered tertiary organopalladium complexes, and access to these compounds might be prohibitive. Indeed, aside from asymmetric catalytic allyl–allyl cross-coupling,[3] the combination of an organoboron reagent and an organic electrophile to furnish a nonracemic quaternary carbon stereocenter selectively has yet to be accomplished.[4] In this letter, we describe a site-selective cross-coupling of allylboronates that, when conducted in sequence with enantiotopic-group-selective cross-coupling, enables a modular assembly of enantiomerically enriched quaternary carbon centers from geminal bis(boronates), alkenyl halides, and C(sp^2) electrophiles (Scheme 1).

With respect to the development of the sequence represented in Scheme 1, we recently established an enantiotopic-group-selective cross coupling to construct requisite γ,γ'-disubstituted allylboronates.[5] However, the utility of these reagents in asymmetric cross-coupling reactions has little precedent. Important recent studies in the cross-coupling of allylboron reagents and C(sp^2) electrophiles have shed light on critical aspects of regioselectivity in C–C bond formation. Moderate branch-selectivity in cross-coupling of crotyl boronates and aryl electrophiles was first observed by Kalinin.[6] This reaction was developed more broadly by Miyaura, who found that these reactions could be accomplished enantioselectively with chiral catalysts and that they could exhibit very high regioselectivity for the γ-coupled products ostensibly by S_E2' transmetalation followed by rapid reductive elimination.[7] Our own group recently disclosed an enantioselective, intramolecular allyl-aryl cross-coupling to furnish carbocycles with high levels of selectivity.[8] With more hindered γ,γ-disubstituted reagents, Organ found that Pd-PEPPSI complexes catalyze linear-selective prenylation of electrophiles,[9] while Buchwald observed that with appropriate choice of phosphine ligand, either the linear adduct or the branched *tert*-prenyl cross-coupling product could be obtained selectively.[10] Studies by Crudden and Aggarwal,[11] and more recently by Hall,[12] determined that cross-coupling of secondary allylic boronates could furnish tertiary stereocenters and that such reactions occur with enantiospecificity. However, to our knowledge the issue of chirality transfer in the generation of quaternary centers has yet to be addressed.

With the goal of developing a cross-coupling reaction sequence that might be accomplished in a single flask process, our studies commenced by examining the reaction between nonracemic allylboronate **1** and aromatic electrophiles (Scheme 2). A critical criteria for the eventual development of a tandem single flask process was to employ the same conditions for the allyl-aryl cross coupling that were employed for the enantiotopic-group-selective coupling in Scheme 1 (KOH/dioxane/H_2O). In the final rendition, it was envisaged that one need not isolate the intermediate allylboronate prior to its

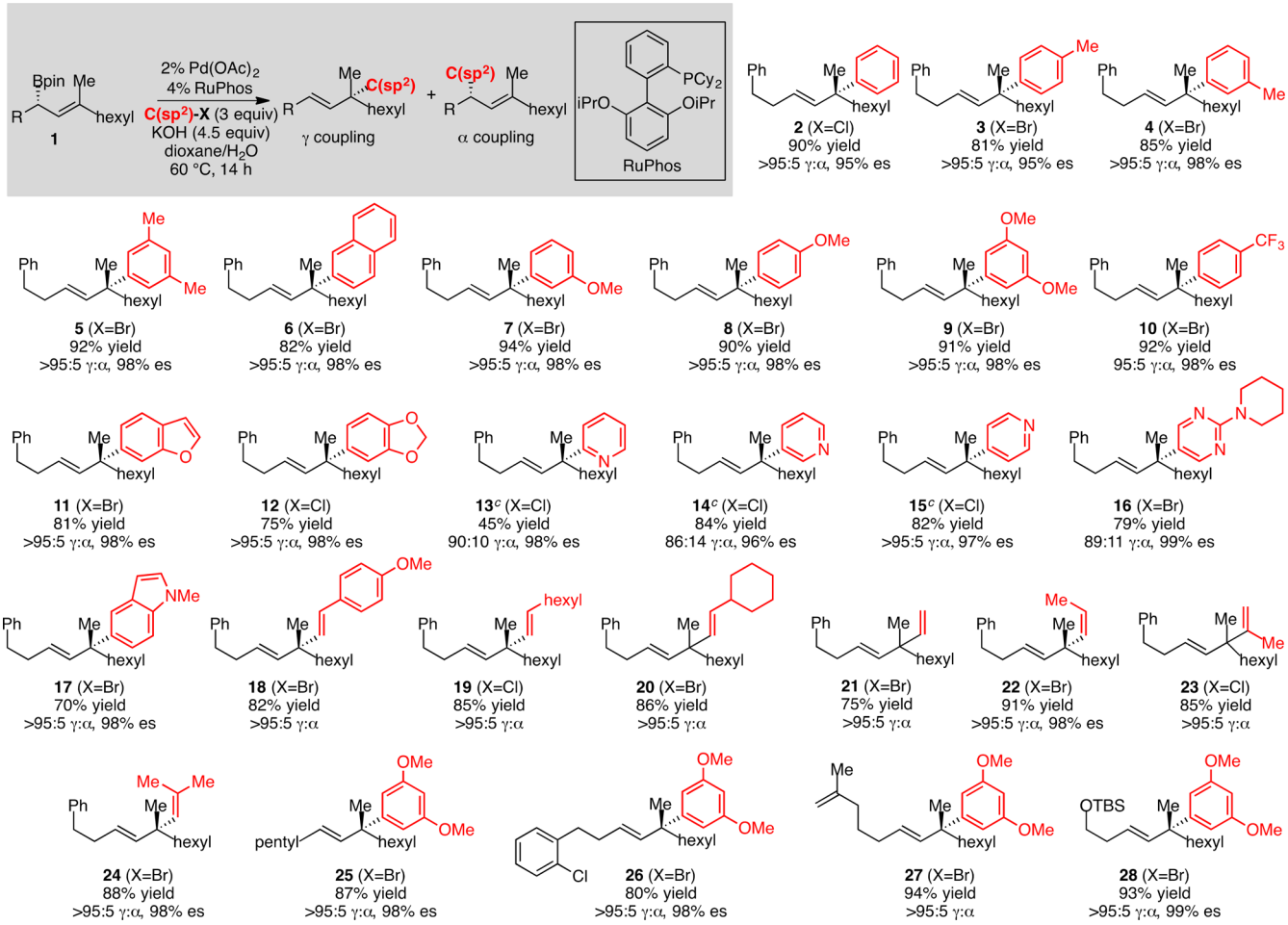
Scheme 1. Sequential Cross-Coupling Approach to the Asymmetric Construction of Quaternary Carbon Stereocenters



Received: May 31, 2016

DOI: 10.1021/acs.orglett.6b01580
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Survey of Substrates for Pd/RuPhos Catalyzed Cross-Coupling of Allylboronates and Electrophiles[a,b]



[a]Reactions conducted on 0.1 mmol scale at 60 °C for aryl electrophiles or 50 °C for alkenyl electrophiles. [b]Yield is isolated yield of purified material. Regioisomer ratios were determined by ^{1}H NMR analysis, enantiospecificity determined by chiral SFC analysis. [c]Employed 3.0 equiv of chloropyridine·HCl and 7.5 equiv of KOH.

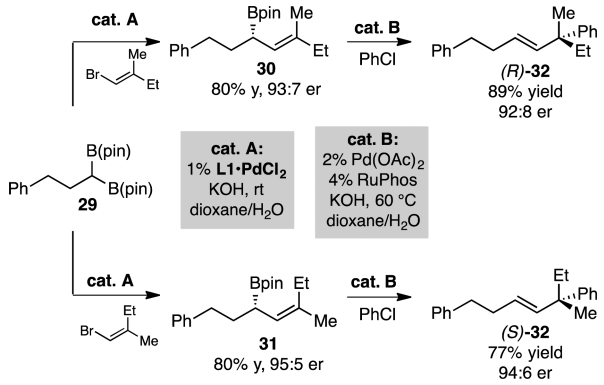
engagement in a second cross-coupling. As depicted in Scheme 2, it was found that efficient, site selective, and highly enantiospecific cross-couplings could be obtained by employing $Pd(OAc)_2$ in the presence of RuPhos[13] ligand. With this catalyst combination and reaction conditions, efficient reactions and very high levels of γ:α cross-coupling products were observed. Moreover, the reaction products were isolated with >20:1 *E*/*Z* olefin stereoisomer ratios and with excellent levels of enantiospecificity (generally >95% es). As the examples in Scheme 2 indicate, the reaction appears to be effective with both electron-rich and electron-poor aryl bromides as the electrophile. It was also found that aryl chlorides and iodides participated with similar efficiency: compound **8** could be accessed from 4-chloroanisole or 4-iodoanisole in 95% yield and 88% yield, respectively, and in identical selectivity as with the aryl bromide electrophile. In addition to effective couplings with aryl electrophiles, heteroaromatic compounds also appear to participate in the reaction (products **13**−**17**), and products **18**−**24** demonstrate that alkenyl electrophiles engage in stereospecific cross-couplings and provide a route to important 1,4 "skipped dienes"[14] that bear a quaternary carbon stereocenter. Also of note, products **26**−**28** suggest that versatile aryl chloride, alkene, and silyl ether functional groups can be accommodated in the allylboronate partner. Lastly, while the data in Scheme 2 is for reactions conducted on 0.1 mmol scale, when the synthesis of **9** was conducted on 2 mmol scale, the reaction proceeded with equal efficiency and selectivity (91% yield, >95:5 γ:α, 99% es).

The high level of stereospecificity in the Pd/RuPhos catalyzed allyl-aryl cross-coupling suggests that judicious choice of substrates can allow the same enantiomer of chiral ligand to furnish both enantiomers of chiral cross-coupling product. This feature is demonstrated in Scheme 3, where it is shown that cross-coupling of boronate **29** with either *E* or *Z*-1-bromo-2-methyl-1-butene[15] can furnish diastereomeric cross-coupling products **30** and **31** in near equal levels of stereoselection. Subjection of **30** and **31** to catalytic allyl-aryl cross-coupling furnishes enantiomeric products (*R*)-**32** and (*S*)-**32**, both in high levels of enantiomeric purity. The absolute configuration of the enantiomers of **32** was established by ozonolysis and oxidation (Jones reagent) to the derived carboxylic acid followed by comparison of optical rotation to that for the known compound.[16]

With an effective cross-coupling that delivers the γ-coupling product selectively from γ,γ-disubstituted allylboronates, single-flask cascade cross-coupling sequences were investigated. First, to determine whether residual **L1·PdCl$_2$** catalyst used for the cross-coupling of geminal bis(boronates) would undermine the

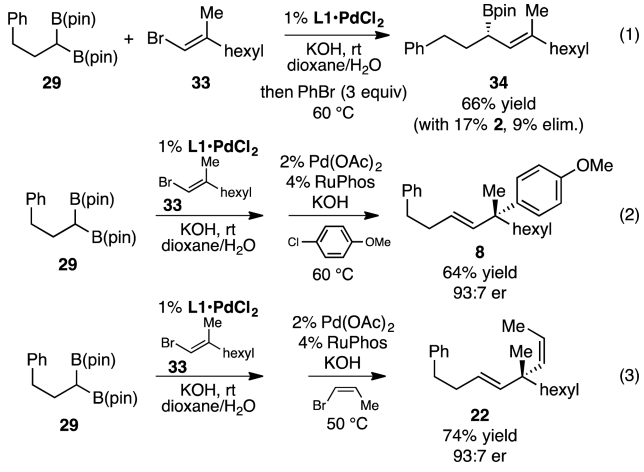
DOI: 10.1021/acs.orglett.6b01580
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Sequential Cross-Coupling to Furnish Enantiomeric Products from the Same Enantiomer of Catalyst



subsequent enantiospecific allyl-aryl cross-coupling reaction, we probed whether **L1·PdCl$_2$** would effect cross-coupling of bromobenzene and *in situ* generated allylboronate. As depicted in eq 1 (Scheme 4), heating with PhBr at the end of a cross-

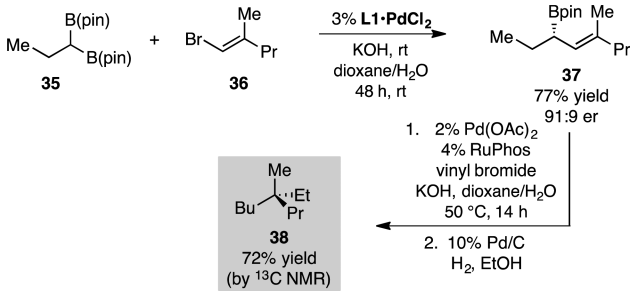
Scheme 4. Single-Flask Sequential Cross-Couplings



coupling between geminal bis(boronate) **29** and alkenyl bromide **33** resulted in low conversion of allylboronate **34** thus **L1·PdCl$_2$** appears to be ineffective at allyl-aryl cross-coupling. To probe the capacity for a single-flask cascade sequence, **29** and **33** were then subjected to cross-coupling with **L1·PdCl$_2$** with KOH in dioxane/water, then 4-chloroanisole was added followed by Pd(OAc)$_2$ and RuPhos. Upon heating to 60 °C for an additional 14 h, coupling product **8** was isolated in 64% yield and 93:7 er (eq 2). A similar single-flask reaction sequence furnished **22** with comparable yield and selectivity.

We considered that an intriguing example of the utility of the cascade cross-coupling sequence to deliver quaternary compounds might lie in the construction of nonracemic **38** (Scheme 5), the simplest all-carbon quaternary-center-containing compound.[17] This compound has recently been addressed by Aggarwal[18] and Cramer[19] through approaches employing asymmetric homologation and selective cleavage of enantiotopic C−C bonds, respectively. As depicted in Scheme 5, **38** was readily prepared in a three-step sequence involving asymmetric cross-coupling of bis(boronate) **35** with alkenyl halide **36**, to give **37**. Subsequent stereospecific cross-coupling of **37** with vinyl bromide followed catalytic hydrogenation

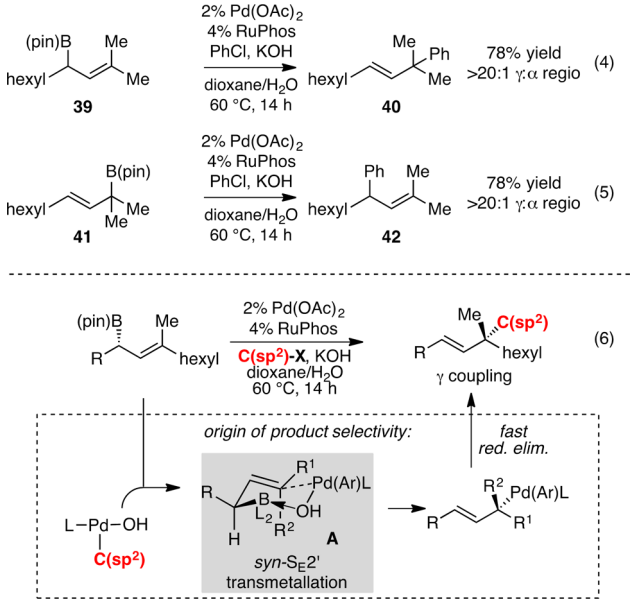
Scheme 5. Catalytic Synthesis of Chiral Hydrocarbon 38



furnished the target hydrocarbon **38** in 72% yield as determined by ^{13}C NMR versus an internal standard.

In terms of reaction mechanism, one of two reasons could account for the γ-selectivity in the RuPhos/Pd catalyzed allyl-aryl cross-coupling reaction. In line with studies by Buchwald[10] on the construction of quaternary carbons by Pd-catalyzed coupling of allylboronates and related studies by Aggarwal and Cruuden,[11b] it could be that stereospecific S$_E$2′ transmetalation is followed by rapid reductive elimination; alternatively, the transmetalation (either S$_E$2′ or S$_E$2) generates a π-allyl complex that favors reductive elimination at the more substituted carbon. To probe these possibilities, substituted secondary allylboronate **39** was subjected to Pd/RuPhos catalyzed cross-coupling and found to react with >98% γ-selectivity to give **40** (eq 4, Scheme 6); in contrast, when regioisomeric tertiary

Scheme 6. Mechanistic Experiments and the Origin of Regioselectivity



allylboronate **41** was subjected to the reaction conditions, regioisomer **42** was produced in excellent selectivity (eq 5). This pair of observations effectively rules out the possibility for π-allyl isomerization of (allyl)palladium intermediates. Collectively, the site-selectivity of the reaction, the configuration of the product alkene, and the correlation between allylboronate configuration and product configuration is most in line with an inner-sphere *syn*-S$_E$2′ transmetalation that operates by structure **A** below (eq 6, Scheme 6).

DOI: 10.1021/acs.orglett.6b01580
Org. Lett. XXXX, XXX, XXX−XXX

In summary, we have reported a stereospecific cross-coupling reaction that applies to highly substituted allylboronates and furnishes quaternary stereocenters with outstanding stereoselection. Along with enantiotopic-group-selective cross-coupling, the allyl-aryl cross-coupling can be run as a part of a two step sequence to create useful chiral hydrocarbons directly from simple precursors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01580.

Procedures, characterization, and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: morken@bc.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The NIH (GM-64451) is acknowledged for financial support; B.P. is grateful for a LaMattina graduate fellowship.

■ REFERENCES

(1) For recent reviews: (a) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (b) Hong, A. Y.; Stolz, B. M. *Eur. J. Org. Chem.* **2013**, *2013*, 2745. (c) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181. (d) Marek, I.; Minko, Y.; Pasco, M.; Mejuch, T.; Gilboa, N.; Chechik, H.; Das, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 2682. (e) Eppe, G.; Didier, D.; Marek, I. *Chem. Rev.* **2015**, *115*, 9175.

(2) For a review of stereospecific cross-coupling, see: Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587.

(3) (a) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716. (b) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 7092.

(4) For an alternative synthesis of nonracemic asymmetric quaternary carbon centers from organoboronates, see: (a) Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nat. Chem.* **2014**, *6*, 584. (b) Llaveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 10958.

(5) (a) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 17918. (b) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534.

(6) Kalinin, V. N.; Denisov, F. S.; Bubnov, Y. N. *Mendeleev Commun.* **1996**, *6*, 206.

(7) (a) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 1368. (b) Yamamoto, Y.; Takada, S.; Miyaura, N.; Iyama, T.; Tachikawa, H. *Organometallics* **2009**, *28*, 152.

(8) Schuster, C. H.; Coombs, J. R.; Kasun, Z. A.; Morken, J. P. *Org. Lett.* **2014**, *16*, 4420.

(9) Farmer, J. L.; Hunter, H. N.; Organ, M. G. *J. Am. Chem. Soc.* **2012**, *134*, 17470.

(10) Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10642.

(11) (a) Glasspoole, B. W.; Ghozati, K.; Moir, J. W.; Crudden, C. M. *Chem. Commun.* **2012**, *48*, 1230. (b) Chausset-Boissarie, L.; Ghozati, K.; LaBine, E.; Chen, J. L.-Y.; Aggarwal, V. K.; Crudden, C. M. *Chem. - Eur. J.* **2013**, *19*, 17698.

(12) Rybak, T.; Hall, D. G. *Org. Lett.* **2015**, *17*, 4156.

(13) (a) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965. (b) For cross-coupling alkylB(pin) reagents with aryl halides, see: Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem.* **2012**, *124*, 543.

(14) Jie, M.; Pasha, M. K.; Syed-Rahmatullah, M. S. K. *Nat. Prod. Rep.* **1997**, *14*, 163.

(15) Lim, S.; Wipf, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068.

(16) Ruano, J. L. G.; Martin-Castro, A. M.; Tato, F.; Torrente, E.; Poveda, A. M. *Chem. - Eur. J.* **2010**, *16*, 6317.

(17) (a) Hoeve, W. T.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2754. (b) Fujita, T.; Obata, K.; Kuwahara, S.; Miura, N.; Nakahashi, A.; Monde, K.; Decatur, J.; Harada, N. *Tetrahedron Lett.* **2007**, *48*, 4219. (c) Fujita, T.; Obata, K.; Kuwahara, S.; Nakahashi, A.; Monde, K.; Decatur, J.; Harada, N. *Eur. J. Org. Chem.* **2010**, *2010*, 6372. (d) Simaan, S.; Goldberg, A. F. G.; Rosset, S.; Marek, I. *Chem. - Eur. J.* **2010**, *16*, 774.

(18) Pulis, A. P.; Blair, D. J.; Torres, E.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2013**, *135*, 16054.

(19) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340.

DOI: 10.1021/acs.orglett.6b01580
Org. Lett. XXXX, XXX, XXX−XXX