Outer-Sphere Direction in Iridium C−H Borylation

Philipp C. Roosen,[†] Venkata A. Kallepalli,[†] Buddhadeb Chattopadhyay,[†] Daniel A. Singleton,*[,‡] Robert E. Maleczka, Jr.,*[,†] and Milton R. Smith, III*[,†]

[†]Department of Chemistry, Michigan State University, East Lansing, Michigan 48824-1322, United States
[‡]Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842, United States

Ⓢ *Supporting Information*

ABSTRACT: The NHBoc group affords ortho selective C−H borylations in arenes and alkenes. Experimental and computational studies support an outer sphere mechanism where the N−H proton hydrogen bonds to a boryl ligand oxygen. The regioselectivities are unique and complement those of directed ortho metalations.

Over the past decade, advances in the transition-metal-catalyzed functionalization of C−H bonds have transformed synthetic chemistry.[1] In this context, the borylation of C−H bonds has shown promise because it bestows the C−H functional group with the synthetic versatility for which B−C bonds are renowned. A central challenge in these reactions is controlling their selectivity. Steric effects often dominate the regioselectivity of C−H borylations of aromatics.[2] This makes C−H borylations complementary to widely applied directed ortho metalations (D*o*Ms),[3] but the intrinsic functional group and practical limitations of D*o*Ms have intensified efforts to develop selective ortho C−H borylations.

Ortho C−H borylation has been accomplished by catalyst or substrate modification (Scheme 1).[4] Catalyst control can be achieved with ligands and/or metals that make 14-electron intermediates accessible.[4b,c,e,f] Substrates that contain a directed metalation group (DMG) likely coordinate to the metal to form a 16-electron intermediate, **1**, which has a vacant site to facilitate the cleavage of an ortho C−H bond. Usually, chelation-directed selectivity is not observed for 16-electron catalytic intermediates, such as Ir(Bpin)₃(dtbpy) (**2**, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine, pin = pinacolate). For these catalysts ortho borylation can be accomplished by a relay-directed mechanism in which the substrate can reversibly attach to the metal by a σ-bond metathesis process.[4a,d] To date, the substrates in relay-directed borylation have all contained pendant Si−H bonds, and the reactions presumably proceed through a 16-electron intermediate **3** in which the ortho C−H bond is poised for borylation. Both the chelation-directed and relay-directed mechanisms are inner-sphere processes, where direction is achieved by coordination to iridium.

In *outer-sphere direction*,[5] a ligand on the catalyst recognizes functionality in the substrate. This distinct paradigm for selectivity, based on ideas from molecular recognition, can provide selectivities that complement those from other directing mechanisms.[6] Our efforts to understand the electronic effects in C−H borylation suggested that an outer-sphere mechanism can direct borylation.[7] Herein we outline a proof-of-concept where NHBoc groups direct C−H functionalizations with selectivities that are unprecedented in the C−H borylation and D*o*M literature.

The potential for outer-sphere direction in Ir-catalyzed C−H borylations was suggested by an anomaly predicted for pyrrole in a recent combined computational and experimental study.[7b] An analysis of 21 combinations of substrates and metal complexes supported the importance of proton-transfer character in the C−H activation transition state (TS). There was a strong linear correlation between the $\Delta G°$ and $\Delta G^{\ddagger}$ for C−H activation and the NPA charge on the aryl group after activation, as reflected by the subset of five-membered heterocyclic intermediates (**5**) shown in Figure 1.[8] This charge/reactivity relationship was remarkably predictive, but a large deviation was observed for pyrrole. Borylation at the 2-position of pyrrole is 2.3 kcal/mol more favorable than would be expected from a least-squares fit of other substrate/catalyst combinations.

Geometries for the TS and the resulting intermediate for pyrrole are shown in Figure 2. Two features are noteworthy. First, the NH···O distances between the pyrrole and one of the boryl oxygens are short, ranging from 2.05 to 2.19 Å. Second, the ∠Ir−C−N are ~10° less than the ∠Ir−C−C. Both of these indicate significant NHO hydrogen interaction in the TS and the
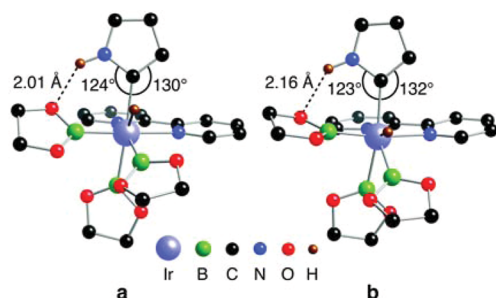
Scheme 1. Strategies for ortho-Directed C−H Borylation
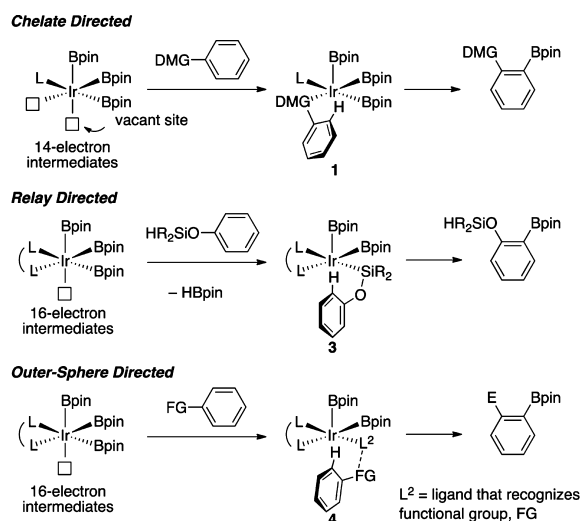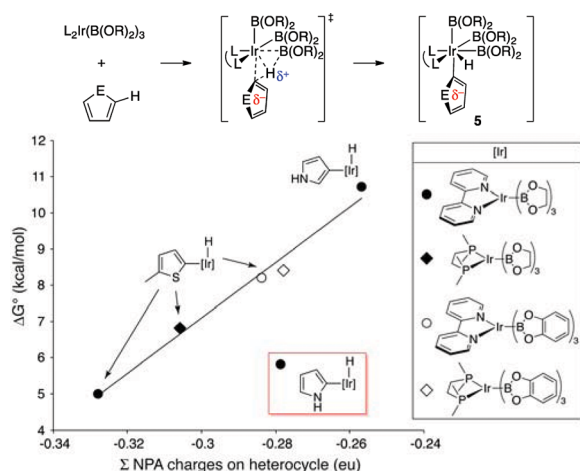
Figure 1. Calculated energies of intermediates (**5**) vs the total Normal Population Analysis (NPA) charge on the C−H activated heterocycles in **5**. Computational data are excerpted from ref 7b.


Figure 2. Lowest-energy M06/SDD(Ir)/6-31+G**(C H O N B) TS (a) and intermediate (b) for C−H activation of pyrrole at the 2-position by model complex Ir(bipy)(Beg)$_3$ (eg = ethyleneglycolate). The NH−O distances and distortions for Ir−C−C and Ir−C−N angles indicate N−H−O hydrogen bonding.

intermediate. This clearly accounts for the lowering of ΔG in Figure 1.

While H-bonding likely accelerates C−H borylations of pyrrole, this interaction only reinforces regioselectivity that is already preferred. Because outer-sphere H-bonding interactions have had a significant impact in other catalytic systems,[9,6b,c] we expected that similar interactions could be harnessed in C−H borylations and the resulting regioselectivities could be complementary.

Because preliminary studies of primary anilines were hampered by poor conversion, *tert*-butoxycarbonyl (Boc) protected anilines were examined. *N*-Boc protected compounds are viable substrates for C−H borylation.[10] This is illustrated in Scheme 2, where the borylation of **6** gives meta functionalization

Scheme 2. Boc Substitution and Borylation Regioselectivity
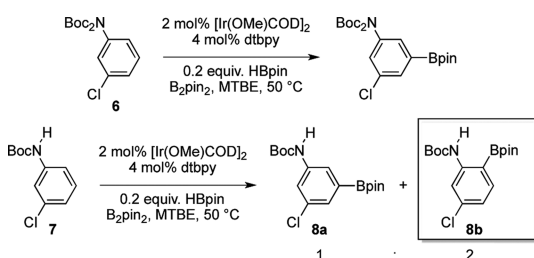
typical for 1,3-disubstituted benzenes. Since one Boc group sufficiently protects primary amines,[10b] substrate **7** was examined next. *Remarkably, replacing one Boc group with H alters the regioselectivity to favor ortho borylation product 8b.*[11]

The shift in selectivity for **7** could arise from a number of mechanisms, three of which are depicted in Scheme 3. In

Scheme 3. Experiments to Probe Mechanism
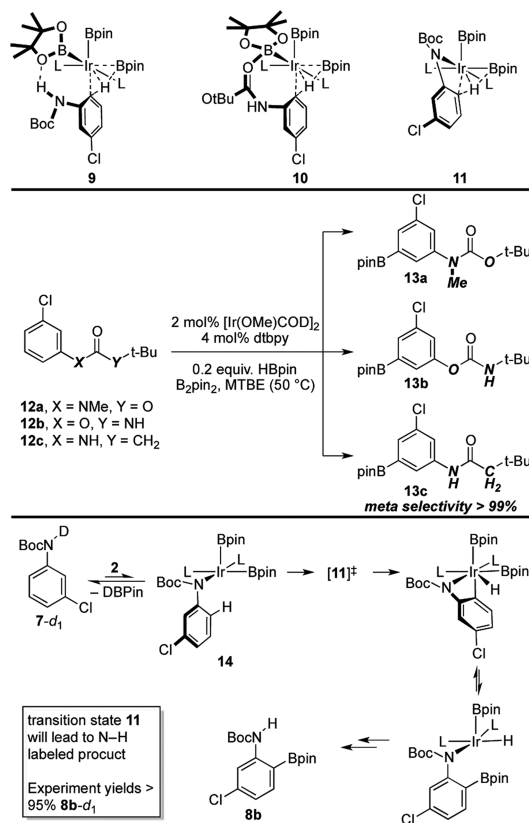
addition to H-bonding TS **9**, selectivity could arise from coordination of the carbamate O to a boryl B in TS **10**. Alternatively, inner-sphere N−H/Ir−B σ-bond metathesis could account for ortho selectivity via TS **11**.

Substrates in **12a−c** were chosen to probe for intermediates **9−11**. For **12a**, TSs **9** and **11** are impossible since H has been replaced by CH$_3$. The only product detected is meta isomer **13a**, consistent with pathways via **9** or **11**. For **12b**, the NH and O groups of **7** are transposed. This would affect selectivity via **9** or **11**, because the ring sizes in the TSs increase. Conversely, the effects on TS **10** should be slight. Exclusive formation of meta product **13b** makes participation of **10** unlikely. The meta selectivity for amide **12c** eliminates **10** because its carbonyl O is more basic than those in carbamates **12a−b**,[12] but it calls **9** to question because the H-bonding mechanism of **9** seems equally plausible for **12c**.

TSs **9** and **11** can be distinguished by isotopic labeling. As indicated in Scheme 3, a pathway involving **11** requires N−D scission. Consequently, C−H borylation and product elimination would produce significant quantities of **8b**-d_0. When **7**-d_1 is subjected to borylation, >95% of product is *N*-deuterated.

The experimental data in Scheme 3 excludes **10** and **11**, but it provides no support for **9**. If the H-bonding mechanism is correct, then it might be expected that the acidity of the N−H bond would affect the selectivity. However, attempts to improve

selectivity with more acidic N−H bonds were unsuccessful. For example, *N*-aryl triflamides gave N-borylation. Since solutions containing both HBpin and *N*-aryl triflamides are stable, an Ir complex catalyzes N-borylation. In a plausible mechanism, σ-bond metathesis of the Ir−B bond with the highly acidic triflimide N−H bond generates intermediate **14** (Scheme 3) and subsequent N−B elimination yields the *N*-borylated triflamide.

An experimental result supporting the H-bonding mechanism of **9** was the observation that increased basicity of the dipyridyl ligands enhances ortho selectivity (Figure 3). We propose that
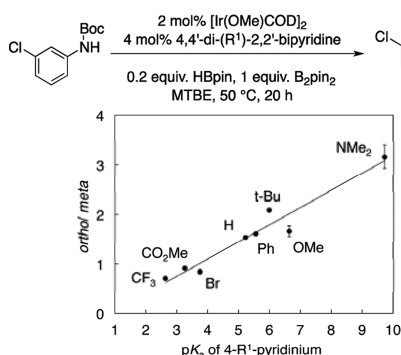
Figure 3. Plot of the ortho/meta product ratios using 4,4′-di(R₁)-2,2′-dipyridyl catalysts vs pK_a's of 4-R¹-pyridium ions.

the pinacolate oxygens in complexes with more electron-rich dipyridyl ligands are more basic, and this accounts for the increased ortho selectivity. While more electron-rich dipyridyl ligands have been shown to increase borylation rates,[13] this is the first case where dipyridyl electronic effects significantly alter regioselectivities.

The mechanism of the ortho direction and an explanation of its failure with **12c** was clarified by theoretical calculations. In M06/SDD(Ir)/6-31+G**(C H O N B) calculations, a series of TSs were located for C−H activation of PhNHCO₂Me by the model complex (bpy)Ir(Beg)₃ (**15**, eg = ethyleneglycolate). These calculations predict the ortho borylation to be strongly favored, and the TS (Figure 4) shows a clear NH−O H-bond. The
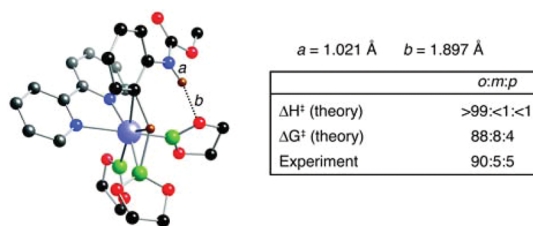
Figure 4. Lowest energy TS for C−H activation of PhNHCO₂Me by model complex **15**. The *o:m:p* ratios predicted by theory and those found for borylation catalyzed by **2** are given.

predicted *o:m:p* ratio (based on the lowest-energy TSs for each possibility) is 88:8:4, which is very close to the experimental value for borylation of PhNHCO₂Me by **2** (*o:m:p* = 90:5:5 from GC-FID). The experimental ratio is a direct measurement of relative rates for directed and nondirected borylation. The agreement between theory and experiment strongly supports the NH−O H-bonding mechanism. The calculated ortho TS also suggests a steric explanation for the failure of H-bonding direction in **12c**; when the OCH₃ of the carbamate is replaced by an ethyl group and the Beg groups are replaced by BPin groups,

there is a tight steric interaction (with H−H distances <1.0 Å) that would preclude the ortho structure. An interesting observation is that the ortho transition structure is very strongly favored enthalpically, but the restricted motion associated with the H-bond is disfavored entropically, so the final selectivity is limited by entropy/enthalpy compensation.

For Boc-protected anilines with a single meta substituent, there is a trade-off between H-bond direction and the usual preference for reaction at the least hindered position (Table 1,

**Table 1. ortho-Borylation of *N*-(Boc)-Anilines**[a]

[a]See Supporting Information for details on conditions. Yields refer to isolated material except as noted. [b]Yield determined by ¹H NMR. [c]Yield is for the major isomer. [d]Isolated as a 92:8 mixture.

entry 1). This is not an issue for 4-substituted substrates where the ortho selectivity is high. Except for the fluorine-substituted substrates in entries 5 and 6, these products were isolated as single regioisomers. For entries 11 and 12, 3 equiv of arene were used to minimize diborylation. Converting Bpin products to their BF₃K salts can in cases ease isolation, leading to the higher yield in entry 12 versus 11. All regiochemical assignments were based on NMR spectroscopy and confirmed by X-ray crystallography for entries 4 and 7−9.

Entry 2 in Table 1 shows that substrates with more acidic protons are viable through in situ protection as borates by excess pinacolborane. Entries 1, 3−7, and 10 produce boronates with halogen groups that can be further manipulated. Entries 11 and 12 are noteworthy because the selectivity diverges from that of the acetamide analog, which borylates ortho to CN exclusively.[14]

The comparison with D*o*M in Scheme 4 highlights the new selectivity offered by H-bond direction. When there is a distinguishable choice among ortho C−H bonds, D*o*M is dominated by acidity. Thus, for substrates **16** and **17** (entries 5 and 7 in Table 1), the more acidic C−H bonds flanked by NHBoc and a halogen will metalate first.[15] In contrast the Ir-catalyzed process is selective for the less hindered C−H bond ortho to NHBoc. For substrates **18** and **19**, the O-aryl carbamate is a stronger director for DoM than NHBoc, but it provides no H-bond. Consequently, the preferred site for C−H borylation is the

Scheme 4. C−H Borylation and DoM Regioselectivities
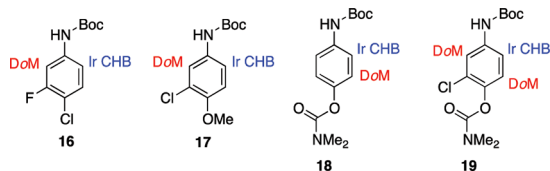
least reactive position for DoM. *These examples clearly show that C−H borylation via an outer-sphere H-bonding mechanism gives regioselectivities that are unprecedented for DoM.* It is noteworthy that C−H borylations of substrates in Scheme 4 do not require low temperatures that must be maintained during DoM to minimize generation of benzyne intermediates.[15,16]

Finally, this chemistry can be extended to Boc-protected enamines such as **20** where the regioselectivity for the vinyl C−H that is β to N exceeds 99:1. *Remarkably, the Ph C−H bonds and the stereochemistry of the double bond in product **21** are unperturbed.* Recent reports reflect interest in borylenamines and related compounds,[17] including a route using C−H borylation,[17c] but the reaction here provides a *cis* disposition of N and B groups that is unavailable by other methods.

In summary, we have shown that the NHBoc group offers ortho selectivity in Ir-catalyzed C−H borylation that cannot be obtained with DoM, or any other methodology. Experiment and theory make a convincing case for an outer-sphere mechanism were the NHBoc proton bonds to Bpin oxygen in the TS. We currently are applying this chemistry in synthesis and are pursuing more general strategies for outer-sphere directed C−H borylations.
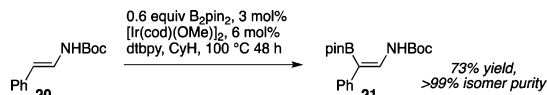
■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full characterization, copies of all spectral data, experimental procedures, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

singleton@mail.chem.tamu.edu; maleczka@chemisty.msu.edu; smithmil@msu.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Diaz-Requejo, M. M.; Perez, P. J. *Chem. Rev.* **2008**, *108*, 3379. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(2) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(3) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206. (b) Hurst, T. E.; Macklin, T. K.; Becker, M.; Hartmann, E.; Kügel, W.; Parisienne-La Salle, J. C.; Batsanov, A. S.; Marder, T. B.; Snieckus, V. *Chem.—Eur. J.* **2010**, *16*, 8155.

(4) (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (b) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058. (c) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159. (d) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068. (e) Ros, A.; Estepa, B.; Lopez-Rodriguez, R.; Alvarez, E.; Fernandez, R.; Lassaletta, J. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11724. (f) Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 134. (g) Ros, A.; Lopez-Rodriguez, R.; Estepa, B.; Alvarez, E.; Fernandez, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 4573. (h) Xiao, B.; Li, Y.-M.; Liu, Z.-J.; Yang, H.-Y.; Fu, Y. *Chem. Commun.* **2012**, *48*, 4854.

(5) (a) Although "outer-sphere" commonly refers to eletron transfer, it has been used to describe mechanisms for hydrogen transfer and nucleophilic addition to π-allyl Pd compounds: Samec, J. S. M.; Backvall, J. E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237. (b) Trost, B. M.; Xu, J. Y.; Schmidt, T. *J. Am. Chem. Soc.* **2009**, *131*, 18343.

(6) (a) Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941. (b) Fackler, P.; Berthold, C.; Voss, F.; Bach, T. *J. Am. Chem. Soc.* **2010**, *132*, 15911. (c) Vetticatt, M. J.; Desai, A. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 13104.

(7) (a) Chotana, G. A.; Vanchura, B. A., II; Tse, M. K.; Staples, R. J.; Maleczka, R. E., Jr; Smith, M. R., III. *Chem. Commun.* **2009**, 5731. (b) Vanchura, B. A., II; Preshlock, S. M.; Roosen, P. C.; Kallepalli, V. A.; Staples, R. J.; Maleczka, R. E., Jr; Singleton, D. A.; Smith, M. R., III. *Chem. Commun.* **2010**, *46*, 7724.

(8) (a) The originally proposed Ir^III/V mechanism[8a] has been supported both computationally[8b] and exprimentally[8c]: (a) Cho, J. Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305. (b) Tamura, H.; Yamazaki, H.; Sato, H.; Sakaki, S. *J. Am. Chem. Soc.* **2003**, *125*, 16114. (c) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.

(9) (a) Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 5115. (b) Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378.

(10) (a) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004. (b) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E., Jr.; Smith, M. R., III. *J. Org. Chem.* **2009**, *74*, 9199. (c) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946.

(11) In ref 3b, the following observation was noted: "For reasons currently unappreciated, *N-tert*-butoxycarbonyl 3-methoxyaniline led to mixtures of unidentified products."

(12) Lequestel, J. Y.; Laurence, C.; Lachkar, A.; Helbert, M.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2091.

(13) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056.

(14) Chotana, G. A.; Rak, M. A.; Smith, M. R., III. *J. Am. Chem. Soc.* **2005**, *127*, 10539.

(15) Mayes, B. A.; Chaudhuri, N. C.; Hencken, C. P.; Jeannot, F.; Latham, G. M.; Mathieu, S.; McGarry, F. P.; Stewart, A. J.; Wang, J. Y.; Moussa, A. *Org. Process Res. Dev.* **2010**, *14*, 1248.

(16) (a) Clark, R. D.; Caroon, J. M. *J. Org. Chem.* **1982**, *47*, 2804. (b) Reavill, D. R.; Richardson, S. K. *Synth. Commun.* **1990**, *20*, 1422. (c) Yoshida, Y.; Hamada, Y.; Umezu, K.; Tabuchi, F. *Org. Process Res. Dev.* **2004**, *8*, 958.

(17) (a) He, Z.; Yudin, A. K. *J. Am. Chem. Soc.* **2011**, *133*, 13770. (b) Hussain, N.; Hussain, M. M.; Ziauddin, M.; Triyawatanyu, P.; Walsh, P. J. *Org. Lett.* **2011**, *13*, 6464. (c) Takaya, J.; Kirai, N.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 12980.