JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

# Retention or Inversion in Stereospecific Nickel-Catalyzed Cross-Coupling of Benzylic Carbamates with Arylboronic Esters: Control of Absolute Stereochemistry with an Achiral Catalyst

Michael R. Harris,[†] Luke E. Hanna,[†] Margaret A. Greene,[†] Curtis E. Moore,[‡] and Elizabeth R. Jarvo*[,†]

[†]Department of Chemistry, 4114 Natural Sciences 1, University of California, Irvine, California 92697, United States

[‡]Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, MC 0358, La Jolla, California 92093, United States

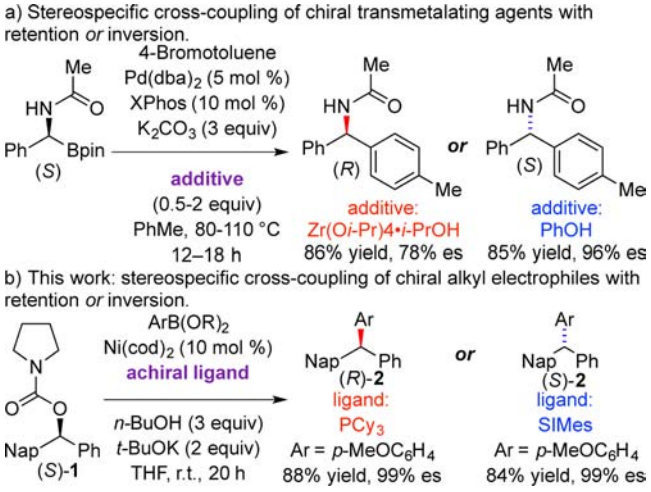
Supporting Information

**ABSTRACT:** Stereospecific coupling of benzylic carbamates and pivalates with aryl- and heteroarylboronic esters has been developed. The reaction proceeds with selective inversion or retention at the electrophilic carbon, depending on the nature of the ligand. Tricyclohexylphosphine ligand provides the product with retention, while an N-heterocyclic carbene ligand provides the product with inversion.

The mechanisms of alkyl cross-coupling reactions are hard-wired with implications for the stereochemical outcome at the reactive center.[1] Simple changes to the reaction conditions do not typically perturb the inherent bias for racemization, retention, or inversion at the reactive center. For example, palladium-catalyzed reactions of alkyl electrophiles are typically stereospecific and proceed with inversion at the stereogenic center,[2,3] while nickel-catalyzed reactions of alkyl halides proceed with racemization at the electrophilic carbon[4] and judicious use of a chiral catalyst permits stereoconvergent reactions.[5] Overcoming the intrinsic preference of a reaction that typically proceeds with inversion at the stereogenic center to make it proceed with retention is quite unusual and requires a significant change to the mechanism of the transformation. For stereospecific reactions, special cases using $\alpha$-chiral *transmetalating agents* have been reported in which modification of the reaction conditions or substrate structure can affect a switch in the sense of the absolute stereochemistry.[6] Transmetalation typically occurs with retention at the stereogenic center;[7,8] select examples that proceed with inversion have been reported.[9] In seminal contributions, Hiyama demonstrated that palladium-catalyzed couplings of alkylsilanes could proceed with retention or inversion, depending on the reaction conditions.[10] Recently, the Suginome group has developed stereodivergent reactions of $\alpha$-(acetylamino)benzylboronic esters that are controlled by the choice of additive to afford either retention or inversion selectively (Scheme 1a).[11,12]

In this communication, we demonstrate catalyst control of the stereochemical course with respect to the *electrophilic* partner in a cross-coupling reaction. Stereospecific nickel-catalyzed cross-coupling reactions of benzylic alcohol derivatives typically proceed with inversion at the electrophilic carbon.[13,14] Here we report nickel-catalyzed cross-coupling of benzylic esters in which the achiral ligand structure dictates whether the reaction proceeds with retention or inversion (Scheme 1b). Use of SIMes, an N-heterocyclic carbene (NHC) ligand, affords inversion, while $PCy_3$ gives retention. To the best of our knowledge, these results constitute the first cross-coupling reactions of alkyl electrophiles that undergo two distinct stereospecific mechanistic pathways to provide either retention or inversion at the electrophilic carbon.

**Scheme 1. Control of Product Stereochemistry in Stereospecific Reactions**




In previous work, we established the synthesis of enantioenriched triarylmethanes by stereospecific nickel-catalyzed cross-coupling of ethers with aryl Grignard reagents.[13b] The triarylmethane moiety is present in medicinal chemistry targets, natural products, and synthetic materials.[15,16] Despite recent advances in the preparation of racemic triarylmethanes,[17] there are few methods for their enantioselective synthesis.[18] As part of our ongoing interest in developing nickel-catalyzed stereospecific reactions of alkyl electrophiles, we chose to examine cross-coupling reactions of arylboronic esters for triarylmethane synthesis. The functional group tolerance and ready availability of a wide range of boronic esters makes them attractive coupling partners.

**Received:** December 3, 2012
**Published:** February 18, 2013





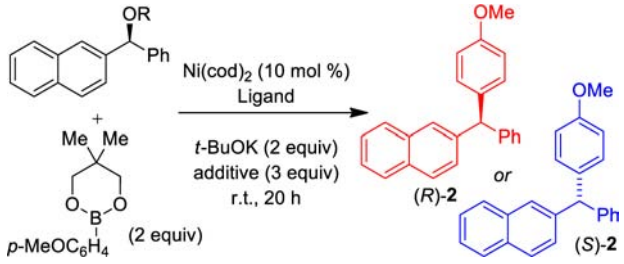
dx.doi.org/10.1021/ja311783k | J. Am. Chem. Soc. 2013, 135, 3303−3306

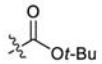
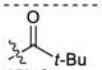
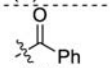
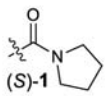
We began by examining a range of benzylic alcohol derivatives (Table 1). Our initial reaction conditions resulted in modest conversion of carbonate (*S*)-**3** and low enantiospecificity (es) (entry 1).[19] To our surprise, in contrast to the Kumada coupling, the product, (*R*)-**2**, resulted from *retention* at the electrophilic carbon. An improvement to 43% es was observed when the solvent was changed from toluene to tetrahydrofuran (THF) (entry 2). Alcohol additives further improved the yield and stereochemical fidelity of the reaction, with *n*-BuOH providing the highest es (87%; entry 4). More sterically encumbered alcohols provided more modest improvements, while water and the electron-deficient alcohol trifluoroethanol proved detrimental to the reaction (entries 3, 5, and 7). The enantiospecificity of the reaction showed a marked dependence on the identity of the leaving group. While the use of pivalate (*S*)-**4** in the cross-coupling reaction resulted in lower enantiomeric excess of the product (entry 8), the benzoate and carbamate derivatives (*S*)-**5** and (*S*)-**1** showed a significant increase in product ee, providing 91 and 95% es, respectively (entries 10 and 12). An additional small improvement in yield and es resulted from using a 1:1 THF/toluene mixture as the solvent (cf. entries 12 and 15).

We examined other ligands[20] under the reaction conditions and found that the NHC ligand SIMes[21] afforded comparable yields and enantiospecificity of **2**, but the major product was the *S* enantiomer, resulting from *inversion* at the electrophilic carbon.[22] Catalyst control of the stereochemical outcome of the reaction was consistent across the range of esters and carbamates that we examined: $PCy_3$ and SIMes reliably afforded opposite enantiomers of the product (Table 1, entries 8−11, 15, and 16).[23] Under the optimal reaction conditions, addition of *n*-BuOH was found to the improve stereochemical fidelity when either ligand was used (cf. entries 13−16).

Having optimized the reaction conditions for stereospecfic synthesis of either enantiomer of the product, we turned our attention to the scope of the reaction with respect to the boronic ester (Table 2). Electron-donating and -withdrawing substituents on the arylboronic ester were well-tolerated under the reaction conditions (entries 1−8), which are mild and allow for broad functional group tolerance. Boronic esters containing ketone, free alcohol, and carbamate functional groups all coupled in good yield and es (entries 9−14). Boronic esters containing heterocyclic groups, including pyrimidine, furan, and indole, underwent smooth cross-coupling (entries 15−20). The reaction conditions developed for the formation of either enantiomer of **2** were general across the range of boronic esters that we examined: of 20 examples, 18 provided high es. Therefore, either enantiomer of a given product can be obtained from the same enantiomer of the starting material through the use of the appropriate ligand, $PCy_3$ or SIMes.

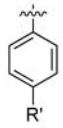
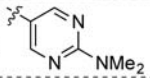
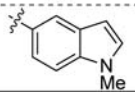
**Table 1. Optimization of the Reaction Conditions**




| Entry | R | ligand[a] | solvent | additive | % yield[b] | es[c] | retention/ inversion |
|---|---|---|---|---|---|---|---|
| 1 |  (S)-3 | $PCy_3$ | PhMe | none | 46 | 7 | retention |
| 2 | | $PCy_3$ | THF | none | 53 | 43 | retention |
| 3 | | $PCy_3$ | THF | $H_2O$ | 74 | 10 | retention |
| 4 | | $PCy_3$ | THF | *n*-BuOH | 76 | 87 | retention |
| 5 | | $PCy_3$ | THF | *i*-PrOH | 46 | 78 | retention |
| 6 | | $PCy_3$ | THF | *t*-BuOH | 55 | 43 | retention |
| 7 | | $PCy_3$ | THF | $F_3CCH_2OH$ | < 5 | na | retention |
| 8 |  (S)-4 | $PCy_3$ | THF | *n*-BuOH | 53 | 76 | retention |
| 9 | | SIMes | THF | *n*-BuOH | 60 | 77 | inversion |
| 10 |  (S)-5 | $PCy_3$ | THF | *n*-BuOH | 57 | 91 | retention |
| 11 | | SIMes | THF | *n*-BuOH | 83 | >99 | inversion |
| 12 |  (S)-1 | $PCy_3$ | THF | *n*-BuOH | 62 | 95 | retention |
| 13 | | $PCy_3$ | THF/PhMe | none | 67 | 35 | retention |
| 14 | | SIMes | THF/PhMe | none | 82 | 92 | inversion |
| **15** | | **$PCy_3$** | **THF/PhMe** | ***n*-BuOH** | **88** | **99** | **retention** |
| **16** | | **SIMes** | **THF/PhMe** | ***n*-BuOH** | **84** | **99** | **inversion** |

[a]$PCy_3$ (20 mol %); SIMes (11 mol %). [b]Isolated yields after column chromatography. [c]Enantiospecificity (es) = $(ee_{product}/ee_{starting\ material}) \times 100\%$.

**Table 2. Scope with Respect to Arylboronic Esters[a]**

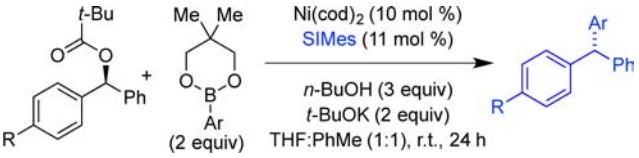

| Entry | Ar | ligand[b] | yield (%)[c] | SM ee (%)[d] | product ee (%)[d] | es (%) | retention/ inversion |
|---|---|---|---|---|---|---|---|
| 1 | R' = OMe | $PCy_3$ | 88 | 93 | 92 | 98 | retention |
| 2 |  OMe | SIMes | 84 | 93 | 93 | >99 | inversion |
| 3 | $NMe_2$ | $PCy_3$ | 86 | 93 | 92 | 99 | retention |
| 4 | $NMe_2$ | SIMes | 71 | 93 | 92 | 98 | inversion |
| 5 | F | $PCy_3$ | 82 | 93 | 90 | 97 | retention |
| 6 | F | SIMes | 80 | 97 | 88 | 91 | inversion |
| 7 | $CF_3$ | $PCy_3$ | 88 | 97 | 57 | 59 | retention |
| 8 | $CF_3$ | SIMes | 70 | 93 | 91 | 98 | inversion |
| 9 | COMe | $PCy_3$ | 76 | 93 | 89 | 96 | retention |
| 10 | COMe | SIMes | 98 | 98 | 97 | 99 | inversion |
| 11 | $CH_2OH$ | $PCy_3$ | 67 | 93 | 82 | 88 | retention |
| 12 | $CH_2OH$ | SIMes | 0 | 97 | ND | ND | ND |
| 13 | $CH_2NHBoc$ | $PCy_3$ | 84 | 93 | 91 | 98 | retention |
| 14 | $CH_2NHBoc$ | SIMes | 94 | 98 | 97 | 97 | inversion |
| 15 |  | $PCy_3$ | 86 | 93 | 89 | 96 | retention |
| 16[e] | | SIMes | 75 | 98 | 92 | 94 | inversion |
| 17 |  | $PCy_3$ | 79 | 93 | 94 | >99 | retention |
| 18 | | SIMes | 65 | 98 | 83 | 85 | inversion |
| 19 |  | $PCy_3$ | 90 | 93 | 93 | 99 | retention |
| 20 | | SIMes | 71 | 93 | 92 | 98 | inversion |

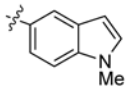
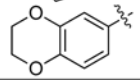
[a]All data are averages of two experiments, unless otherwise indicated. [b]$PCy_3$ (20 mol %); SIMes (11 mol %). [c]Isolated yields after column chromatography. [d]Determined by chiral supercritical fluid chromatography (SFC). [e]Data were obtained from a single experiment.


dx.doi.org/10.1021/ja311783k | *J. Am. Chem. Soc.* 2013, 135, 3303−3306

We set as our goal the cross-coupling of oxidative addition partners that do not include a naphthylene moiety. These electrophiles are typically less reactive in cross-coupling reactions[13c] and were found not to be competent for triarylmethane synthesis via Kumada coupling.[13b] Indeed, neither the corresponding carbamates nor the use of $PCy_3$ as ligand provided acceptable yields of product. However, benzhydril pivalates underwent smooth cross-coupling under our optimized reaction conditions when SIMes was used as the ligand (Table 3). Efficient cross-coupling was achieved for

**Table 3. Scope of Oxidative Addition Partners**[a]




| Entry | R | Ar | yield (%)[b] | SM ee (%)[c] | product ee (%)[c] | es (%) |
|---|---|---|---|---|---|---|
| 1 | Ph | *p*-$MeOC_6H_4$ | 85 | 96 | 84 | 88 |
| 2 | Ph | *p*-$(Me_2N)C_6H_4$ | 75 | 82 | 79 | 96 |
| 3 | Ph | *p*-$(BocNHCH_2)C_6H_4$ | 54 | 98 | 92 | 94 |
| 4 | Ph |  | 66 | 96 | 96 | >99 |
| 5 |  | | 80 | 93 | 87 | 94 |
| 6 |  | | 60 | 93 | 93 | 99 |

[a]All data are averages of two experiments. [b]Isolated yields after column chromatography. [c]Determined by chiral SFC.

pivalates with a range of arylboronic esters, including an indoleboronic ester (entries 1–4). Functionality on the electrophile was also tolerated: furan- and benzodioxane-substituted pivalates coupled in good yield with excellent es (entries 5 and 6).

In summary, we have developed a nickel-catalyzed Suzuki–Miyaura cross-coupling reaction for the synthesis of enantioenriched triarylmethanes. The reaction proceeds with high stereochemical fidelity. The choice of achiral ligand controls whether the reaction proceeds with inversion or retention at the electrophilic carbon, and therefore, either enantiomer of the product can be formed from a single enantiomer of the starting material. This method expands the range of triarylmethanes that can be prepared in enantioenriched form, as simple benzhydril pivalates and a variety of functionalized arylboronic esters (including ones containing heterocyclic groups) can be used in the reaction. Efforts to expand further the scope of the reaction and elucidate the mechanistic details are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and characterization data, including X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

erjarvo@uci.edu

### Author Contributions

‡C.E.M. solved the X-ray structure of the compound in Table 2, entry 19 (*S* enantiomer).

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by NIH NIGMS (R01GM100212), the University of California Cancer Research Coordinating Committee, the University of California (Chancellor's Fellowship to M.R.H.), the Ford Family Foundation (predoctoral fellowship to M.R.H.), and DOE (GAANN PA200A120070 to L.E.H.). We thank Frontier Scientific for generous donations of boronic acids. Dr. Joseph Ziller and Dr. John Greaves are acknowledged for X-ray crystallographic and mass spectrometry data, respectively.

## ■ REFERENCES

(1) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.
(2) (a) Lau, K. S. Y.; Fries, R. W.; Stille, J. K. *J. Am. Chem. Soc.* **1974**, *96*, 4983. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. (c) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235. (d) Rodriquez, N.; de Arellano, C. R.; Asensio, G.; Medio-Simon, M. *Chem.—Eur. J.* **2007**, *13*, 4223. (e) Lopez-Perez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514. (f) He, A.; Falck, J. R. *J. Am. Chem. Soc.* **2010**, *132*, 2524. (g) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485.
(3) Pd-catalyzed *allylic* substitutions can occur with inversion or retention, depending on the nucleophile. See: Trost, B. M.; VanVranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
(4) Stille, J. K.; Cowell, A. B. *J. Organomet. Chem.* **1977**, *124*, 253.
(5) (a) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694. (b) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794 and references cited therein. (c) Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8347.
(6) For a discussion, see: Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 16856.
(7) For labeling studies, see: (a) Bock, P. L.; Boschetto, D. J.; Rasmussen, J. R.; Demers, J. P.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 2814. (b) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458. (c) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461. (d) Taylor, B. L. H.; Jarvo, E. R. *J. Org. Chem.* **2011**, *76*, 7573.
(8) (a) Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1. (b) Hölzer, B.; Hoffmann, R. W. *Chem. Commun.* **2003**, 732. (c) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (d) Lange, H.; Fröhlich, R.; Hoppe, D. *Tetrahedron* **2008**, *64*, 9123. (e) Imao, D.; Glasspoole, B. W.; Laberge, S. V.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (f) Li, H.; He, A.; Falck, J. R.; Liebeskind, L. S. *Org. Lett.* **2011**, *13*, 3682. (g) Reference 5.
(9) (a) LaBadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 669. (b) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666. (c) Sandrock, D. L.; Jean-Gérard, L.; Chen, C.-Y.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 17108. (d) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (e) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894.
(10) (a) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793. (b) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58.
(11) (a) Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738. (b) Reference 9d.
(12) For enantiodivergent reactions of alkyllithium reagents, see: Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. M. *Nature* **2008**, *456*, 778.
(13) (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (b) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790. (c) Greene, M. A.;

Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293. (d) For a review, see: Taylor, B. L. H.; Jarvo, E. R. *Synlett* **2011**, 2761.
(14) For recent studies of the stereochemical course of nickel-catalyzed reactions of epoxides and aziridines, see: (a) Beaver, M. G.; Jamison, T. F. *Org. Lett.* **2011**, *13*, 4140. (b) Sylvester, K. T.; Wu, K.; Doyle, A. G. *J. Am. Chem. Soc.* **2012**, *134*, 9541. (c) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890.
(15) For biological activity, see: (a) Palchaudhuri, R.; Nesterenko, V.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 10274. (b) Shagufta; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S. R.; Panda, G. *Bioorg. Med. Chem.* **2006**, *14*, 1497. (c) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289. (d) Ellsworth, B. A.; Ewing, W. R.; Jurica, E. U.S. Patent Appl. 2011/0082165A1, Apr 7, 2011. (e) Baba, K.; Maeda, K.; Tabata, Y.; Doi, M.; Kozawa, M. *Chem. Pharm. Bull.* **1988**, *36*, 2977. For materials, see: (f) Herron, N.; Johansson, G. A.; Radu, N. S. U.S. Patent Appl. 2005/0187364, Aug 25, 2005. (g) Xu, Y.-Q.; Lu, J.-M.; Li, N.-J.; Yan, F.; Xia, X.; Xu, Q. *Eur. Polym. J.* **2008**, *44*, 2404.
(16) For physical properties of triarylmethanes, see: (a) Breslow, R.; Chu, W. *J. Am. Chem. Soc.* **1973**, *95*, 411. (b) Finocchiaro, P.; Gust, D.; Mislow, K. *J. Am. Chem. Soc.* **1974**, *96*, 3198. (c) Duxbury, D. F. *Chem. Rev.* **1993**, *93*, 381.
(17) (a) Zhang, J.; Bellomo, A.; Creamer, A. D.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 13765. (b) Yu, J.-Y.; Kuwano, R. *Org. Lett.* **2008**, *10*, 973. (c) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198. (d) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817. (e) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913. (f) For a representative Freidel–Crafts strategy, see: Esquivias, J.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629.
(18) (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (b) Sun, F.-L.; Zheng, X.-J.; Gu, Q.; He, Q.-L.; You, S.-L. *Eur. J. Org. Chem.* **2010**, 47.
(19) For es, see: Denmark, S. E.; Vogler, T. *Chem.—Eur. J* **2009**, *15*, 11737.
(20) For results with other ligands, see the Supporting Information (SI).
(21) SIMes = 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate.
(22) We hypothesize that ligation of the carbamate to the nickel complex directs the oxidative addition when $PCy_3$ is employed (see Scheme SI4 in the SI). For a comparison of NHC and $PR_3$ ligands, see: Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841.
(23) Changing the $PCy_3$ loading from 20 to 11 mol % did not affect the stereochemical outcome (see the SI).