

# Efficient Asymmetric Synthesis of *P*-Chiral Phosphine Oxides via Properly Designed and Activated Benzoxazaphosphinine-2-oxide Agents

Zhengxu S. Han,\* Navneet Goyal, Melissa A. Herbage, Joshua D. Sieber, Bo Qu, Yibo Xu, Zhibin, Li, Jonathan T. Reeves, Jean-Nicolas Desrosiers, Shengli Ma, Nelu Grinberg, Heewon Lee, Hari P. R. Mangunuru,<sup>†</sup> Yongda Zhang, Dhileep Krishnamurthy, Bruce Z. Lu, Jinhua J. Song, Guijun Wang,<sup>†</sup> and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc., 900 Old Ridgebury Road, P.O. Box 368, Ridgefield, Connecticut 06877, United States

## Supporting Information

**ABSTRACT:** A general, efficient, and highly diastereoselective method for the synthesis of structurally and sterically diverse *P*-chiral phosphine oxides was developed. The method relies on sequential nucleophilic substitution on the versatile chiral phosphinyl transfer agent 1,3,2-benzoxazaphosphinine-2-oxide, which features enhanced and differentiated P–N and P–O bond reactivity toward nucleophiles. The reactivities of both bonds are fine-tuned to allow cleavage to occur even with sterically hindered nucleophiles under mild conditions.

For decades, chemists have been interested in the asymmetric synthesis of *P*-chiral phosphines because of their proven ability to impart excellent enantioselectivities in either transition-metal-catalyzed asymmetric processes<sup>1</sup> or as organocatalysts.<sup>2</sup> Although the prominent *P*-chiral ligand DIPAMP was prepared by Knowles and co-workers in the 1970s,<sup>3</sup> methods for the synthesis of optically active *P*-chiral phosphines have emerged slowly. Representative methods include the formation and separation of diastereomeric mixtures of menthyl phosphinates,<sup>4</sup> auxiliary-based transformations,<sup>5,6</sup> enantioselective deprotonation of phosphine–boranes and sulfides,<sup>7</sup> enzymatic resolution,<sup>8</sup> transition-metal-catalyzed asymmetric phosphine alkylations,<sup>9</sup> dynamic kinetic asymmetric oxidation of racemic phosphines,<sup>10</sup> and transformations of H-menthyl phosphinates.<sup>11</sup> Despite these elegant approaches, the currently available methods are often limited in terms of substrate scope and practicality, especially for the synthesis of sterically crowded *P*-chiral phosphines.

We have long been interested in developing an efficient and general method to prepare structurally, electronically, and sterically diverse *P*-chiral phosphine ligands to fine-tune the stereoselectivities of our many asymmetric processes. Recently, we developed a series of powerful bulky *P*-chiral phosphine ligands, such as MeO-BIBOP (I), MeO-BOP (II), and *P*-chiral biaryl ligands (III) (Figure 1), that have been effectively applied to a wide range of transformations, including Cu-catalyzed asymmetric propargylation,<sup>12a</sup> Rh-catalyzed asymmetric hydrogenation,<sup>12b</sup> and Pd-catalyzed asymmetric Suzuki–Miyaura coupling<sup>12c</sup> and Miyaura borylation reactions,<sup>12d</sup> with high stereoselectivities. Ligands I–III were all prepared from a key

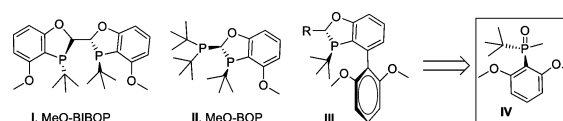
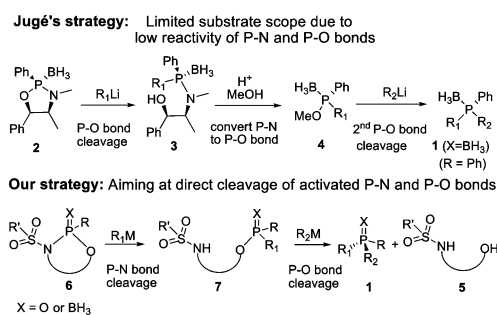


Figure 1. Bulky *P*-chiral phosphines with MeO functionality.

building block, the bulky *P*-chiral phosphine oxide IV. Unfortunately, attempts to synthesize IV in a stereoselective fashion using existing methods were unsuccessful, and we had to resort to a resolution-based route, which was a very tedious process. In searching for an efficient asymmetric route for the synthesis of IV and related structures, we designed and developed a new general method for the efficient and stereoselective synthesis of *P*-chiral phosphine oxides (1) with diverse structures and functionalities from the well-designed chiral phosphinyl transfer agent 1,3,2-benzoxazaphosphinine-2-oxide (Scheme 1).

## Scheme 1. Strategy for the Synthesis of 1



Chiral amino alcohols have been employed as chiral auxiliaries for the asymmetric synthesis of *P*-chiral phosphines. Jugé and co-workers have elegantly demonstrated that the ephedrine-derived chiral template 2 can be opened by organolithium reagents stereospecifically to give 3. Subsequent methanolysis can cleave the P–N bond to generate intermediate 4 containing a second P–O bond, which can then be displaced with another

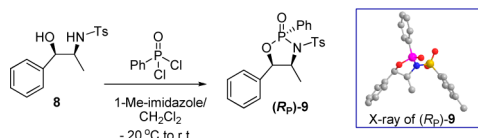
Received: December 26, 2012

organolithium reagent to furnish *P*-chiral phosphine derivatives (Scheme 1).<sup>6</sup> The methanolysis to convert the P–N bond in **3** to the P–O bond in **4** is necessary because of the inertness of the P–N bond toward attack by carbon-based organometallic nucleophiles. Indeed, direct cleavage of the P–N bond in **3** with a carbon nucleophile has not been achieved to date. The generally low reactivity of the P–O and P–N bonds in these chiral templates has also restricted the substrate scope and rendered this method unsuitable for the synthesis of sterically hindered *P*-chiral building blocks such as **IV**. Bulky organolithium reagents either do not react with **2** or require more forcing conditions that can result in partial loss of stereospecificity during nucleophilic substitution at the P center.<sup>13</sup>

To overcome these limitations and develop a method with broad applicability, we designed a strategy in which the P–N bond is activated by an arylsulfonyl group on the N atom (Scheme 1). On the basis of our prior experience from the synthesis of chiral sulfinamides and sulfoxides, we anticipated that the P–N and P–O bonds in chiral template **6** would have differentiated bond strengths and therefore differentiated reactivity toward nucleophilic substitutions.<sup>14</sup> Thus, the sequential cleavage of the P–N bond and the P–O bond in **6** by two different organometallic reagents was expected to provide **1**.

Initially, compound **8** derived from *N*-*p*-tolylsulfonyl-(1*R*,2*S*)-norephedrine (Scheme 2) was examined to test this strategy.

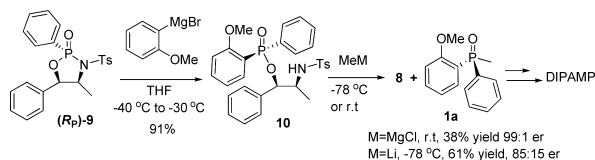
#### Scheme 2. Synthesis of Enantiomerically Pure (*R<sub>p</sub>*)-9



Reaction conditions were surveyed for the synthesis of 1,3,2-oxazaphospholidine-2-oxide (*R<sub>p</sub>*)-**9**. The selectivity depended on the nature of the base and solvent.<sup>15</sup> The use of 1-methylimidazole (1-MeIm) in dichloromethane (DCM) gave the highest dr (97:3). (*R<sub>p</sub>*)-**9** is a crystalline solid, and its diastereomerically pure form was obtained by recrystallization. The absolute stereochemistry was unambiguously confirmed by single-crystal X-ray crystallography.<sup>16</sup> This methodology is amenable to large-scale synthesis, and >100 g of (*R<sub>p</sub>*)-**9** was readily prepared in 75% yield with 99.5:0.5 dr.

Chiral template (*R<sub>p</sub>*)-**9** was then examined for chemoselective P–N and P–O bond cleavage to synthesize **1a**, a key chiral starting material for DIPAMP (Scheme 3). Treatment of (*R<sub>p</sub>*)-**9**

#### Scheme 3. Synthesis of **1a** through (*R<sub>p</sub>*)-9



with 2-MeO-PhMgBr in tetrahydrofuran (THF) at –40 °C to –30 °C exclusively cleaved the sulfonyl-activated P–N bond with inversion of configuration at P,<sup>16</sup> affording phosphinate **10** as a diastereomerically pure crystalline product in 91% isolated yield. Notably, the introduction of the tosyl group enhanced the electrophilicity of the P–N bond in such a way that it was cleaved

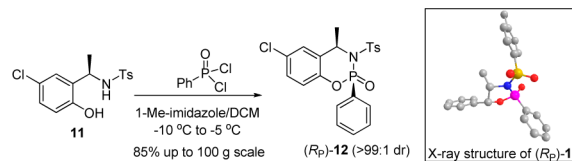
in preference to the P–O bond. This is in contrast to the relative bond strength of the P–O and P–N bonds in Jugé's chiral template **2**.

Cleavage of the P–O bond in **10** by treatment with MeMgCl was then studied. The reaction was sluggish even at ambient temperature with 6 equiv of MeMgCl, providing (*S*)-**1a**<sup>10a</sup> with inversion of configuration at P in only 38% yield, albeit with excellent stereoselectivity (99:1 er). Elevating the temperature failed to improve the yield of **1a**, and many impurities formed. Switching to the more active nucleophile MeLi (4 equiv) improved the yield to 61%, but the stereoselectivity suffered, as **1a** was obtained with 85:15 er. Additionally, the substrate scope was limited, as even slightly hindered lithium reagents such as EtLi or *i*PrLi provided the respective products in very poor yields (Scheme 3). These observations again underscored the challenges associated with the P–O bond cleavage and the need for further activation.

As reported previously,<sup>17a</sup> P–OR bond reactivity is affected by the basicity of the leaving group, which can be predicted by the *pK<sub>a</sub>* of the resultant alcohol ROH: the reactivity of a P–OR bond increases as the *pK<sub>a</sub>* of the resultant ROH decreases. We envisaged that a P–O bond derived from a phenol derivative (*pK<sub>a</sub>* ≈ 10) would be much more reactive than that from an alkyl alcohol backbone (*pK<sub>a</sub>* ≈ 15).<sup>17b</sup> Therefore, the new aminophenol-based auxiliary **11** was designed and readily prepared on a large scale from readily available (*R*)-2-(1-aminoethyl)-4-chlorophenol.<sup>18</sup>

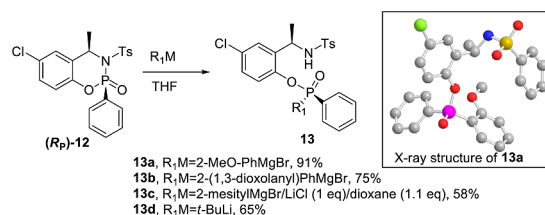
Reaction conditions for the synthesis of (*R<sub>p</sub>*)-**12** in enantiomerically pure form were first examined.<sup>15</sup> Studies showed that, analogous to **8**, high conversion and high diastereoselectivity were observed with 1-MeIm in DCM, yielding (*R<sub>p</sub>*)-**12** with 98:2 dr. Diastereomerically pure (*R<sub>p</sub>*)-**12** was obtained by crystallization, and its absolute configuration was confirmed by X-ray crystallographic analysis (Scheme 4).<sup>16</sup> The synthesis is simple and has been scaled to >100 g in 85% isolated yield.

#### Scheme 4. Synthesis of Enantiomerically Pure (*R<sub>p</sub>*)-12



To demonstrate the potential of this new method, the synthesis of **1a** was first investigated. As anticipated, the reaction of 2-MeO-PhMgBr with (*R<sub>p</sub>*)-**12** in THF at –20 °C selectively cleaved the P–N bond to yield **13a** in 91% yield with inversion of configuration at P, as confirmed by the single crystal X-ray structure (Scheme 5).<sup>16</sup> Notably, the reaction between 4 equiv of MeMgCl and **13a** occurred at –10 °C, cleaving the P–O bond in

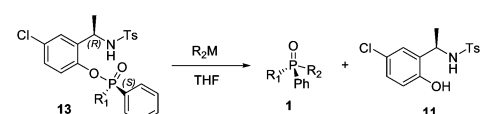
#### Scheme 5. Ring Opening for the Synthesis of **13**



15 min to provide enantiomerically pure (*S*)-**1a**<sup>10a</sup> in 91% yield with inversion of configuration at P (Table 1, entry 1). This indicates that **13a** has a more reactive P–O bond than **10**.

Encouraged by the above results, we examined the synthesis of sterically hindered chiral phosphine oxides from **13a**. While slow reactions were observed when *i*PrMgBr and *t*BuMgCl were used, the P–O bond was cleaved at –70 °C with *i*PrLi and *t*BuLi to furnish **1b** and **1c**, respectively, in good yields with excellent enantiomeric purities (Table 1, entries 2 and 3). Moreover,

Table 1. Synthesis of *P*-Chiral Phosphine Oxides<sup>a</sup>



Entry	13	R <sub>2</sub> M	Product	yield(%)	er <sup>b</sup>
1	<b>13a</b>	MeMgBr	<b>1a</b>	91	>99.5:0.5 <sup>d</sup>
2	<b>13a<sup>c</sup></b>	<i>i</i> PrLi	<b>1b</b>	63	>99.5:0.5 <sup>d</sup>
3	<b>13a</b>	<i>t</i> BuLi	<b>1c</b>	84	98.2:1.8
4	<b>13a</b>	ferrocene-Li	<b>1d</b>	82	99.6:0.4
5	<b>13a</b>	alkene-MgBr	<b>1e</b>	70	>99.5:0.5
6	<b>13a</b>	alkyne-Li	<b>1f</b>	62	95:5
7	<b>13b</b>	MeMgCl	<b>1g</b>	73	99:1
8	<b>13b</b>	ferrocene-Li	<b>1h</b>	82	98:2
9	<b>13c</b>	MeMgCl	<b>1i</b>	73	98.7:1.3
10	<b>13c</b>	ferrocene-Li	<b>1j</b>	58	99.1:0.9

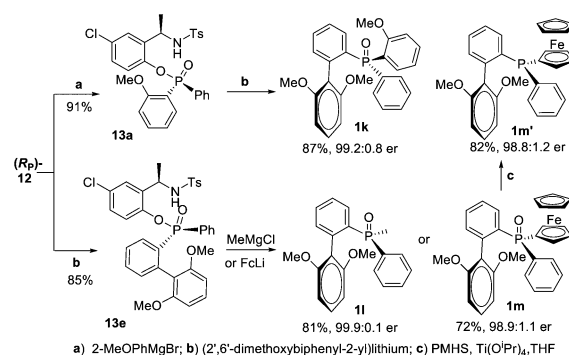
<sup>a</sup>See the SI for the reaction conditions. <sup>b</sup>Measured by chiral HPLC. <sup>c</sup>See the SI for the X-ray structure. <sup>d</sup>The other enantiomer was not observed.

compounds with other functionalities, such as a ferrocene (**1d**), an alkene (**1e**), or an alkyne (**1f**), were readily prepared in good yields and enantiomeric purities (entries 4–6). Notably, **13b** containing a latent aldehyde was a competent coupling partner, allowing the preparation of enantiomerically enriched **1g** and **1h**, which can be used as key precursors for ligand design (entries 7 and 8). Additionally, treatment of (*R<sub>P</sub>*)-**12** with the hindered 2-mesitylmagnesium bromide under Turbo conditions successfully

cleaved the P–N bond to yield **13c**, whereas no reaction was observed between 2-mesityllithium and Juge's chiral template **2**.<sup>1b</sup> From **13c**, compounds **1i** and **1j** were synthesized in good yields and selectivities (entries 9 and 10). (*R<sub>P</sub>*)-**12** was also active toward a hindered alkyl organometallic reagent, and the reaction with *t*BuLi afforded **13d** in good yield. Treatment of (*R<sub>P</sub>*)-**12** with EtMgBr and *i*PrMgBr also furnished the desired products, but in low isolated yields. These results may be due to the acidity of the  $\alpha$ -proton present in the products, and further optimization of the reaction conditions to exploit these nucleophiles is under investigation.

Chiral versions of Buchwald-type ligands can also be prepared effectively using this method (Scheme 6). Treatment of **13a** with

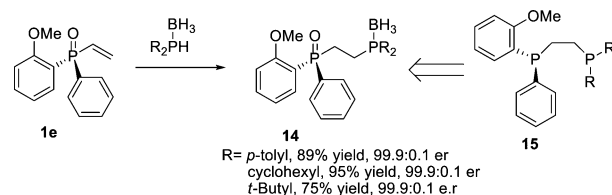
Scheme 6. Synthesis of Chiral Buchwald Ligands



(2',6'-dimethoxybiphenyl-2-yl)lithium (DMOBP-Li) yielded enantiomerically pure **1k** in high yield. The reaction between DMOBP-Li and (*R<sub>P</sub>*)-**12** provided intermediate **13e** in high yield, from which **1l** and **1m** were successfully prepared. Importantly, reduction of **1m** with polymethylhydrosiloxane (PMHS) in the presence of Ti(OiPr)<sub>4</sub> in THF afforded the free phosphine ligand **1m'** in excellent yield without erosion of the enantiopurity.

The structurally diverse chiral phosphine oxides **1** are key starting materials for the design of mono- or bidentate (**15**) *P*-chiral ligands. As a preliminary example, **1e** was reacted with dialkyl- or diarylphosphine–borane adducts, providing enantiomerically pure **14** in high yield (Scheme 7).

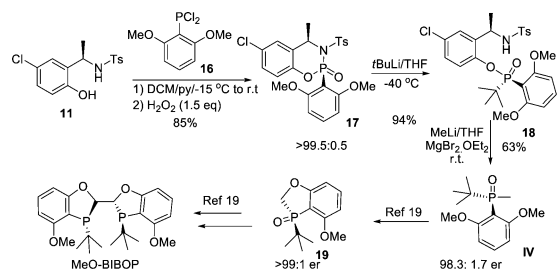
Scheme 7. Synthesis of Bidentate *P*-Chiral Ligands



Finally, the new method was applied to the asymmetric synthesis of the bulky *P*-chiral phosphine oxide **IV** (Scheme 8), which is a versatile intermediate that can be converted into many important *P*-chiral ligands, such as **I–III**.<sup>12,19</sup> Treatment of **11** with dichloro(2,6-dimethoxyphenyl)phosphine (**16**) followed by H<sub>2</sub>O<sub>2</sub> oxidation afforded diastereomerically pure **17** in 85% isolated yield. Treatment of **17** with *t*BuLi at –40 °C gave **18** in excellent yield. Subsequent reaction of **18** with MeLi in the presence of 20 mol % MgBr<sub>2</sub>·OEt<sub>2</sub> afforded sterically hindered intermediate **IV** as a crystalline product in 63% yield with 98.3:1.7 er. According to the literature procedure,<sup>19</sup> conversion



Scheme 8. Effective Synthesis of MeO-BIBOP



of **IV** to **19** was accomplished successfully without erosion of the chirality.

In summary, we have described a general, highly diastereoselective, and efficient synthesis of *P*-chiral phosphine oxides via sequential nucleophilic substitutions using 1,3,2-benzoxazaphosphinine-2-oxide (**12**). This cyclic intermediate contains enhanced and properly differentiated P–N and P–O bond reactivities, ensuring that the first nucleophile selectively cleaves the P–N bond while the second nucleophile cleaves the P–O bond with double inversion of configuration at the P center. This method overcomes the limitations of earlier methods in the synthesis of sterically hindered compounds and offers a practical, stereoselective, and high-yield route to *P*-chiral phosphine oxides that are key intermediates for accessing *P*-chiral phosphine ligands such as the powerful BIBOP family of ligands for asymmetric catalysis.<sup>12</sup> Further applications of this chemistry to the synthesis of new ligands and their use in asymmetric transformations are under investigation.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Experimental procedures, characterization data and spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

[steve.han@boehringer-ingenheim.com](mailto:steve.han@boehringer-ingenheim.com)

### Present Address

<sup>†</sup>Department of Chemistry and Biochemistry, Old Dominion University, Norfolk, VA 23529.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Scott Pennino and Keith McKellop for HRMS analysis.

## ■ REFERENCES

- (1) (a) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pamies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077. (b) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev.* **2007**, *251*, 25. (c) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *15*, 3272. (d) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497. (e) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2012**, *23*, 1. (f) Ohkuma, T.; Kitamura, M.; Noyori, R. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 1.
- (2) For reviews, see: (a) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (b) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909. (d) Benaglia, M.; Rossi, S. *Org. Biomol. Chem.* **2010**, *8*, 3824.

(3) (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. (b) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998 and references cited therein.

(4) (a) Korpiun, O.; Mislow, K. *J. Am. Chem. Soc.* **1967**, *89*, 4784. (b) Korpiun, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842.

(5) Adam, H.; Collins, R. C.; Jones, S.; Warner, C. J. A. *Org. Lett.* **2011**, *13*, 6576.

(6) (a) Juge, S.; Genet, J. P. *Tetrahedron Lett.* **1989**, *30*, 2783–2786. (b) Moulin, D.; Sago, S.; Bauduin, C.; Darcel, C.; Jugé, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3939. (c) Bauduin, C.; Moulin, D.; Kaloun, E. B.; Darcel, C.; Jugé, S. *J. Org. Chem.* **2003**, *68*, 4293.

(7) (a) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075. (b) Ohashi, A.; Kikuchi, S.-I.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, 2535. (c) Gammon, J. J.; Gessner, V. H.; Barker, G. R.; Granander, J.; Whitwood, A. C.; Strohmman, C.; O'Brien, P.; Kelly, B. *J. Am. Chem. Soc.* **2010**, *132*, 13922. (i) Granander, J.; Secci, F.; Canipa, S. J.; O'Brien, P.; Kelly, B. *J. Org. Chem.* **2011**, *76*, 4794.

(8) (a) Serre, A. N.; Kazlauskas, R. J. *J. Org. Chem.* **1994**, *59*, 7609. (b) Shioji, K.; Ueno, Y.; Kurauchi, Y.; Okuma, K. *Tetrahedron Lett.* **2001**, *42*, 6569. (c) Wikteli, D.; Johansson, M. J.; Luthman, K.; Kann, N. *Org. Lett.* **2005**, *7*, 4991.

(9) (a) Blank, N. F.; McBroom, K. C.; Glueck, D. S.; Kassel, W. S.; Rheingold, A. L. *Organometallics* **2006**, *25*, 1742. (b) Harvey, J. S.; Malcolmson, S. J.; Dunne, K. S.; Meek, S. J.; Thompson, A. L.; Schrock, R. R.; Hoveyda, A. H.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 762. (c) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6021 and references cited therein.

(10) (a) As confirmed by chiral HPLC: Bergin, E.; O'Connor, C. T.; Robinson, S. B.; McGarrigle, E. M.; O'Mahony, C. P.; Gilheany, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 9566. (b) Rajendran, K. V.; Kennedy, L.; Gilheany, D. G. *Eur. J. Org. Chem.* **2010**, 5642.

(11) Gatineau, D.; Giordano, L.; Buono, G. *J. Am. Chem. Soc.* **2011**, *133*, 10728.

(12) (a) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600. (b) Tang, W.; Capacci, A. G.; White, A.; Ma, S.; Rodriguez, S.; Qu, B.; Savoie, J.; Patel, N. D.; Wei, X.; Haddad, N.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 1104. (c) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M. H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Cao, J. J.; Li, W.; Rodriguez, S.; Lu, B.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2012**, *14*, 2258. (d) Tang, W.; Keshipeddy, S.; Zhang, Y.; Wei, X.; Savoie, J.; Patel, N. D.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 1366.

(13) (a) Leyris, A.; Nuel, D.; Giordano, L.; Achard, M.; Buono, G. *Tetrahedron Lett.* **2005**, *46*, 8677. (b) den Heeten, R.; Swennenhuis, B. H. G.; van Leeuwen, P. W. N. M.; de Vries, J. G.; Kamer, P. C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6602. (c) Zupancic, B.; Mohar, B.; Stephan, M. *Org. Lett.* **2010**, *12*, 3022 and references cited therein. (d) Brown, J. M.; Laing, J. C. P. *J. Organomet. Chem.* **1997**, *529*, 435. (e) Maienza, F.; Spindler, F.; Thommen, M.; Pugin, B.; Malan, C.; Mezzetti, A. *J. Org. Chem.* **2002**, *67*, 5239. (f) Mohar, B.; Modéc, B.; Sterk, D.; Stephan, M. M. S. *J. Org. Chem.* **2007**, *72*, 8010. (g) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156.

(14) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.; Han, Z.; Gallou, I. *Aldrichimica Acta* **2005**, *38*, 93.

(15) See the Supporting Information (SI) for results on the effect of bases and solvents on the selectivity.

(16) See the SI for information on single-crystal X-ray structures.

(17) (a) Um, I.-H.; Shin, Y.-H.; Han, J.-Y.; Mishima, M. *J. Org. Chem.* **2006**, *71*, 7715. (b) pK<sub>a</sub> values for ROH: Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795.

(18) See the SI for the synthesis of **11**.

(19) (a) Tang, W.; Qu, B.; Capacci, A. G.; Rodriguez, S.; Wei, X.-T.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 176. (b) Rodriguez, S.; Qu, B.; Haddad, N.; Reeves, D. C.; Tang, W.; Lee, H.; Krishnamurthy, D.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 533.