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Synthesis and exploration of electronically modified (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX in palladium-catalyzed enantio- and diastereoselective allylic alkylation: a practical alternative to (*R*)-(*p*-CF_3)$_3$-*t*-BuPHOX

Robert A. Craig II, Brian M. Stoltz *

Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, United States

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ABSTRACT

The synthesis of the novel electronically modified phosphinooxazoline (PHOX) ligand, (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX, is described. The utility of this PHOX ligand is explored in both enantio- and diastereoselective palladium-catalyzed allylic alkylations. These investigations prove (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX to be an effective and cost-efficient alternative to electronically modified PHOX ligands derived from the prohibitively expensive (*R*)-*t*-leucine.

Introduction

Phosphinooxazoline (PHOX) ligands, developed by Helmchen,[1] Williams,[2] and Pfaltz,[3] have proven to be a privileged ligand scaffold in transition metal catalysis.[4] PHOX ligands have found application in a variety of asymmetric transition metal-catalyzed transformations including asymmetric hydrogenation,[5] azomethine ylide cycloadditions,[6] intermolecular Heck couplings,[7] and hydrosilylation[8] as well as transition metal-catalyzed allylic substitution[4,9] and protonation[10] reactions. Our lab has extensively explored the utility of the PHOX ligand scaffold in the palladium-catalyzed enantioselective allylic alkylation of carbocyclic[11] and heterocyclic[12] substrates. These investigations have revealed electronically modified PHOX ligands (i.e. (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((***S*****)-L1**), Fig. 1)[13] can profoundly enhance the rate of reaction as well as yield, enantiomeric excess (*ee*) and/or diastereomeric ratio of a product containing an all-carbon quaternary center (e.g. use of (***S*****)-L1** vs (***S*****)-L2** to construct lactam **2**,[12e] cyclohexanone **4**,[13c] cyclohexenone **6**,[13b] and cyclohexanone diastereomers **9** and **10**,[14] Schemes 1A–C and 2, respectively).

Most commonly, transition metal complexes employing *tert*-leucinol-derived PHOX ligands (e.g. (***S*****)-L1** and (***S*****)-L2**, Fig. 1) enable the formation of the corresponding products with the best enantiomeric and diastereomeric ratios. Although (*R*)-*t*-BuPHOX has been employed in natural product synthesis[15] and explored in transition-metal catalyzed allylic alkylations,[10a,16] these examples are quite rare considering the nearly prohibitive cost of the requisite starting material for ligand synthesis, (*R*)-*t*-leucine.[17] Previously, 5,5-geminally disubstituted (*R*)-valine-derived PHOX ligands (e.g. (***R*****)-L3** and (***R*****)-L4**, Fig. 2) have been constructed as cost-effective alternatives to (*R*)-*t*-BuPHOX ((***R*****)-L2**).[18] We sought to extend this precedent to the synthesis of electronically modified congener (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX ((*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2}, (***R*****)-L5**, Fig. 2) and explore its efficacy as a ligand in palladium-catalyzed enantio- and diastereoselective allylic alkylation reactions.

Results and discussion

Synthesis of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((*R*)-L5)

Synthesis of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R*****)-L5**) was initiated with acid chloride **11**[19] and the hydrogen chloride salt of (*R*)-valine derivative **12**[18] (Scheme 3). Intermolecular coupling of acid chloride **11** and amino alcohol **12** in the presence of excess Et_3N provides amide **13** in 79% yield. Intramolecular cyclization of amide **13** under acidic conditions furnishes oxazoline **14** in 87% yield.

* Corresponding author. Tel.: +1 626 395 6064; fax: +1 626 395 8436.
E-mail address: stoltz@caltech.edu (B.M. Stoltz).

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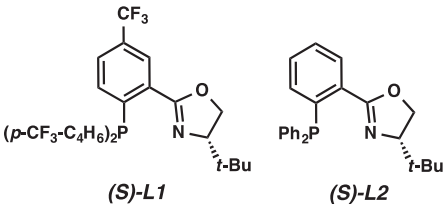
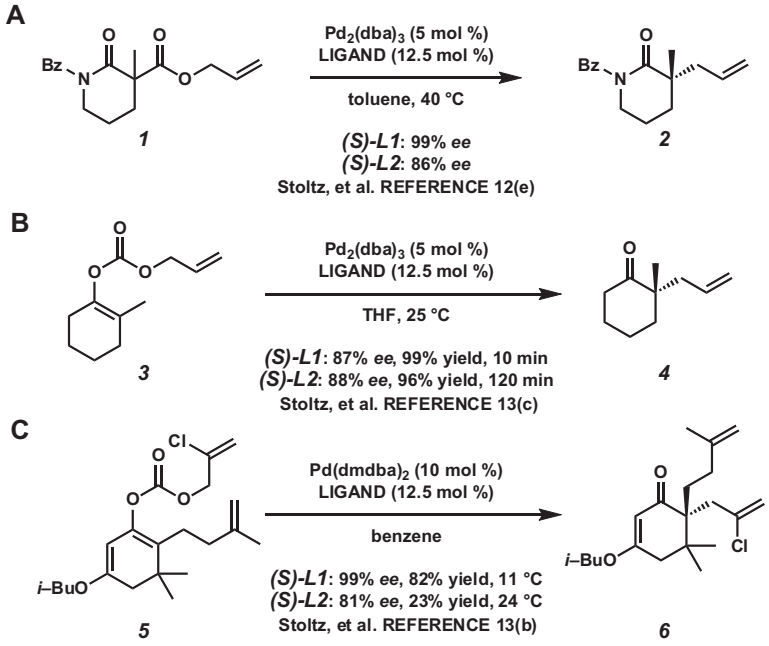


Figure 1. Electronically modified and unmodified (*S*)-*t*-BuPHOX ligands.

Completion of desired ligand (***R***)-**L5** was accomplished over two steps, beginning with the copper-mediated coupling of phosphine oxide **15** with bromide **14** at elevated temperature.[20] This procedure produces phosphine oxide **16** in 63% yield. Reduction of phosphine oxide **16** was subsequently accomplished in neat Ph_2SiH_2 at 140 °C over 48 hours, providing the desired ligand (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) in 81% yield in the final step of the synthetic sequence.



Scheme 1. Comparison of electronically modified (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((***S***)-**L1**) and unmodified (*S*)-*t*-BuPHOX ((***S***)-**L2**) in intramolecular palladium-catalyzed enantioselective allylic alkylation.

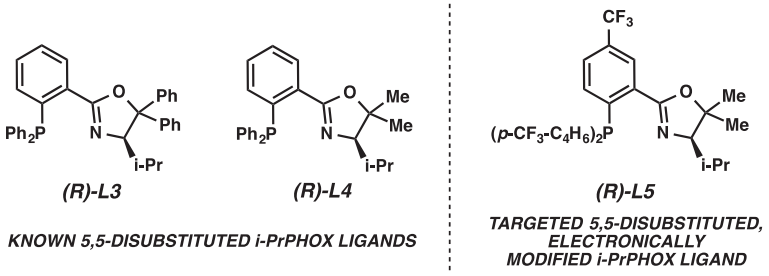
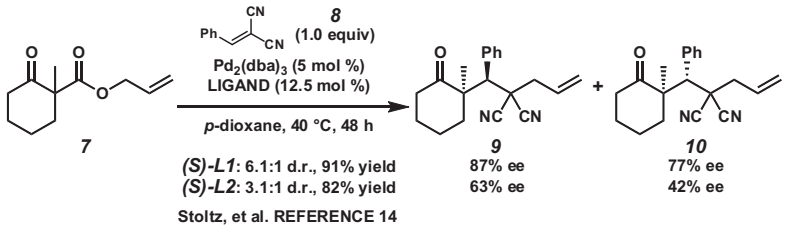
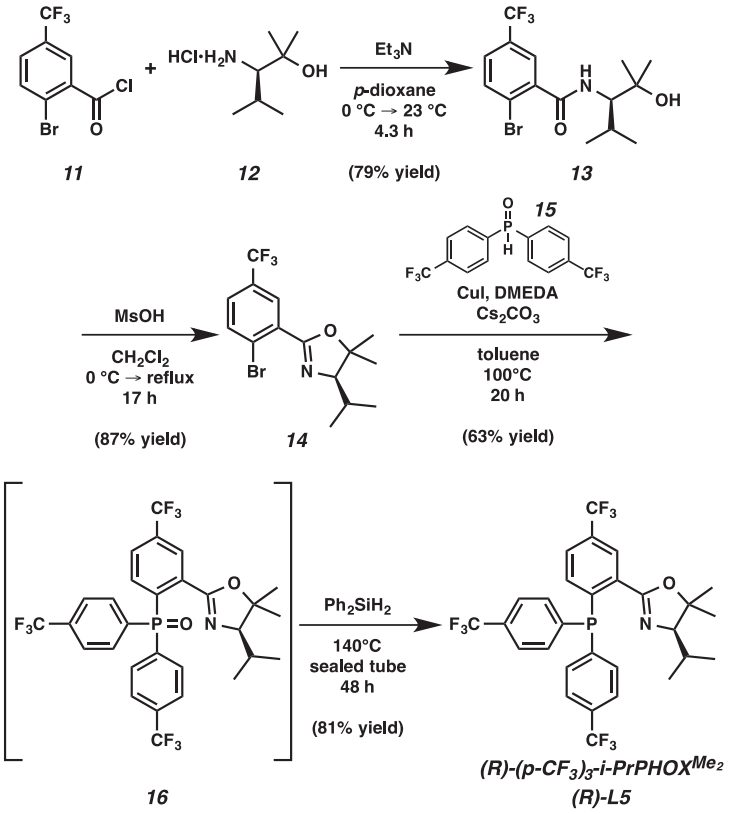


Figure 2. 5,5-Geminally disubstituted (*R*)-valine-derived PHOX ligands.



Scheme 2. Comparison of electronically modified (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((***S***)-**L1**) and unmodified (*S*)-t-BuPHOX ((***S***)-**L2**) in diastereoselective decarboxylative alkylation cascade.

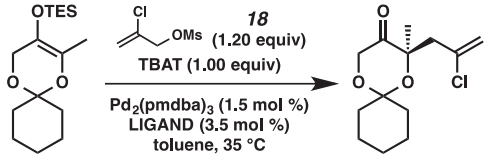


Scheme 3. Synthesis of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**).

Use of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} in palladium-catalyzed asymmetric transformations

Application of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) was initially explored in the intermolecular palladium-catalyzed enantioselective allylic alkylation of silyl enol ether **17** with mesylate **18** (Scheme 4). Previously we disclosed the initial development and optimization of this transformation using (*S*)-*t*-BuPHOX ((***S***)-**L2**), which afforded chloroallylketone (***S***)-**19** in 82% yield and 92% ee (entry 1).[12d] Substitution of (***S***)-**L2** with the electronically modified (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((***S***)-**L1**) provided the product ((***S***)-**19**) in a slightly diminished 91% ee (entry 2). Switching the ligand to (*S*)-5,5-diphenyl-*i*-PrPHOX ((***S***)-**L3**) furnished chloroallylketone (***S***)-**19** in 90% *ee* (entry 3). Moving into the opposite enantiomeric series, the use of (*R*)-5,5-dimethyl-*i*-PrPHOX ((***R***)-**L4**) provided chloroallylketone (***R***)-**19** in a somewhat diminished 89% *ee* (entry 4) compared to the originally optimized reaction conditions (entry 1). Alternatively, we were pleased to find that (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) afforded chloroallylketone (***R***)-**19** in the same 91% ee (entry 5) in the opposite enantiomeric series compared to the use of (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX (entry 2). It is noteworthy that the required reaction time (20 h) and isolated yield (80-82%) of chloroallylketone **19** were independent of the ligand employed. Thus, (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) can allow access to the enantiomeric series of products to those afforded in reactions employing (***S***)-**L1** without any loss in product *ee* in a cost-effective manner, being derived from (*R*)-valine, which is less than 2% of the cost of (*R*)-*t*-leucine.

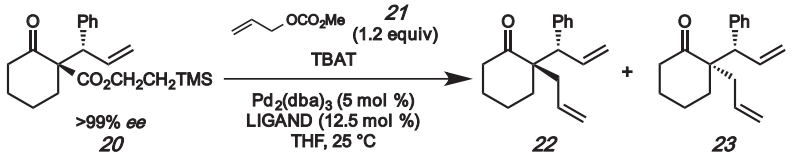
The utility of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) was further demonstrated in the intermolecular palladium-catalyzed diastereoselective decarboxylative allylic alkylation of β-ketoester **20** with allyl electrophile **21** (Scheme 5).[16a] While the system displays an inherent selectivity for the formation of diastereomer **22** in a 2:1 ratio with diastereomer **23** when achiral PHOX ligand **L6** was employed (entry 1),[21] the use of (*S*)-*t*-BuPHOX ((***S***)-**L2**) can override this substrate bias, providing diastereomer **23** as the major product (entry 2). Comparatively, the use of (*R*)-*t*-BuPHOX ((***R***)-**L2**) reinforces the inherent selectivity, providing diastereomer **22** in a 12:1 ratio with minor diastereomer **23** in a combined 73% yield (entry 3). Pleasingly, the employment of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) further improved this transformation, furnishing an 18:1 mixture of products in favor of diastereomer **22** in an improved 85% combined yield (entry 4). These studies revealed that (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) was the optimal ligand for the highly diastereoselective formation of allylic alkylation product



Entry	Ligand	Amino Acid Ligand Precursor	Amino Acid Cost per gram ($) [a] S - Enantiomer - R		Product ee (%) [b]
1	*(S)-L2*	*tert*-Leucine	33	351	–92
2	*(S)-L1*	*tert*-Leucine	33	351	–91
3	*(S)-L3*	Valine	0.60	6	–90
4	*(R)-L4*	Valine	0.60	6	89
5	*(R)-L5*	Valine	0.60	6	91

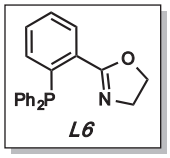
[a] Cost per gram of amino acid from Sigma-Aldrich, accessed 4/30/2015.
[b] Enantiomeric excess (*ee*) measured by analytical chiral GC.

Scheme 4. Ligand comparison in enantioselective palladium-catalyzed intermolecular allylic alkylation.



Entry	Ligand	% yield [a]	dr (22:23) [b]
1	L6	79	2:1
2	(S)-L2	79	1:2
3	(R)-L2	73	12:1
4	(R)-L5	85	18:1

[a] Isolated yield of 22 and 23. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture and analytical GC analysis



Scheme 5. Diastereoselective decarboxylative allylic alkylation employing (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**).

22. Additionally, other research groups have found (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) to be a uniquely effective ligand for the palladium-catalyzed diastereoselective allylic alkylation of other carbocyclic substrates.[22]

Conclusion

Herein, we have disclosed the synthesis of a new, electronically modified phosphinooxazoline (PHOX) ligand, (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX ((*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2}, (***R***)-**L5**). Derived from (*R*)-valine, this cost-effective alternative to (*R*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((***R***)-**L1**) has proved effective in both palladium-catalyzed enantio- and diastereoselective allylic alkylations, furnishing the alkylation products in comparable ee and improved diastereomeric ratio. Efforts to further explore the utility of the readily available (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ligand in palladium-catalyzed stereoselective transformations are currently underway.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.06.039.

References and notes

1. Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.
2. Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149–3150.
3. Von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566–568.
4. (a) Carroll, M. P.; Guiry, P. J. *Chem. Soc. Rev.* **2014**, *43*, 819–833; (b) Hargaden, G. C.; Guiry, P. J. *Chem. Rev.* **2009**, *109*, 2505–2550; (c) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151–4202; (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345; (e) Williams, J. M. *Synlett* **1996**, 705–710.
5. (a) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. *Chem. Rev.* **2014**, *114*, 2130–2169; (b) Braunstein, P.; Graiff, C.; Naud, F.; Pfaltz, A.; Tiripicchio, A. *Inorg. Chem.* **2000**, *39*, 4468–4475.
6. Stohler, R.; Wahl, F.; Pfaltz, A. *Synthesis* **2005**, 1431–1436.
7. (a) Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161–164; (b) Hashimoto, Y.; Horie, Y.; Hayashi, M.; Saigo, K. *Tetrahedron: Asymmetry* **2000**, *11*, 2205–2210.
8. (a) Frölander, A.; Moberg, C. *Org. Lett.* **2007**, *9*, 1371–1374; (b) Sudo, A.; Yoshida, H.; Saigo, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3205–3208.
9. (a) Liu, Y.; Liniger, M.; McFadden, R. M.; Roizen, J. L.; Malette, J.; Reeves, C. M.; Behenna, D. C.; Seto, M.; Kim, J.; Mohr, J. T.; Virgil, S. C.; Stoltz, B. M. *Beilstein J. Org. Chem.* **2014**, *10*, 2501–2512; (b) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A., Jr.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223; (c) García-Yebra, C.; Janssen, J. P.; Rominger, F.; Helmchen, G. *Organometallics* **2004**, *23*, 5459–5470.
10. (a) Doran, R.; Carroll, M. P.; Akula, R.; Hogan, B. F.; Martins, M.; Fanning, S.; Guiry, P. J. *Chem. Eur. J.* **2014**, *20*, 15354–15359; (b) Carroll, M. P.; Müller-Bunz, H.; Guiry, P. J. *Chem. Commun.* **2012**, 11142–11144; (c) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042; (d) Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349.
11. (a) Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2015**, *137*, 1040–1043; (b) Reeves, C. M.; Behenna, D. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16*, 2314–2317; (c) Reeves, C. M.; Eidamshaus, C.; Kim, J.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6718–6721; (d) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228–1231; (e) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927; (f) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.
12. (a) Numajiri, Y.; Jiménez-Osés, G.; Wang, B.; Houk, K. N.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 1082–1085; (b) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 179–183; (c) Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2013**, *19*, 4414–4418; (d) Craig, R. A., II; Roizen, J. L.; Smith, R. C.; Jones, A. C.; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5716–5719; (e) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133; (f) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876.
13. (a) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554; (b) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810–811; (c) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531.
14. Streuff, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2010**, *2*, 192–196.
15. (a) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814–6818; (b) Levine, S. R.; Krout, M. R.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 289–292; (c) Petrova, K. V.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2009**, *11*, 293–295.
16. (a) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2013**, *135*, 10626–10629; (b) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844–4849.
17. The cost of (*R*)-*t*-leucine ranges between $350 and $400 per gram, depending on the size of the order from Sigma-Aldrich, as advertised on their sigmaaldrich.com, accessed 30 April, 2015. The synthesis of *t*-BuPHOX ligands, however, can be accomplished with ease on large scale, see: Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 194–211.
18. (a) Bélanger, É.; Pouliot, M.-F.; Courtemanche, M.-A.; Paquin, J.-F. *J. Org. Chem.* **2012**, *77*, 317–331; (b) Bélanger, É.; Pouliot, M.-F.; Paquin, J.-F. *Org. Lett.* **2009**, *11*, 2201–2204.
19. Acid chloride **11** was synthesized in two steps from 2-bromo-5-(trifluoromethyl)benzonitrile by a known procedure, see: Ref. 13b.
20. The procedure for the coupling of phosphine oxide **15** with oxazoline **14** and sequential reduction was adapted from Ref. 13a.
21. Control experiments were performed using achiral PHOX ligand **L6**, bearing no substituent on the oxazoline ring, see Ref. 16a for full details.
22. Professor Stephen F. Martin, University of Texas at Austin, personal communication.