Tetrahedron Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 27 May 2015
Accepted 10 June 2015
Available online xxxx

Keywords:
Allylic alkylation
Diastereoselective
Enantioselective
Palladium-catalyzed
Phosphinooxazoline

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.

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http://dx.doi.org/10.1016/j.tetlet.2015.06.039
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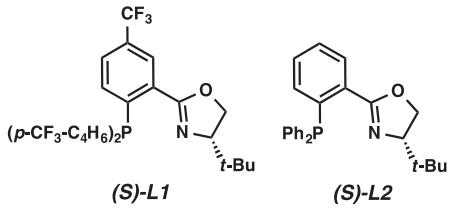
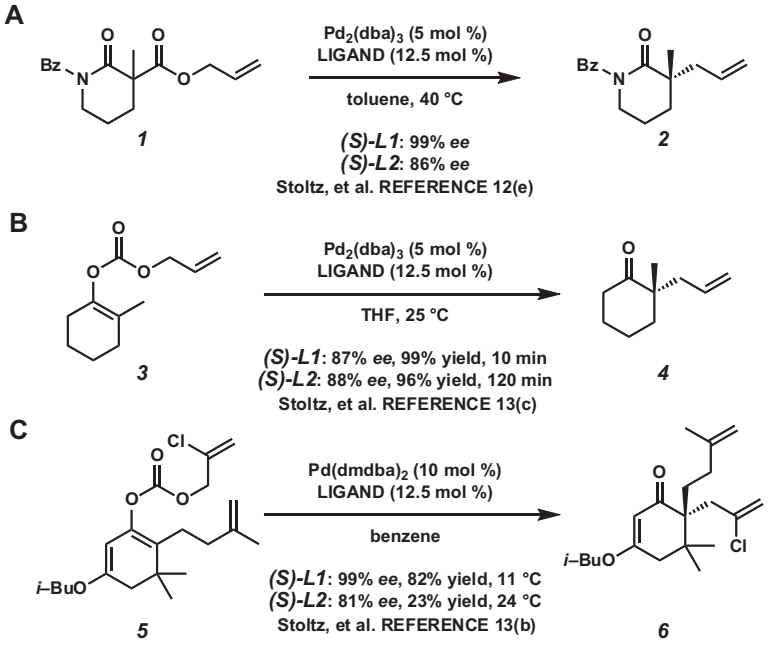


Figure 1. Electronically modified and unmodified (*S*)-*t*-BuPHOX ligands.

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.

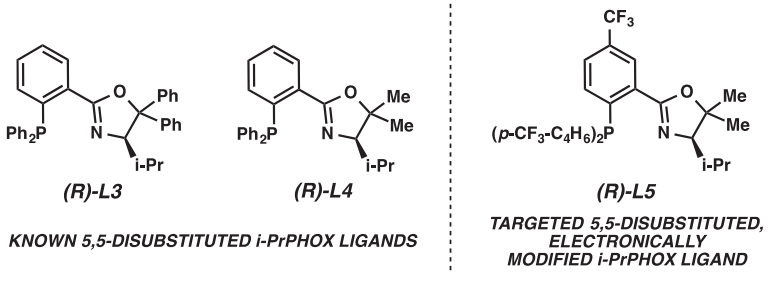
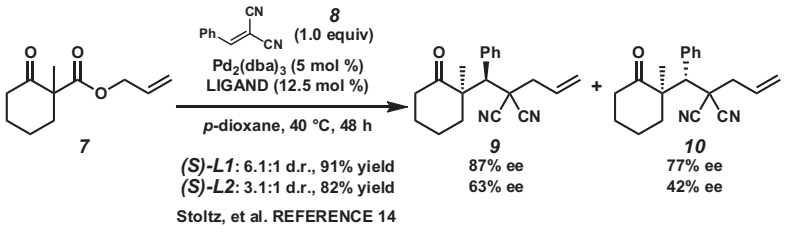
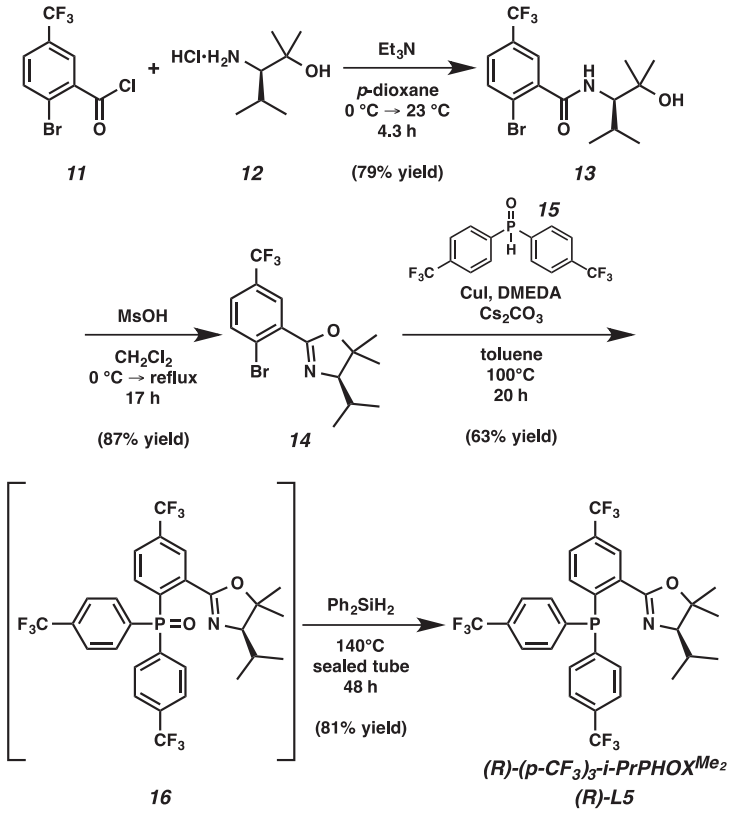


Figure 2. 5,5-Geminally disubstituted (*R*)-valine-derived PHOX ligands.



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.

Please cite this article in press as: Craig II, R. A.; Stoltz, B. M. *Tetrahedron Lett.* (2015), http://dx.doi.org/10.1016/j.tetlet.2015.06.039

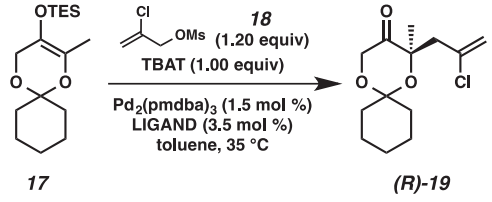


Scheme 3. Synthesis of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**).

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.

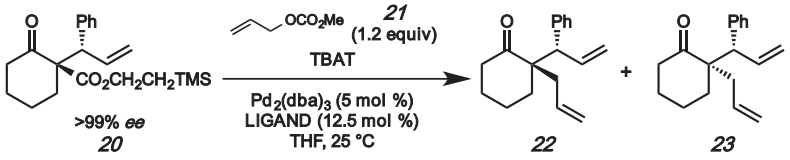
The utility of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) was further demonstrated in the intermolecular palladium-catalyzed diastereoselective decarboxylative allylic alkylation of β-ketoester **20** with allyl electrophile **21** (Scheme 5).[16a] While the system displays an inherent 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

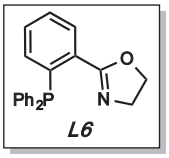
[a] Cost per gram of amino acid from Sigma-Aldrich, accessed 4/30/2015.
[b] Enantiomeric excess (*ee*) measured by analytical chiral GC.

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

The authors wish to thank the NIH-NIGMS (R01GM080269), Amgen, the Gordon and Betty Moore Foundation, and Caltech for financial support. R.A.C. gratefully acknowledges the support of this work provided by a fellowship from the National Cancer Institute of the National Institutes of Health under Award Number F31A17435.

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.