Tetrahedron Letters 56 (2015) 5445–5448

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Reversible nucleophilic addition can lower the observed enantioselectivity in palladium-catalyzed allylic amination reactions with a variety of chiral ligands

Nicholas S. Caminiti, Madison B. Goodstein, Isabelle N.-M. Leibler, Bryan S. Holtzman, Zitong B. Jia, Michael L. Martini, Nathaniel C. Nelson, Richard C. Bunt *

Department of Chemistry & Biochemistry, Middlebury College, Middlebury, VT 05753, United States

ARTICLE INFO

Article history:
Received 20 July 2015
Revised 6 August 2015
Accepted 8 August 2015
Available online 12 August 2015

Keywords:
Enantioselective
Palladium catalysis
Allylic amination
Reversibility
Chiral ligand

ABSTRACT

Palladium-catalyzed allylic amination is an important synthetic reaction that is also frequently used as a benchmark for the design and evaluation of new chiral ligands. The effect of reversible nucleophilic addition on the reaction of benzylamine with (*E*)-1,3-diphenylallyl ethyl carbonate (**1**) in CH_2Cl_2 was examined with 12 different chiral ligands across a range of scaffolding types. In 8 out of 12 cases the observed ee was significantly higher when DBU or Cs_2CO_3 was added to suppress the proton-driven reversibility. For chiral ligand screening with this test reaction, adding DBU or Cs_2CO_3 provides a better measure of the ligand's inherent enantioselectivity.

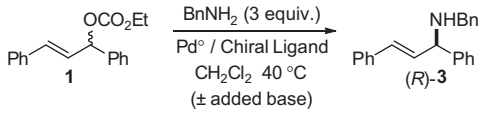
Enantioselective allylic substitutions have proven very effective for synthesizing chiral molecules,[1] and palladium-catalyzed allylic aminations, in particular, have been widely studied due to their utility.[2] During our ongoing Hammett studies of electronically modified phosphinooxazoline (PHOX) ligands,[3,4] we noted some unusual and inconsistent enantioselective results with palladium-catalyzed benzyl amine additions to 1,3-diphenylallyl substrates that led us to believe that reversible product formation was lowering the observed enantioselectivities. Previous mechanistic studies by Amatore and Jutland[5] have established the reversibility of product formation with secondary amine nucleophiles and achiral bidentate ligands. Additionally, regiospecific formation and isomerization during palladium-catalyzed synthesis of unsymmetrical allylic amine products (branched vs linear) have demonstrated that the reaction conditions have a large impact on the reversibility of product formation.[6–8] Yudin[6a,g] showed that adding 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), but few other bases they screened,[9] significantly increased the reaction selectivity for the kinetically favored, branched allyl amine isomer by preventing or greatly reducing its proton-driven isomerization to the linear product that proceeds via reformation of the π-allylpalladium intermediate.

Because of our own observations with modified PHOX ligands and the widespread use of allylic amination as a benchmark test reaction for asymmetric catalysis and chiral ligand design,[10] we undertook a wider study of enantioselective palladium-catalyzed allylic aminations. Herein, we present the first examples of asymmetric palladium catalysis in which the reversible nucleophilic addition of benzylamine can lower the observed enantioselectivity. We found that DBU and Cs_2CO_3, a base not previously examined, can mitigate these effects with most of the chiral ligands tested.

Initially, we examined the enantioselectivity obtained with the (*S*)-PHOX ligand (**4**) as a function of reaction time using racemic carbonate **1** and benzylamine as the nucleophile (Scheme 1). We employed CH_2Cl_2 as the solvent because it showed a greater propensity than THF for product isomerization[6a] and we wanted to test the enantioselectivity under potential 'worst case' conditions. We found that in the absence of added base the observed ee of (*R*)-**3** dropped significantly over time (Fig. 1). In contrast, when 3.2 equiv of DBU or Cs_2CO_3 were employed as a base additive for the reaction, the observed ee remained both high and constant over time. Based on TLC and GC/MS analysis, the reaction with ligand **4** went to completion in 2–3 h without added base and 15–30 min with added base.[11] Consequently, the 0.25 h and 1 h time points without DBU or Cs_2CO_3 are particularly notable because they show significant erosion of the product ee before the reaction is even complete.

* Corresponding author. Tel.: +1 802 443 2559; fax: +1 802 443 2072.
E-mail address: rbunt@middlebury.edu (R.C. Bunt).

http://dx.doi.org/10.1016/j.tetlet.2015.08.010
0040-4039/



Scheme 1. Standard test reaction for enantioselective amination.

The observed ee with no base at 24 h has a larger standard deviation because the catalyst does not always remain active well beyond the time necessary for the reaction to go to completion. Once the active catalyst 'dies' (formation of palladium black or other catalytically inactive species), the ee stays fixed at that value regardless of the length of time the reaction is allowed to proceed. Control reactions in which isolated samples of (*R*)-**3** were resubjected to the reaction conditions without additional starting material (**1**) did not show any change in the ee. However, when a small amount of **1** was included, the ee of **3** decreased by much more than could be accounted for by the additional amount of **3** produced in the reaction (data not shown). Thus, an actively functioning catalyst is necessary to observe the back reaction of **3**, which lowers the ee. We found that the rigorous exclusion of oxygen using strict purge/backfill protocols with argon helped maintain the active catalyst lifetime. The general robustness of π-allylpalladium chemistry to air and water can obscure this point, as indeed, such measures are not typically necessary.[12]

The racemization mechanism that equilibrates (*R*)-**3** and (*S*)-**3** is shown in Scheme 2. With ligand **4**, for example, the π-allylpalladium complex (**2**) initially forms (*R*)-**3**-H$^+$ with high enantioselectivity. The discrete Pd(0)–alkene complex has been omitted from Scheme 2 for simplicity as the timing of its formation or breakdown with respect to the proton transfer step does not impact this analysis. (*R*)-**3**-H$^+$ is then reversibly deprotonated by either the excess benzylamine, another product molecule, or the ethyl carbonate leaving group acting as a base (A$^-$) to give (*R*)-**3**. As the reaction proceeds, more protons are generated and eventually the palladium-catalyzed back reactions (dashed arrows) to reform **2** become favorable. Because (*R*)-**3** is present in higher concentrations due to the catalyst's high enantioselectivity, its back reaction is favored over the back reaction of (*S*)-**3**. Effectively (*R*)-**3** and (*S*)-**3** are in equilibrium because (*S*)-**3** can also reform **2**, albeit at a slower rate initially. If the reaction is allowed to proceed long enough and the palladium-catalyst remains active, an equal mixture of (*R*)-**3** and (*S*)-**3** will result regardless of the initial ligand enantioselectivity as an ultimate consequence of thermodynamics.

We next investigated the scope of reversible product formation and the generality of DBU and Cs_2CO_3 in preventing it. We selected a variety of commercially available chiral ligands (**5**–**15**) having both C_1 and C_2 symmetry across a range of scaffolding types including many of the so called 'privileged' chiral ligands[13] (Fig. 2). We carried out the same test reaction for each one, but

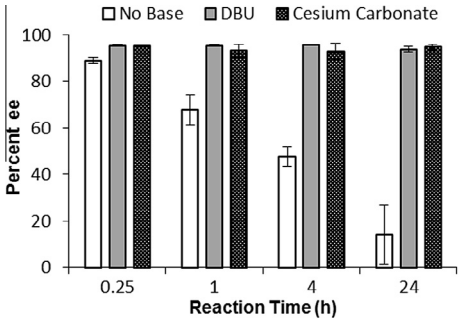
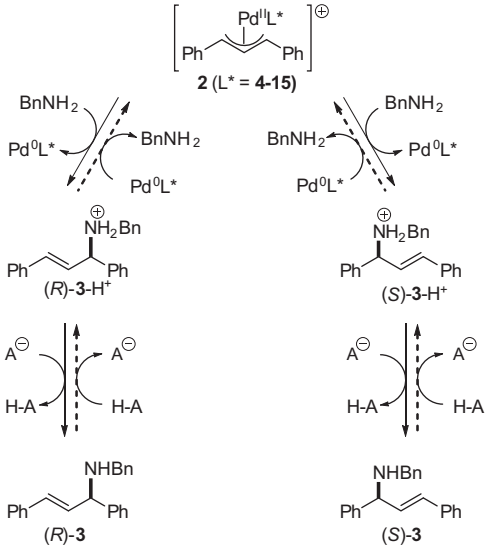


Figure 1. Effect of reaction time and added base on the observed ee of (*R*)-**3** with ligand **4** (PHOX). Each time point is the average of **4**–**7** individual reaction trials with error bars showing ±1 standard deviation.



Scheme 2. Mechanism for equilibration of (*R*)-**3** and (*S*)-**3**.

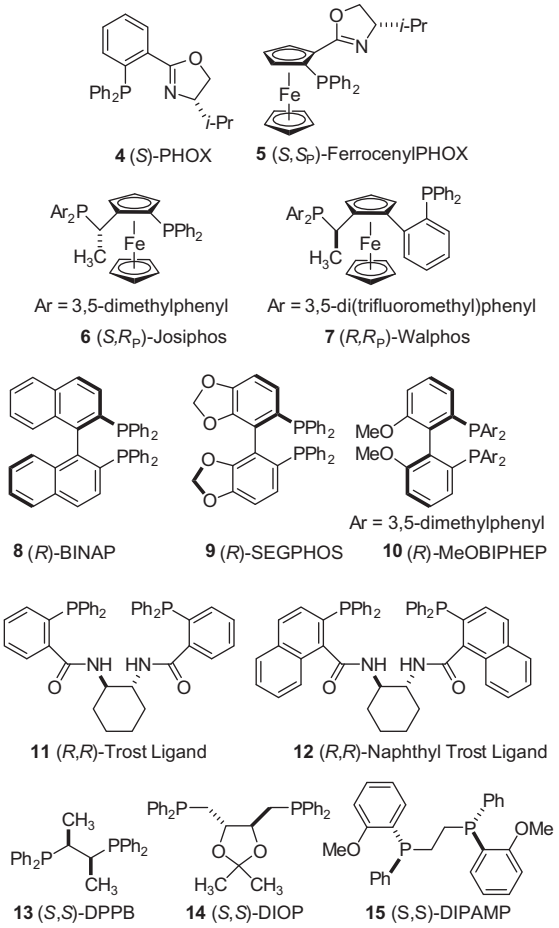


Figure 2. Structures of chiral ligands **4**–**15**.

did not attempt to optimize the reaction conditions (time, temperature, or solvent) to obtain the best enantioselectivity for each chiral ligand. Rather, we kept the reaction conditions standard (Scheme 1) and looked for differences in the ee when DBU or Cs_2CO_3 were added (Table 1). We used 4 h as the initial reaction time for each ligand. If the reaction was not complete in 4 h, we used 24 h for that ligand.

Table 1
Observed ee[a] of (*R* or *S*)-**3** with chiral ligands **4**–**15**

Chiral ligand	Time (h)	% ee no base	% ee DBU	% ee Cs_2CO_3
4	4	48 ± 5 (*R*)	96 ± 1 (*R*)	93 ± 4 (*R*)
5	4	27 ± 5 (*R*)	76 ± 1 (*R*)	77 ± 7 (*R*)
6	24	11 ± 4 (*S*)	64 (±2) (*S*)	62 ± 3 (*S*)
7	24	62 ± 2 (*S*)	41 ± 3 (*S*)	35 ± 8 (*S*)
8	4	5 ± 4 (*R*)	95 ± 2 (*R*)	97 ± 2 (*R*)
9	4	9 ± 2 (*R*)	98 ± 1 (*R*)	97 ± 1 (*R*)
10	4	13 ± 2 (*R*)	91 ± 1 (*R*)	93 ± 3 (*R*)
11	24	30 ± 2 (*S*)	68 ± 3 (*S*)	66 ± 2 (*S*)
12	24	78 ± 2 (*R*)	8 ± 2 (*S*)	28 ± 7 (*R*)
13	24	4 ± 1 (*S*)	60 ± 2 (*S*)	70 ± 2 (*S*)
14	4	6 ± 3 (*R*)	NR[b]	14 ± 2 (*R*)
14	24	6 ± 2 (*R*)	NR[b]	14 ± 1 (*R*)
15	24	20 ± 5 (*R*)	29 ± 6 (*R*)	19 ± 4 (*S*)

[a] Average of **3**–**7** individual reaction trials with error range of ±1 standard deviation. The ee was determined by chiral HPLC (Chiralcel OJ, 15% *i*-PrOH/Hexanes).
[b] No reaction, only starting material observed by TLC.

Overall, eight out of the twelve ligands tested (**4**–**6**, **8**–**11**, and **13**) followed a pattern similar to that depicted in Figure 1. The observed ee was significantly higher when DBU or Cs_2CO_3 was added to the reaction. These results suggest that the proton-driven reversibility shown in Scheme 2 is a pervasive, potential problem for ligand evaluation and screening. For example, amination with ligand **5** to form (*R*)-**3** without added base under otherwise fairly similar conditions (CH_2Cl_2, 25 °C, 24 h) has been reported in 41% ee[10a] (vs 76% or 77% ee with DBU or Cs_2CO_3 in this study). It seems likely that in many other cases as well, the addition of DBU or Cs_2CO_3 would give a better measure of a chiral ligand's inherent enantioselectivity for asymmetric amination.

Four of the ligands tested (**7**, **12**, **14**, and **15**), however, showed somewhat disparate results. Both **7** and **12** gave higher ee's without added base. It is possible for these ligands that reversible nucleophilic addition is already slow or simply not the reason for the lower enantioselectivity, or both. Furthermore, it is not surprising that DIOP (**14**) and DIPAMP (**15**) gave low ee's under all conditions tested as they are more well known for success in asymmetric hydrogenation reactions.[14]

The ferrocene based ligands (**5**–**7**) all have the possibility for matched versus mismatched diastereomers (carbon-centered chirality vs planar chirality of ferrocene).[15] Although we did not specifically test for this, mismatched chirality could explain the somewhat lower ee's obtained even with added base for all three ligands. Alternatively, they may simply be inherently less selective catalysts for this reaction. Regardless, with Walphos (**7**), DBU and Cs_2CO_3 affected the catalyst system in some way that resulted in lower enantioselectivity than with no base.

With the naphthyl Trost ligand (**12**), the addition of DBU and Cs_2CO_3 resulted in both a much lower ee (vs no base). In fact, DBU formed a slight excess of the opposite enantiomer of the product. The coordination behavior of the Trost ligands (**11** and **12**) can be complicated due to the 13-membered ring formed when acting as a *P*,*P*-chelate for palladium in their most enantioselective mode.[16] However, oligomerization and P,O-chelation are also possible,[17] particularly for naphthyl ligand **12**.[18] Monophosphine analogs of **11** that can only exhibit P,O-chelation also showed reduced enantioselectivity and gave the opposite enantiomer of the product in other test reactions.[19] Thus, it seems possible that for **12** the lower ee and reversal of chirality observed with DBU is due to increased oligomerization or a P,O-chelation mode induced in some manner by the added base.

With DIOP (**14**), the reaction with DBU showed only starting material at 24 h even though the reactions went to completion in 4 h both without base and with Cs_2CO_3. Coordination of the imino nitrogen of DBU to palladium could hinder catalyst turnover, though nothing obvious suggests that this should be a special problem for DIOP. Regardless, the low enantioselectivity observed for **14** agrees with literature findings for related alkylation reactions.[20]

DIPAMP (**15**), likewise, showed low enantioselectivity with or without base, similar to literature findings for related alkylation reactions.[21] Surprisingly though, with Cs_2CO_3 the opposite product enantiomer was obtained. As with ligand **12** and DBU, Cs_2CO_3 in this case must have altered the catalyst in some way. Perhaps a P,O-chelation mode is also possible with **15**, but it is without literature precedent that we are aware of. With ee's only in the 20–30% range, the differences in ΔG between the (*R*) and (*S*) pathways are only 1–1.5 kJ/mol. Consequently, any mechanistic rationale is rather speculative.

In summary, for the majority of ligands tested, the reversibility of the nucleophilic addition step can lower the observed reaction enantioselectivity. The magnitude of the effect is time, ligand, and based on Yudin's work,[6a] solvent dependent. Adding either DBU or Cs_2CO_3 preserves, or at least more closely approximates, the inherent enantioselectivity of the chiral ligand by preventing or substantially minimizing reprotonation of the initial amine product. DBU and Cs_2CO_3 have largely similar effects, but they show some differential impacts on the catalyst reactivity and absolute configuration of the product in some cases. We are continuing to investigate the reaction and ligand parameters that influence reversibility and therefore loss of enantioselectivity in palladium-catalyzed allylic aminations.

Acknowledgments

We thank the Donors of The Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (CHE-071451) for support of this research. N.S.C., M.B. G., and I.N.-M.L. thank Middlebury College for summer financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.010.

References and notes

1. *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*; Kazmaier, U., Ed.Topics in Organometallic Chemistry; Springer: Berlin, 2012; 38,.
2. (a) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427–440; (b) Faller, J. W.; Wilt, J. C. *Organometallics* **2005**, *24*, 5076–5083; (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943; (d) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689–1708; (e) Togni, A.; Burckhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031–1037.
3. (a) Armstrong, P. B.; Dembicer, E. A.; Desbois, A. J.; Fitzgerald, J. T.; Gehrmann, J. K.; Nelson, N. C.; Noble, A. L.; Bunt, R. C. *Organometallics* **2012**, *31*, 6933–6946; (b) Armstrong, P. B.; Bennett, L. M.; Constantine, R. N.; Fields, J. L.; Jasinski, J. P.; Staples, R. J.; Bunt, R. C. *Tetrahedron Lett.* **2005**, *46*, 1441–1445; (c) Constantine, R. N.; Kim, N.; Bunt, R. C. *Org. Lett.* **2003**, *5*, 2279–2282.
4. For reviews of PHOX ligands see: (a) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336–345; (b) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203–214; (c) Williams, J. M. J. *Synlett* **1996**, 705–710.
5. Amatore, C.; Genin, E.; Jutand, A.; Menash, L. *Organometallics* **2007**, *26*, 1875–1880.
6. (a) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2013**, *78*, 1559–1575; (b) Wang, X.; Meng, F.; Wang, Y.; Han, Z.; Chen, Y.-J.; Liu, L.; Wang, Z.; Ding, K. *Angew. Chem.* **2012**, *124*, 9410–9416; (c) Wang, Y.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Biomol. Chem.* **2012**, *10*, 6908–6913; (d) Hirakawa, T.; Ikeda, K.; Ikeda, D.; Tanaka, T.; Ogasa, H.; Kawatsura, M.; Itoh, T. *Tetrahedron* **2011**, *67*, 8238–8247; (e) Dubovyk, I.; Pichugin, D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5924–5926; (f) De luliis, M. Z.; Watson, I. D. G.; Yudin, A. K.; Morris, R. H. *Can. J. Chem.* **2009**, *87*, 54–62; (g) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172–114173; (h) Watson, I. D. G.; Yudin, A. *J. Am. Chem. Soc.* **2005**, *127*, 17516–17529.
7. For an example with ruthenium see: Kawatsura, M.; Uchida, K.; Terasaki, S.; Tsujo, H.; Minakawa, M.; Itoh, T. *Org. Lett.* **2014**, *16*, 1470–1473.

8. For reversible nucleophilic additions used in catalyst screening by MS see: (a) Ebner, C.; Müller, C. A.; Markert, C.; Pfaltz, A. *J. Am. Chem. Soc.* **2011**, *133*, 4710–4713; (b) Müller, C. A.; Pfaltz, A. *Angew. Chem.* **2008**, *120*, 3411–3414.
9. DBN and *tert*-butylimino-tri(pyrrolidino)phosphorane, (BTPP) gave results similar to DBU, Ref. 6a.
10. (a) Wu, H.; Xie, F.; Wang, Y.; Zhao, X.; Liu, D.; Zhang, W. *Org. Biomol. Chem.* **2015**, *13*, 4248–4254; (b) Coll, M.; Pamies, O.; Dieguez, M. *Org. Lett.* **2014**, *16*, 1892–1895; (c) Grabulosa, A.; Doran, S.; Brandariz, G.; Muller, G.; Benet-Buchholz, J.; Riera, A.; Verdaguer, X. *Organometallics* **2014**, *33*, 692–701; (d) Bravo, M. J.; Favier, I.; Saffon, N.; Ceder, R. M.; Muller, G.; Gomez, M.; Rocamora, M. *Organometallics* **2014**, *33*, 771–779; (e) Khiri-Meribout, N.; Bertrand, E.; Bayardon, J.; Eymin, M.-J.; Rousselin, Y.; Cattery, H.; Fortin, D.; Harvey, P. D.; Jugo, S. *Organometallics* **2013**, *32*, 2827–2839; (f) Wang, Y.; Vaismaa, M. J. P.; Rissanen, K.; Franzen, R. *Eur. J. Org. Chem.* **2012**, 1569–1576; (g) Harada, T.; Nemoto, T.; Jin, L.; Hamada, Y. *Chem. Pharm. Bull.* **2011**, *59*, 412–415; (h) Sun, Y.-W.; Jiang, J.-J.; Zhoa, M.-X.; Wang, F.-J.; Shi, M. *J. Organomet. Chem.* **2011**, *696*, 2850–2856; (i) Kultyshev, R. G.; Miyazawa, A. *Tetrahedron* **2011**, *67*, 2139–2148; (j) Shen, C.; Xia, H.; Zheng, H.; Zhang, P.; Chen, X. *Tetrahedron: Asymmetry* **2010**, *21*, 1936–1941; (k) Panossian, A.; Fernandez-Perez, H.; Popa, D.; Vidal-Ferran, A. *Tetrahedron: Asymmetry* **2010**, *21*, 2281–2288; (l) Caldentey, X.; Pericas, M. A. *J. Org. Chem.* **2010**, *75*, 2628–2644; (m) Mazuela, J.; Paptchikhine, A.; Tolstoy, P.; Pamies, O.; Dieguez, M.; Andersson, P. G. *Chem.-Eur. J.* **2010**, *16*, 620–638; (n) Chen, J.; Lang, F.; Li, D.; Cun, L.; Zhu, J.; Deng, J.; Liao, J. *Tetrahedron: Asymmetry* **2009**, *20*, 1953–1956.
11. The rate is presumable faster with added base due to the greater concentration of unprotonated $BnNH_2$ as nucleophilic addition is typically the turnover limiting step. For a discussion of allylic alkylation kinetics is asymmetric catalysis see: Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Owen-Smith, G. J. J.; Purdie, M. *J. Am. Chem. Soc.* **2008**, *130*, 14471–14473.
12. Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
13. *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, Germany, 2011.
14. Shang, G.; Li, W.; Zhang, X. Transition Metal-Catalyzed Homogeneous Asymmetric Hydrogenation. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 3rd ed.; Wiley: New York, 2010; pp 343–436.
15. Dai, L.-X.; Tu, R.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659–667.
16. (a) Agrawal, D.; Schröder, D.; Sale, D. A.; Lloyd-Jones, G. C. *Organometallics* **2010**, *29*, 3979–3986; (b) Butts, C. P.; Filali, E.; Lloyd-Jones, G. C.; Norrby, P.-O.; Sale, D. A.; Schramm, Y. *J. Am. Chem. Soc.* **2009**, *131*, 9945–9957.
17. (a) Racys, D. T.; Eastoe, J.; Norrby, P.-O.; Grillo, I.; Rogers, S.; Lloyd-Jones, G. C. *Chem. Sci.* **2015**. http://dx.doi.org/10.1039/C5SC01181G; (b) Lloyd-Jones, G. C. *Synlett* **2001**, 161–183; (c) Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Commun.* **2000**, 2447–2448; (d) Butts, C. P.; Crosby, J.; Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1999**, 1707–1708.
18. Amatore, C.; Jutand, A.; Mensah, L.; Ricard, L. *J. Organomet. Chem.* **2007**, *692*, 1457–1464.
19. Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817–5820.
20. (a) Marques, C. S.; Burke, A. J. *Tetrahedron: Asymmetry* **2007**, *18*, 1804–1808; (b) Fiaud, J. C.; de Gournay, A. H.; Larcheveque, M.; Kagan, H. B. *J. Organomet. Chem.* **1978**, *154*, 175–185; (c) Trost, B. M.; Dietsche, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 1800–1801.
21. Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *9*, 1649–1651.