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Distinctive *Meta*-Directing Group Effect for Iridium-Catalyzed 1,1-Diarylalkene Enantioselective Hydrogenation

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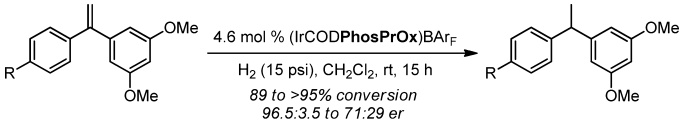
ABSTRACT



An iridium-catalyzed asymmetric hydrogenation of 1,1-diarylkenes is described. Employing a novel, modular phosphoramidite ligand, PhosPrOx, in this transformation affords biologically relevant 1,1-diarylmethine products in good enantiomeric ratios (96.5:3.5 to 71:29). We propose that a *meta*-directing group, 3,5-dimethoxyphenyl, is responsible for the observed enantioselection, the highest reported, to date, for iridium-catalyzed hydrogenation of 1,1-diarylalkenes lacking *ortho*-directing groups.

For several years, we and others have taken a keen interest in accessing the biologically relevant 1,1-diarylmethine scaffold.[1] Although several methods exist for effectively accessing these molecules,[2] approaches for their enantioselective synthesis have been limited.[2b,3] Of particular note, Jarvo and co-workers have developed a nickel-catalyzed stereospecific cross-coupling reaction whereby enantiomerically enriched 1,1-diarylethers undergo inversion of configuration in the process to afford similarly enriched 1,1-diarylmethines.[3a,b] Another attractive approach was reported by Carreira and co-workers, where enantiomerically enriched β,β-diarylpropionaldehydes are converted to 1,1-diarylmethines using a stereoretentive rhodium-catalyzed decarbonylation protocol.[3d] We envisioned a complementary method to access this important pharmacophore wherein the stereocenter is set in the key bond forming event. Specifically, we wanted to develop an enantioselective hydrogenation of 1,1-diarylmethylenes, as this approach would be operationally simple and the substrates would be easily accessed. Additionally, this substrate class is especially challenging, as few examples of high enantioselectivity have been reported for the hydrogenation of 1,1-diarylalkenes.

In general, rhodium-, ruthenium-, and iridium-catalyzed asymmetric hydrogenation reactions can be divided into

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(3) (a) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293. (b) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389. (c) Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881. (d) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331. (e) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833. (f) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3011. (g) Prat, L.; Dupas, G.; Duflos, J.; Quéguiner, G.; Bourguignon, J.; Levacher, V. *Tetrahedron Lett.* **2001**, *42*, 4515. (h) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793.

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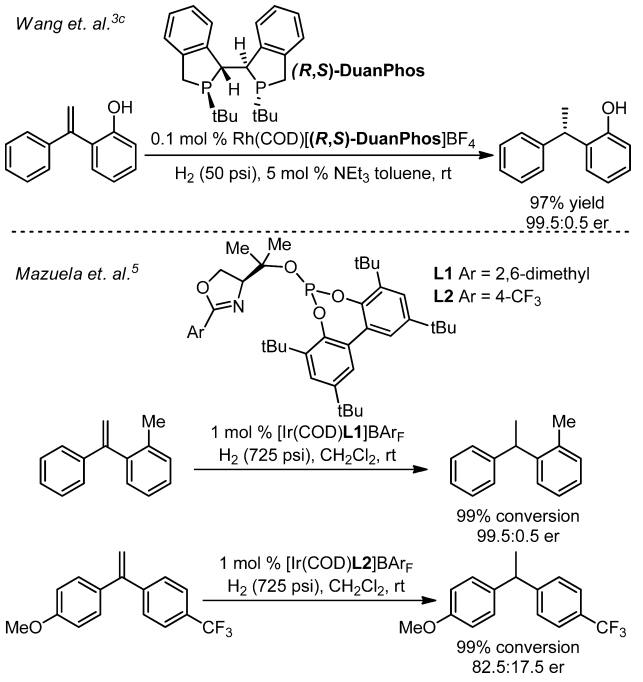
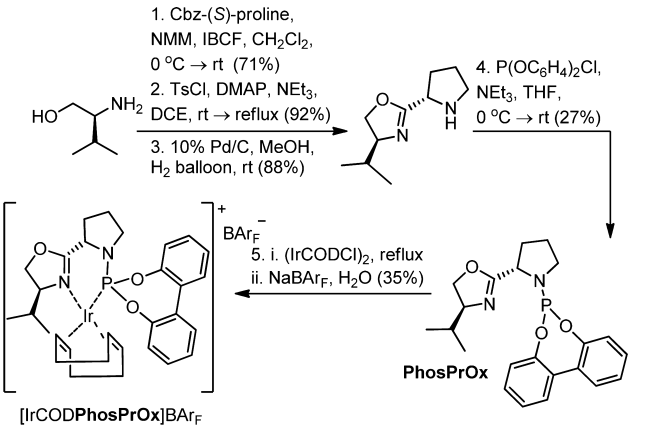


Figure 1. Previous reported enantioselective hydrogenation of 1,1-diarylalkene derivatives.

two broad classes: those that require coordination of a Lewis basic functional group in order to achieve high enantioselectivity and those that require no such coordination that is auxiliary to the alkene. Of these two classes, ruthenium- and rhodium-catalyzed hydrogenations typically fall into the former category, and iridium-catalyzed hydrogenation is associated with the latter.[4] When considering the asymmetric hydrogenation of 1,1-diarylalkenes, the auxiliary coordination requirement of rhodium- and ruthenium-catalyzed systems constrains the potential substrate scope to those with Lewis basic groups at the *ortho* position on the aryl ring, which has been accomplished using oxygen directing groups (Figure 1).[3c] While this coordination constraint does not exist for iridium-catalyzed systems, a steric bias at an *ortho*-position is required to achieve excellent enantioselectivity in the hydrogenation of 1,1-diarylalkenes.[5] In the absence of such bulk proximal to the prochiral site, enantioselectivity dramatically erodes, with the best reported enantiomeric ratio (er) being 82.5:17.5 (Figure 1).[6]

With an interest in developing a hydrogenation system capable of yielding highly enantioenriched 1,1-diarylmethine

Scheme 1. Synthetic Route to Novel Iridium-Phosphoramidite Complex[a]



[a] THF: tetrahydrofuran. NMM: *N*-methylmorpholine. IBCF: isobutyl chloroformate. TsCl: tosyl choride. DMAP: 4-(dimethylamino)pyridine. DCE: 1,2-dichloroethane. COD: cyclooctadiene. $NaBAr_F$: sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate.

products from substrates lacking *ortho*-directing groups, we investigated the use of a new class of modular phosphoramidite ligands. The origin of this new ligand's design is the application of an aminooxazoline core structure with a proline-derived pyrrolidine as a key element for imparting rigidity. Synthesis of this ligand proceeds through standard amino alcohol/amino acid coupling, followed by cyclization to form the oxazoline, and *N*-pyrrolidine deprotection, all of which proceed in good yields and were perfomed according to previously published procedures.[7] The phosphite moiety, a typical element in many iridium-based hydrogenation catalysts, is incorporated to afford the phosphoramidite ligand **PhosPrOx** (Scheme 1).[8] Stirring **PhosPrOx** with $[IrCODCl]_2$ yields the precatalyst [IrCOD**PhosPrOx**]BAr_F, although in poor yield.[9]

We evaluated this new catalyst's performance in the hydrogenation of **1** (see Supporting Information for conditions optimization). Excitingly, hydrogenation using this unique catalyst affords the product in 92:8 er. To the best of our knowledge, this result represents the highest reported er for an iridium-catalyzed hydrogenation of this substrate type (i.e., non-*ortho*-substituted 1,1-diarylalkenes). As this substrate has two rings displaying unique functional groups, the effects of both were systematically evaluated to determine the potential structural origin for face selection.

As a first experiment, removal of one methoxy substituent, as in substrate **2**, led to a significant reduction in

(4) (a) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633. (b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402. (c) Church, T. L.; Andersson, P. G. *Coord. Chem. Rev.* **2008**, *252*, 513.

(5) While this manuscript was under review, an *ortho*-carboxy-directed iridium-catalyzed hydrogenation of 1,1-diarylalkenes was reported: Song, S.; Zhu, S.-F.; Yu, Y.-B.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2012** 10.1002/anie.201208606.

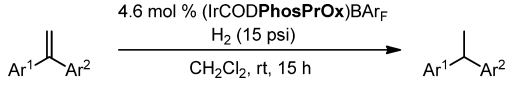
(6) (a) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem.—Eur. J.* **2010**, *16*, 14232. (b) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B. n.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344.

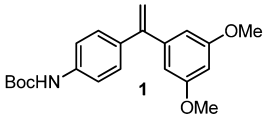
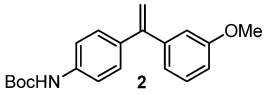
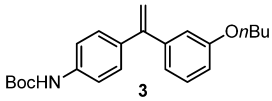
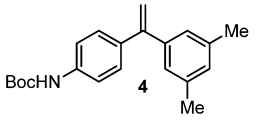
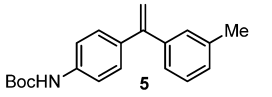
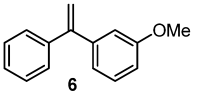
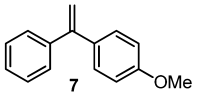
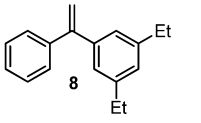
(7) For synthetic procedures, see: (a) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568. (b) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752. (c) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 5473. (d) Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748.

(8) For synthetic procedure, see: Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; De Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943.

(9) For synthetic procedure, see: Smidt, S. P.; Menges, F.; Pfaltz, A. *Org. Lett.* **2004**, *6*, 2023.

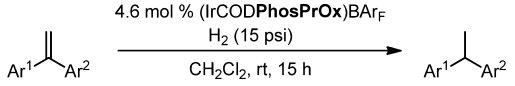
Table 1. Exploration of Substrate *Meta*-Directing Group Effects

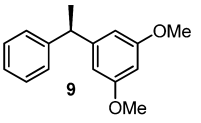
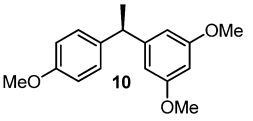
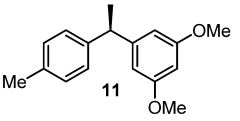
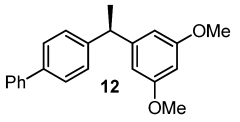
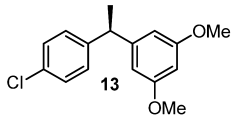
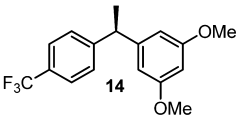
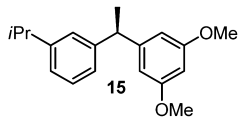
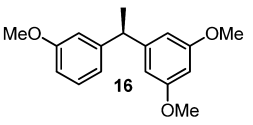


entry	alkene	conversion (%)[a]	er[b]
1	 **1**	89%	92:8
2	 **2**	59%	74:26
3	 **3**	66%	75:25
4	 **4**	70%	63:37
5	 **5**	54%	48.5:51.5
6	 **6**	>95%	74:26
7	 **7**	>95%	53:47
8	 **8**	>95%	49:51

[a] Conversions, measured by ^{1}H NMR, are an average of two experiments. [b] Er, determined by SFC or HPLC instruments fitted with chiral stationary phases, represents average of two experiments.

Table 2. Substrate Scope



entry	product[a]	conversion (%)[b]	er[c]
1	 **9**	>95%	92.5:7.5
2	 **10**	>95%	91.5:8.5
3	 **11**	>95%	88.5:11.5
4	 **12**	>95%	89:11
5	 **13**	>95%	96:4
6	 **14**	>95%[d]	96.5:3.5
7[e]	 **15**	>95%	85.5:14.4
8[e]	 **16**	>95%	71:29

[a] Absolute configurations of products were assigned by analogy (see Supporting Information). [b] Conversion, measured by ^{1}H NMR, is an average of two experiments. [c] Er, determined by SFC instrument fitted with a chiral stationary phase, represents an average of two experiments. [d] Reactions performed using 10 mol % catalyst to achieve >95% conversion. [e] The same sense of stereoinduction is assumed although not confirmed.

enantioselectivity upon hydrogenation (Table 1, entry 2, er = 74:26). Changing this group further to a 3-*n*-butoxy (**3**) had a negligible effect (Table 1, entry 3, er = 75:25). These preliminary results suggest that 3,5-substitution on the aryl ring is required for enhanced enantioselection. To probe whether this is a purely steric effect or if substituents containing heteroatoms are required, 3,5-dimethoxy aryl was replaced by the 3,5-dimethyl variant. This change led to a considerable lowering of er (Table 1, entry 4, er = 63:37), suggesting the importance of the heteroatom substituents. Interestingly, elimination of one of the methyl groups results in a system wherein the catalyst had no alkene facial preference (Table 1, entry 5). This combination of results is consistent with high enantioselectivity resulting from a strongly influential effect of heteroatom substitution, which is augmented by the steric effect of having substituents at both the 3- and 5-positions.

As support for this hypothesis, the other aryl ring should not have a major influence on the outcome of the reaction. Evaluation of a substrate in which the *N*-Boc is truncated leads to an excellent result wherein very similar enantioselectivity is observed (Table 2, entry 1, er = 92.5:7.5). Again, removal of one of the *meta*-substituted methoxy groups (**6**) leads to a significant reduction in enantioselectivity (Table 1, entry 6), and evaluation of the corresponding *para*-methoxy-substituted substrate **7** leads to a nearly racemic mixture of the hydrogenated product.

While we had gathered considerable evidence indicating the importance of etheric aryl substituents, there remained a possibility that the steric bulk of the 3,5-dimethoxy substituents was the crucial feature for enantioselection. To assess this possibility, **8** was synthesized, incorporating 3,5-diethyl substitution as a surrogate to 3,5-dimethoxy. In poignant support of our hypothesis, **8** was hydrogenated to yield a racemic product mixture (Table 1, entry 8).

Returning to the requisite 3,5-dimethoxy substitution pattern on one aryl ring, we evaluated the reaction's enantioselective robustness to variation in the geminal aryl ring. Installing an electron-donating methoxy substituent at the 4-position (**10**) afforded the reduced product with very little change in er (Table 2, entry 2, er = 91.5: 8.5). Incorporating a 4-methyl substituent into the substrate (Table 2, entry 3) resulted in a slightly diminshed er (88.5:11.5). However, a neglible effect upon modification of 4-position steric bulk from methyl (**11**) to phenyl is observed (**12**, Table 2, entry 4, er = 89:11).

The influence of electron-poor substituents on enantioselection was evaluated via 4-chloro (**13**) and 4-trifluoromethyl (**14**) substrates, which were hydrogenated in 96:4 er (Table 2, entry 5) and 96.5:3.5 er (Table 2, entry 6), respectively. These er's represent a significant improvement in enantioselectivity over the best previously reported er (82.5:17.5) obtained via an iridium-catalyzed hydrogenation of a 1,1-diarylalkene that contains aryl substitution only at positions distal (*meta* and *para*) from the prochiral site.[6b]

Convinced of the system's enantioselective robustness to substitution at the 4-position, we next investigated the effect of the 3-position's variation. Hydrogenation of substrate **15**, bearing the bulky and electron-rich 3-isopropyl substitution (Table 2, entry 7), yielded the corresponding diarylmethine in 85.5:14.5 er, representing only a slight decrease in enantioselection from 4-substituted substrates.

Finally, to challenge the 3,5-dimethoxy substitution pattern's capacity for directing facial selection in the presence of other potential directing groups, we evaluated the hydrogenation of **16** (Table 2, entry 8), wherein the 3,5-dimethoxy groups remain intact on one ring, and 3-methoxy substitution is incorporated on the geminal ring. In this scenario, the substitution patterns in both rings are each, in the absence of the other, capable of inducing facial descrimination, although to a lesser extent for 3-methoxy than for 3,5-dimethoxy substitution. Interestingly, **16** was reduced in a 71:29 er, nearly identical to that seen for substrates **2** and **6** (er = 74:26 and 74:26, respectively), which bear 3-methoxy substitution. We hypothesize that 3,5-dimethoxy substitution still acts as the dominant force in this transformation's enantiodetermining step, while the observed er erosion is a result of introducing another group (3-methoxy) with competing directing group capabilities.[10]

While the scope of this transformation is somewhat limited by the 3,5-dimethoxy substitution requirement, this functionality can be considered a removable directing group. That is, aryl methoxy groups can be fully reduced or undergo a demethylation, tosylation, and cross-coupling sequence to rapidly expand the possibilities for the molecular complexity of these enantioenriched diarylmethines.[11]

Through our investigation of iridium-catalyzed asymmetric hydrogenation of substituted 1,1-diarylalkenes, we have developed a novel phosphoramidite ligand, **PhosPrOx**, and uncovered evidence suggesting that the enantioselective outcome of this iridium-mediated reaction cannot be easily assigned to either of the aforementioned asymmetric hydrogenation classes, i.e., asymmetric induction dependent on coordination auxiliary to the alkene or that dependent on the proximity of steric bulk to the prochiral site. Alternatively, we propose that the Lewis basicity of the 3,5-dimethoxy substitution acts as a directing group for the substrate, perhaps by precoordinating the substrate to iridium. Such a directed coordination event would, presumably, orient one alkene face toward iridium, poising the substrate for subsequent alkene coordination and hydrogenation to yield distally substituted 1,1-diarylmethines in the best enantioselectivities reported, to date, for an iridium-catalyzed hydrogenation.

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Supporting Information Available. Experimental procedures, full spectroscopic data, and chiral separations for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) Substituting the 3,5-dimethoxy phenyl directing group for 3,4,5-trimethoxy phenyl, a common biological motif, resulted in low conversion of the starting material to product, and the er was not determined.

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The authors declare no competing financial interest.