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Probing Electronic Effects in the Asymmetric Heck Reaction with the BIPI Ligands

Carl A. Busacca,* Danja Grossbach,† Regina C. So, Erin M. O'Brien, and Earl M. Spinelli

Department of Chemical Development, Boehringer-Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Rd., Ridgefield, Connecticut 06877

cbusacca@rdg.boehringer-ingelheim.com

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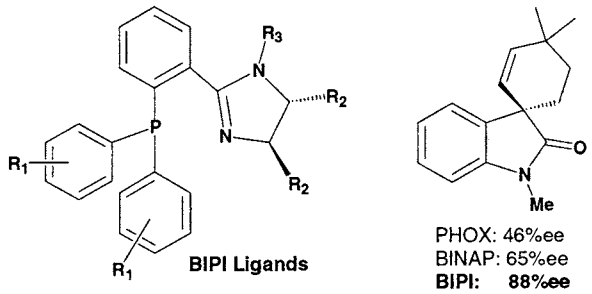
ABSTRACT



The new BIPI ligands are phosphinoimidazolines that can be electronically tuned in three different ligand regions to explore electronic effects in asymmetric catalysis. Their application to the asymmetric Heck reaction (AHR) in the creation of a chiral quaternary center is described. Enantioselectivity is shown for the first time to depend linearly on phosphine electron density. Changing the ligand basicity by variation of the R_2 or R_3 substituents reverses facial selectivity.

In 2001 we patented a novel series of ligands for asymmetric catalysis, the BIPI ligands.[1] Our intellectual starting point was the phosphinooxazolines (PHOX) pioneered by Pfaltz, Helmchen, and Williams.[2] We felt that phosphinoimidazolines would provide a more flexible ligand scaffold, since the basicity of the ligating nitrogen could be easily tuned by replacement of the R_3 substituent. Importantly, the electronic requirements of asymmetric reactions could be probed, and a wide variety of metals and substrates could be accommodated by a single ligand class. The ligands are constructed in modular fashion as shown in Scheme 1.[3] Condensation of an *o*-haloimidate **1** with a chiral diamine **2** furnishes the haloimidazolines **3a,b**. These compounds were all stable crystalline solids, with pK_a values of 8.5−9.5.[3] S_NAr reaction of phosphide nucleophiles with **3a** gave phosphinoimidazolines **4**. The S_NAr reaction required only 1 equiv of nucleophile, despite the presence of the imidazoline NH. This reaction proved to be more sluggish with electron-rich arylfluorides (e.g., R_2 = *p*-OMePh) though and failed completely when addition of electron-deficient phosphines was attempted.

For access to these intermediates, we proceeded through the iodoimidazolines **3b**. These species were first substituted on nitrogen to give **5** and then cross-coupled with a secondary phosphine or phosphine borane[4] complex under palladium catalysis to afford the desired ligand. Introduction of R_3 substituents that were electron-withdrawing facilitated the cross-coupling, likely by increasing the rate of oxidative addition. We found the cross-coupling method of Kraatz[4] in

† Current address: Schering AG Process Research, D-13342 Berlin.

(1) Busacca, Carl A. U.S. Patent 6,316,620, 2001. Boehringer-Ingelheim Phosphinoimidazolines. For a recent application of the BIPI ligands to asymmetric hydrogenation, see: Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713.

(2) For a review, see: Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*(6), 336−345.

(3) Full experimental details for all ligands are found in Supporting Information.

(4) (a) Kraatz, H.-B.; Pletsch, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1617. (b) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244.

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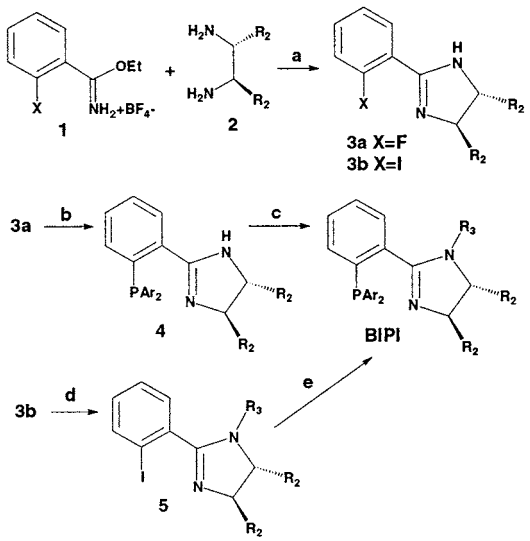
Scheme 1. Ligand Synthesis[a]



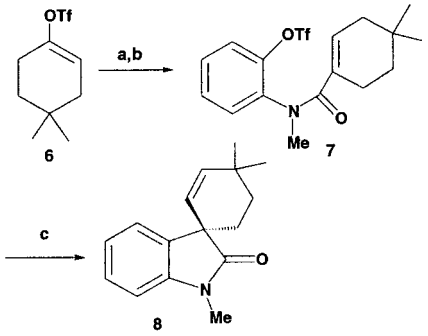
[a] Reagents and conditions: (a) EtOH/reflux or TEA/DCM, 44−98%; (b) Ar_2PM, M = Li, Na, K, THF, 42−90%; (c) R_3X, base, 41−88%; (d) R_3X, base, 70−99%; (e) Ar_2PH, Pd, base, 27−62%.

DMSO to be broadly applicable in this regard. In general, cross-coupling via the iodide was found to be the more general approach, since all ligands could be prepared by this method, regardless of the phosphine nucleophilicity or arylhalide electrophilicity involved. The S_NAr reactions are generally higher yielding, though, and thus were utilized where possible. In all cases, the moderately air-sensitive ligands were then purified by chromatography. We utilized C18 flash chromatography extensively for this purpose. Since oxygen is far less soluble in polar solvents than in nonpolar ones, little or no oxidation occurred during purification with the MeCN−H_2O and alcohol−H_2O eluents used for this technique.[5]

With the newly developed ligands in hand, we chose an asymmetric Heck reaction (AHR) as our first area of study. The majority of the work in this area has been carried out on dihydrofuran and dihydropyrrole substrates.[6] Part of the enantiocontrol in these systems can occur by means of kinetic resolution of the intermediates which *follow* β-hydride elimination.[6b] We were instead interested in studying the "moment of truth" in which the new stereocenter was created and to explore the electronic requirements for this transformation. To accomplish this for the asymmetric Heck reaction, it is therefore necessary to generate a quaternary center without the possibility for olefin isomerization in the product. This can only be achieved through an intramolecular process.[7]

We chose triflate **7** (Scheme 2) as our initial substrate since its oxindole product **8** had previously been prepared by

Scheme 2. Asymmetric Heck Reaction[a]



[a] Reagents and conditions: (a) CO, 100 psi, $Pd(OAc)_2$/dppp, *N*-methylaminophenol, TEA, DMF, 55%; (b) Tf_2O/DMAP, 89% (c) BIPI ligands, Pd_2dba_3, PMP, Ph_2O, 95 °C 18 h.

Overman using BINAP as ligand.[7b] We also utilized the triflate rather than the iodide as our starting point, reasoning that our ligands would likely be similar to the PHOX ligands where triflates were found to be superior.[6c] The substrate was prepared in two steps via carbonylation of vinyltriflate **6** with *N*-methylaminophenol and subsequent sulfonation (Scheme 2).

Our first experiments involved BINAP and the *tert*-butylphosphinooxazoline ligands. We found that BINAP furnished the product **8** in 65% ee[3] and 90% yield, whereas the *t*-Bu-PHOX gave 46% ee in dioxane (20% yield) as determined by chiral HPLC analysis. We envisioned that triflate **7** was therefore an interesting and challenging asymmetric Heck substrate for us to examine with the BIPI ligands.

A single experimental protocol was developed and strictly adhered to for all ligands.[3] The reaction was heated for 18 h at 95 °C and then worked up regardless of the level of completion, and the product chromatographically isolated. We felt this would give us some measure of the practicality of the reaction as the long reaction times common to much of the asymmetric Heck literature would not be used. We used diphenyl ether as solvent after examining several solvents of different dielectric constants and found the less polar solvents gave the highest enantioselectivities. This observation has previously been made with a variety of triflate substrates in the AHR[6c] reaction. This solvent has both a fairly low dielectric constant (e = 3.65) and a high boiling point, 242 °C, making its use convenient.

The initial screening results are collected in Table 1. Several conclusions could readily be made. When basic ligands (R_3 = Me, Bn) were used, we always obtained the enantiomer opposite from that found with the nonbasic ligands (N-acylated) with the same underlying diamine stereochemistry. In addition, the imidazolines substituted on carbon by *alkyl* groups (fused cyclohexyl, *t*-butyl) always gave the enantiomer opposite from that with imidazolines substi-

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(6) (a) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338. (b) Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* **1992**, *428*, 267. (c) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505.

(7) (a) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477. (b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.

Table 1. Enantioselectivities from the Initial Ligand Set

R_1	R_2	R_3	solvent	yield[a] (%)	ee[b] (%)
H	(*S*,*S*)-C_6H_5	benzoyl	Ph_2O	76	42.2 (+)
H	(*R*,*R*)-C_6H_5	*p*-CF_3Bz	Ph_2O	90	41.9 (−)
H	(*S*,*S*)-C_6H_5	2-naph[c]	Ph_2O	68	44.6 (+)
H	(*S*,*S*)-C_6H_5	1-naph[c]	Ph_2O	85	40.6 (+)
H	(*S*,*S*)-C_6H_5	methyl	DMA	17	20.5 (−)
H	(*S*,*S*)-C_6H_5	benzyl	DMA	16	11.9 (−)
H	(*R*,*R*)-$(CH_2)_4$-	acetyl	anis[d]	21	29.2 (+)
H	(*S*,*S*)-*t*-Bu	acetyl	Ph_2O	88	29.1 (−)

[a] Chromatographically isolated yield after 18 h. [b] Determined by chiral HPLC, sign of rotation of major enantiomer. [c] Naphthoyl. [d] Anisole.

tuted by *aryl* groups, irrespective of the N-substituent. The cyclohexyl system is the *least* sterically demanding species we have prepared, and the bis-*tert*-butyl system is the *most* sterically demanding, and yet they give the same major enantiomer in identical ee. Furthermore, higher enantioselectivities are found with the *less* bulky aryl substituents. The alkyl-substituted imidazolines must therefore impart their reversal of facial selectivity by a purely electronic mechanism. This was the premise for the development of the BIPI ligands.

The gross electronic tuning (basic vs nonbasic) therefore allows access to either enantiomeric product. It was also observed, however, that lower catalytic turnover was found with the N-alkyl species, so we focused on the N-aroyl substituents for all of the subsequent Hammett studies. We first examined the N-benzoyl para substituent. The Hammett plot of log er (enantiomer ratio) vs σ_p showed a random distribution, and the ee's spanned a fairly small range, 33−48%. We concluded that this substituent is simply too remote from the metal center to affect the enantioselectivity. We then turned to the phosphine para and meta substituents. We maintained the 2-naphthoyl R_3 substituent for all Hammett studies because it gave the highest ee of the electron-withdrawing groups screened. We also hoped to minimize any conformational changes in the ligands by holding this substituent constant. An eight-point Hammett plot is shown in Figure 1. We were excited to find a clear linear relationship with $\rho = +0.53$ between the electronic constant and enanatioselectivity. Both para- and meta-substituted phosphines fall on the line generated. Here the enantioselectivities cover a broader range (40−78%), and the best result, R_1 = 3,5-difluoro, is significantly better than either BINAP or the PHOX ligand for this substrate. *This dependence of stereoselectivity on phosphine electron density has never been reported in the asymmetric Heck literature*.

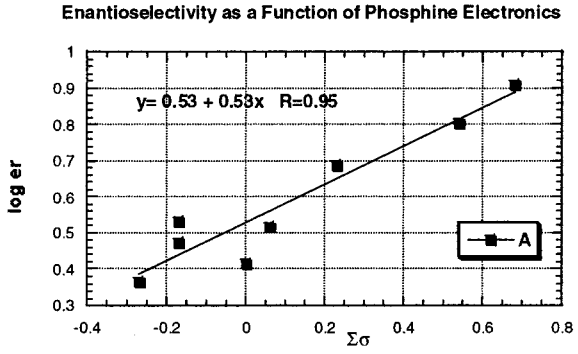
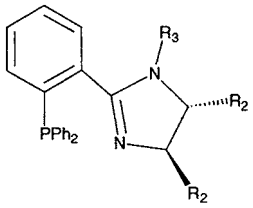


Figure 1. Phosphine Hammett plot.

The diarylimidazoline electronics were then evaluated, using both para and meta substituents. The results are collected in Table 2. For the eight ligands examined, the observed ee range for the transformation was 45−65%, with both electron-donating and electron-withdrawing groups

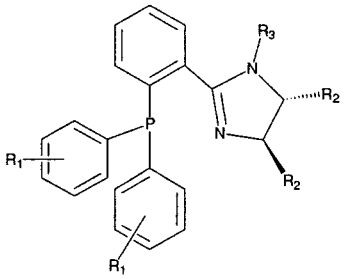
Table 2. Effect of Diamine Electronics on Enantioselectivity



R_1	R_2	R_3	yield[a] (%)	ee[b] (%)
H	(*S*,*S*)-*p*-$OMeC_6H_4$	2-naph[c]	13	51.6 (+)
H	(*R*,*R*)-*p*-MeC_6H_4	2-naph[c]	25	45.2 (−)
H	(*S*,*S*)-C_6H_5	2-naph[c]	68	44.6 (+)
H	(*S*,*S*)-*p*-FC_6H_4	2-naph[c]	61	48.3 (+)
H	(*S*,*S*)-*p*-ClC_6H_4	2-naph[c]	17	61.5 (+)
H	(*R*,*R*)-*p*-$CF_3C_6H_4$	2-naph[c]	12	64.6 (−)
H	(*S*,*S*)-3,5-$Me_2C_6H_3$	2-naph[c]	85	46.7 (+)
H	(*S*,*S*)-3,5-$F_2C_6H_3$	2-naph[c]	93	62.7 (+)

[a] Chromatographically isolated yield after 18 h. All reactions in Ph_2O solvent with PMP as base. [b] Determined by chiral HPLC, sign of rotation of major enantiomer. [c] 2-Naphthoyl.

Table 3. Optimized BIPI Ligands



R_1	R_2	R_3	yield[a] (%)	ee[b] (%)
4-Cl	(*R*,*R*)-3,5-$F_2C_6H_3$	2-naph[c]	25	80.6 (−)
4-Cl	(*R*,*R*)-3,5-$F_2C_6H_3$	2-naph[c]	51[d]	79.3 (−)
4-Cl	(*R*,*R*)-3,5-$F_2C_6H_3$	*p*-OMeBz	28	78.2 (−)
4-Cl	(*R*,*R*)-3,5-$F_2C_6H_3$	*p*-CF_3Bz	26	74.9 (−)
3,5-F_2	(*R*,*R*)-3,5-$F_2C_6H_3$	2-naph[c]	50[d]	86.8 (−)
3,5-F_2	(*R*,*R*)-3,5-$F_2C_6H_3$	2-naph[c]	38	87.6 (−)

[a] Chromatographically isolated yield after 18 h; remainder unreacted s.m. Reactions in Ph_2O with PMP as base unless otherwise noted. [b] Determined by chiral HPLC, sign of rotation of major enantiomer. [c] 2-Naphthoyl. [d] 1-(1′-Cyclohexylethyl)-pyrrolidine as base.

giving higher enantioselectivity than the neutral (R_2 = H) species. Deviation from this neutral species led to lower isolated yields after the proscribed 18 h reaction time for the para-substituted ligands. For the two meta-disubstituted ligands, however, the product was afforded in excellent yield. There appears to be an important steric acceleration of turnover associated with meta disubstitution. The 3,5-difluoro ligand clearly possessed the best combination of enantioselectivity (63% ee) and yield (93%), so we focused on this diamine substitution for our final optimization studies.

To conclude optimization of the BIPI ligands for this substrate, we therefore combined the best substituents from the three regions to prepare a small set of hybrid ligands. These are shown in Table 3. We held the optimized 3,5-difluoro substitution for the diamine constant and used either the 4-chloro or 3,5-difluoro substitution on the phosphine. Three electron-withdrawing R_3 substituents were also examined. Turnover was somewhat diminished with these highly electron-deficient ligands. We found, however, that substituting cyclohexylethyl pyrrolidine for PMP as base led to higher isolated yields after 18 h than was observed with PMP with no loss in stereoselectivity.[8] The 2-naphthoyl R_3 substitution furnished the highest ee, as was observed in the initial ligand set. By combining the best substituents from the three tunable regions, we were able to arrive at an optimized ligand that generated oxindole **8** in 88% ee. This is significantly better than the best enantioselectivity one can obtain with BINAP or PHOX for this difficult substrate.

Using the BIPI ligands as tools to probe the electronic requirements of stereoinduction is under very active research. A study of substrate and reaction scope, crystal structures of metal complexes, and detailed NMR studies will be reported shortly in a full paper.

Supporting Information Available: Tables of ee and log er values and full experimental details and characterization for all compounds cited. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Full details of the effect of bases on turnover will be reported shortly in a full paper.