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Asymmetric Hydrogenation of Unsaturated Ureas with the BIPI Ligands

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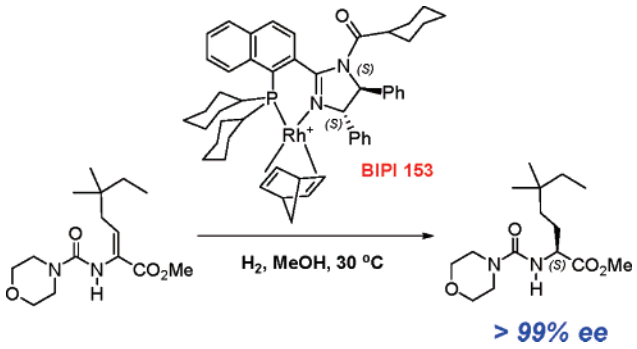
ABSTRACT



Asymmetric hydrogenation of unsaturated urea esters with the BIPI Ligands has been examined. Optimization of the P–N ligand structure has led to the development of chiral rhodium catalysts capable of producing the targets with >99% ee. The critical phosphine borane S_NAr reaction needed for ligand synthesis has been optimized to give the adducts in high yield at ambient temperature with no racemization. An extremely concise, economical, and scalable sequence to these important new ligands for catalysis of asymmetric hydrogenation has been developed.

Several molecules of biological interest to us possess a chiral urea ester moiety. We envisaged that this important subunit could be accessed by asymmetric hydrogenation of the requisite dehydro-urea esters. Enantioselective hydrogenations of unsaturated aminoesters with acyl- and carbamoyl-substitution on nitrogen are well precedented,[1] although the analogous ureas do not appear to have been studied. We report herein an asymmetric hydrogenation of these substrates using newly engineered chiral phosphinoimidazolines, the BIPI ligands,[2] with extremely high levels of stereocontrol (>99% ee).

During our process research analysis, we needed to develop an economical, practical, and scalable process for production of urea **2** in optically pure form. Initial ligand screening and optimization was done using the functionalized urea substrate **1** as shown in Scheme 1. We used cationic rhodium in the form of $Rh(NBD)_2BF_4$, due to the higher hydrogenation rates observed for NBD relative to COD in rhodium-catalyzed hydrogenations.[3] The screening reactions were performed in methanol at 30 °C, under 100 psi H_2, and 0.6 mol % (0.006 equiv) of catalyst. Most of the BIPI ligands containing one or two aryl groups on phosphorus[2,4] failed to give any turnover in this hydrogenation reaction,

(1) For reviews, see: (a) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 121−182. (b) Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7* (3), 355. (c) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37* (9), 633. (d) Noyori, R.; Kitamura, M.: Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101* (15), 5356. (e) McGarrity, J. F.; Brieden, W.; Fuchs, R.; Mettler, H.-P.; Schmidt, B.; Werbitzky, O. In *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley:Weinheim, 2004; pp 283−308.

(2) (a) Busacca, C. A. U.S Patent 6,316,620, 2001. (b) Busacca, C. A.; et al. *J. Org. Chem.* **2004**, *69* (16), 5187. (c) Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien, E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5* (4), 595.

(3) Drexler, H.-J.; Baumann, W.; Spannenberg, A.; Fischer, C.; Heller, D. *J. Organomet. Chem.* **2001**, *621* (1−2), 89.

(4) (a) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4* (26), 4713. (b) Guiu, E.; Claver, C.; Benet-Buchholz, J.; Castillon, S. *Tetrahedron: Asymmetry* **2004**, *15* (21), 3365.

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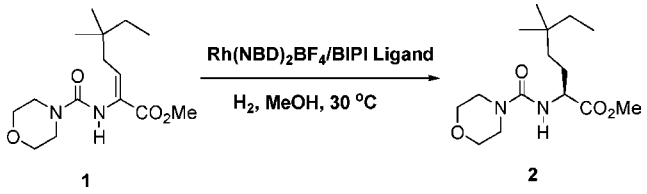
Scheme 1. Asymmetric Hydrogenation

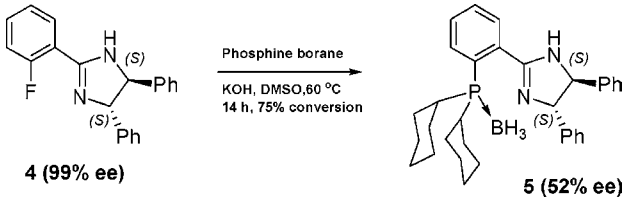


1 2

leading to recovered starting material. Dialkylphosphine substitution was thus found to be a general prerequisite for reactivity.

After evaluation of many available chiral diamines (alkyl and aryl) we chose to hold the chiral backbone of the ligand structure constant as the 1,2-diphenylethylenediamine (DPEDA) derivative. Importantly, both enantiomers of DPEDA are commercially available on a large scale. We decided to form the critical carbon−phosphorus bond by an S_NAr reaction. This type of nucleophilic substitution of arylfluorides is well-known for metal *phosphides*,[5] although S_NAr of phosphide *borane* anions has been far less studied. Recently, Imamoto[6] has described phosphine borane S_NAr reactions under very mild conditions. The latter method employed electrophile activation by formation of the stoichiometric arene chromium tricarbonyl complex. However, this method was not desirable in the process chemistry environment for large-scale operations. As a result, a significant amount of experimentation was required to develop a robust fluoroimidazoline S_NAr reaction with dialkylphosphide boranes. Specifically, two serious problems had to be overcome: incomplete conversion and unexpected and pronounced *racemization* of the S_NAr product. A typical S_NAr result before optimization is shown in Scheme 2.

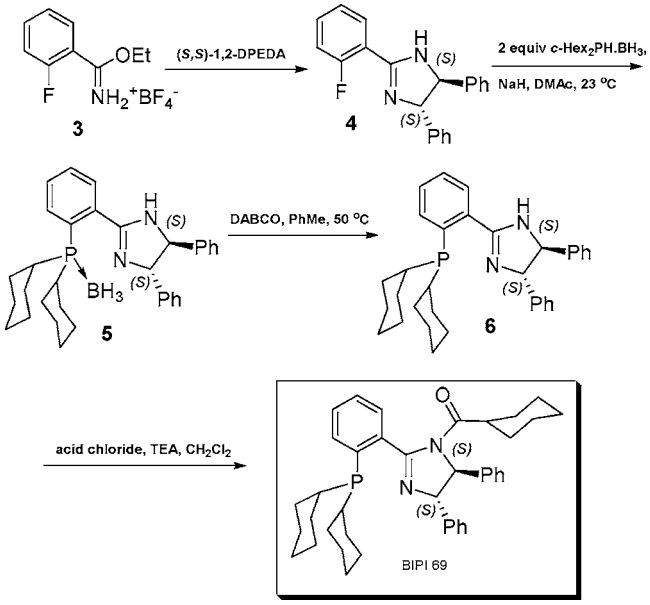
Scheme 2. S_NAr Reaction Prior to Optimization



Utilizing KOH as the base in DMSO, the reaction stalled at 75% conversion. More importantly, the product was found to have undergone extensive racemization under the conditions employed. Solvent, base, cation, and temperature were all found to be critical parameters controlling racemization.[7]

We ultimately discovered that stoichiometric formation of *two* equivalents of the phosphine borane anion prior to addition of the arylfluoride was the key to obtaining both 100% conversion and complete suppression of racemization. As shown in Scheme 3, two equivalents of dicyclohexylphosphine borane anion were generated in DMAc at ambient temperature using 60% NaH. When the aryl fluoride was subsequently charged, a deep orange- or red-colored reaction mixture indicative of the S_NAr reaction was immediately formed. The "obvious" explanation for this 2:1 stoichiometry requirement appeared to be that one equivalent of the phosphide served to deprotonate the imidazoline NH. This concept was readily invalidated, however. When one equivalent of phosphide anion was added to a separate flask containing one equivalent of deprotonated (NaH) fluoroimidazoline, less than 10% conversion occurred. The true explanation for this requirement is more subtle and is an active area of investigation. These S_NAr reactions could be performed at 23 °C, requiring from 4 to 16 hours to be completed (Scheme 3). Reactions in less polar solvents, such as THF, were far more sluggish. The isolated phosphine borane imidazolines[8] (**5**) were then generally deprotected with DABCO in toluene at 50 °C (**6**), and ligand synthesis was completed by addition of an electrophile to functionalize the nitrogen atom.

Scheme 3. Typical Ligand Synthesis



3 4 5 6

We felt it was critical to develop a ligand synthesis that was very direct, highly scalable, and inexpensive to allow for large-scale production. The synthesis outlined here is much shorter than typical routes to furnish highly enantioselective P−P ligands and relies upon a relatively inexpensive chiral diamine rather than a costly chiral diol. The route also avoids the need for optical resolution of intermedi-

(5) (a) Coote, S. J.; Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Synlett* **1993**, 509. (b) Dawson, G. J.; Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34* (19), 3149. (c) Tang, X.; Zhang, D.; Jie, S.; Sun, W.-H.; Chen, J. *J. Organomet. Chem.* **2005**, *690* (17), 3918.

(6) Katagiri, K.; Danjo, H.; Yamaguchi, K.; Imamoto, T. *Tetrahedron* **2005**, *61* (19), 4701.

(7) The mechanism of racemization is under close scrutiny and will be reported elsewhere in due course.

(8) An X-ray crystal structure of **5** is included in the Supporting Information.

ates common to many P−P ligand syntheses. We have recently demonstrated scalability by rapidly preparing >1 kg of BIPI 69 in a very facile campaign.

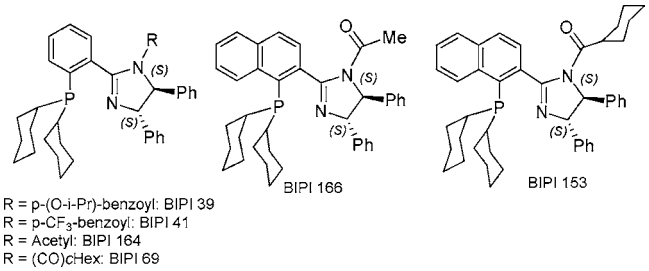


Figure 1. Ligands used.

The ligands used in this study are shown in Figure 1. The BIPI ligands were designed to allow for ready electronic tuning by varying the nitrogen substituent. We had expected that alkyl substitution on nitrogen would be beneficial, since most of the successful P−P ligands for asymmetric hydrogenation of olefins, such as DuPhos, Tangphos, and others,[9] are quite electron rich. To our surprise, alkyl substitution led to catalysts that gave poor turnover and low selectivity (0−10% ee). We then examined different types of acyl substitution on nitrogen. As shown in Table 1, electron rich

Table 1. Asymmetric Hydrogenation of Substrate **1**

entry	ligand no.	er	% ee
1	BIPI 41	85.5:14.5	71
2	BIPI 39	92.5:7.5	85
3	BIPI 164	97.2:2.8	94
4	BIPI 69	97.7:2.3	95
5	BIPI 166	99.1:0.9	98
6	BIPI 153	>200:1	>99

p-isopropoxybenzoyl was more enantioselective (85% ee) than the *p*-CF_3 analogue (71% ee, entries 1−2). We therefore reasoned that an alkyl amide might prove to be better still. This was indeed the case, as *N*-acetyl and *N*-cyclohexanecarbonyl gave the product with 94% ee and 95% ee, respectively (entries 3−4). The final stage of ligand optimization involved changing the "benzo core" from phenyl to naphthyl (entries 5−6). This modification led to a dramatic breakthrough in stereoselectivity, generating urea **2** with 98% ee and >99% ee, respectively, for **BIPI 166** and **BIPI 153**. The reasons for this improvement are not immediately clear, yet we speculate that the peri hydrogen of the naphthyl ring restricts the number of conformations available to the two cyclohexyl substituents. The remaining conformations may be more inherently enantioselective, leading to the extreme selectivity observed.

We next decided to screen our best ligand, **BIPI 153**, against a variety of structurally diverse dehydrourea esters to gain an understanding of the scope of this new asymmetric hydrogenation. The results for six different substrates are collected in Figure 2.

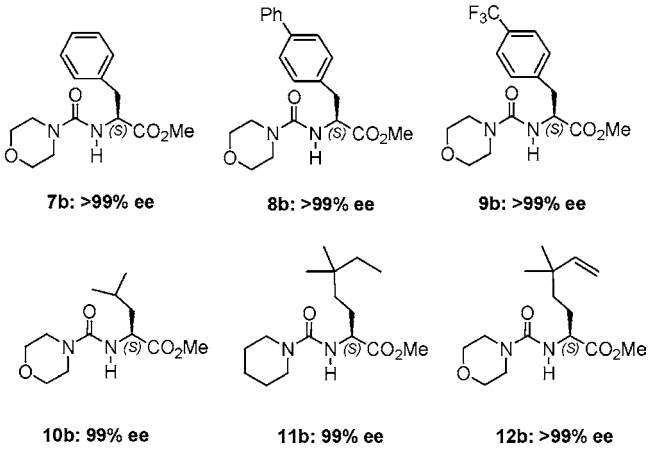


Figure 2. Asymmetric hydrogenation of additional substrates.

The phenylalanine analogues **7b**−**9b** were each generated in >99% ee, and the isoleucine target **10b**, in 99% ee. Variation of the urea functionality (**11b**) was also completely tolerated, as was introduction of a terminal olefin (**12b**), as less than 5% hydrogenation of this moiety was observed, and the product still formed in >99% ee.

We wanted to determine the absolute configuration of these urea products. This was accomplished by converting both (*S*)-phenylalanine methyl ester and (*S*)-isoleucine methyl ester to their morpholine urea derivative using commercial morpholine carbonyl chloride.

In both cases, these materials coeluted on chiral HPLC with the major enantiomer formed through the use of the (*S*,*S*)-BIPI ligands (**7b**, **10b**). Although we did not rigorously assign the absolute stereochemistry of the other products, it seems quite likely that the (*S*,*S*) ligand series will furnish ureas with the (*S*) absolute configuration in most cases.

In conclusion, we have applied the BIPI ligands to the asymmetric hydrogenation of unsaturated urea esters and have uncovered a catalyst, **BIPI 153**, that proceeds with near-perfect enantioselection. The synthetic process to access this ligand class is short, simple, and scalable, and leads to a very practical asymmetric hydrogenation sequence. The high

(9) For examples, see: (a) Cobley, C. J.; Johnson, N. B.; Lennon, I. C.; McCague, R.; Ramsden, J. A.; Zanotti-Gerosa, A. In *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley:Weinheim, 2004; 269−282. (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33* (6), 363. (c) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4* (23), 4159. (d) Liu, D.; Zhang, X. *Eur. J. Org. Chem.* **2005**, *4*, 646. (e) Almena, J.; Monsees, A.; Kadyrov, R.; Riermeier, T. H.; Gotov, B.; Holz, J.; Boerner, A. *Adv. Synth. Cat.* **2004**, *346* (11), 1263. (f) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126* (19), 5966. (g) Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G. *Top. Catal.* **2006**, *40* (1−4), 185. (h) Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19* (1), 3. For P−N ligands, see: (i) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941. (j) Liu, D.; Tang, W.; Zhang, X. *Org. Lett.* **2004**, *6* (4), 513.

levels of stereocontrol observed here have previously been obtained almost exclusively with P−P ligands.[10] Appropriately designed P−N ligands such as these can now clearly be used for this important class of asymmetric transformations as well. Application of the BIPI ligands to a wide range of unsaturated substrates is under active investigation and will be reported in due course.

(10) For P−N ligands in asymmetric hydrogenations of functionalized olefins, see: (a) Bunlaksananusorn, T.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3941. (b) Yamada, I.; Ohkouchi, M.; Yamaguchi, M.; Yamagishi, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1869. (c) Brauer, D. J.; Kottsieper, K. W.; Rossenbach, S.; Stelzer, O. *Eur. J. Inorg. Chem.* **2003**, *9*, 1748.

Supporting Information Available: Full experimental procedures and compound characterization; X-ray crystallographic data for **5**; complete ref 2b. This material is available free of charge via the Internet at http://pubs.acs.org.

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