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Synthesis of tunable phosphinite–pyridine ligands and their applications in asymmetric hydrogenation

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Abstract—A new class of modular conformationally rigid N,P ligands is conveniently synthesized from readily available starting material. Iridium complexes with these ligands have demonstrated excellent enantioselectivity (up to 99% ee) in the asymmetric hydrogenation of aryl alkenes.

Transition-metal catalyzed asymmetric hydrogenation is one of the most powerful methods for preparing chiral compounds. While ruthenium- and rhodium-catalyzed asymmetric hydrogenations of chelating olefins have a long history,[1] unfunctionalized olefins still represent a challenging class of substrates. During the past few years, Pfaltz and others[2a–m] have developed chiral mimics of Crabtree's catalyst,[3] which have been used successfully for asymmetric hydrogenation of arylalkenes. However, since iridium-catalyzed asymmetric hydrogenation is still highly substrate dependent, subtle changes of ligand structure either electronically or sterically often bring in dramatic impacts on enantioselectivities. Therefore, the development of new efficient and tunable chiral ligands for iridium-catalyzed hydrogenation is a continuing challenge.

Among many chiral N,P ligands successfully applied in the asymmetric hydrogenation, the N,P ligands derived from pyridine was reported in only a few cases.[2d,i] The representative examples were ligands **1** and **2** (Fig. 1), but both synthetic routes are long and they made it difficult to finely tune the electronic and steric effect. For designing of a new class of N,P ligands, Andersson[2k] recently summarized the following criteria: (1) contain a nitrogen atom and a phosphorus to get a significant trans effect and reaction site discrimination, (2) be able to form a six-member chelate ring upon complex formation, and (3) contain a rigid backbone fused to the aromatic heterocycle to reduce conformational flexibility. With these criteria in mind, the success of the above ligands **1** and **2** motivated us to develop a new class of modular conformationally rigid and structure tunable pyridine-derived chiral N,P ligands **3**.[4] This ligand contains the following three sites, which can be finely tuned: substituent Ar of phosphorus, substituent R of pyridine ring and size n of the fused ring. Herein, we report a procedure suitable for convenient ligand synthesis and in application of aryl alkenes as a means of hydrogenation with up to 99% ee.

The synthesis of pyridyl phosphinites ligands **3** was summarized in Scheme 1. The acetate **6** was synthesized on a multigram scale in three steps from cheap starting materials such as simple cyclic ketones **4** and ethyl acetoacetate **5** according to the known procedure.[5a–d] Hydrolysis of the acetate **6** with K_2CO_3/methanol afforded the corresponding racemic chloro alcohol **7** in high yields. Chemical resolution of **7** or **6** is the most convenient method to obtain the chiral intermediate **7**. Unfortunately, all attempts for selective crystallization of a diastereomeric salt with chiral acids were unsuccessful, presumably due to the weak basicity of pyridine nitrogen and intramolecular hydrogen bonding.[6] Then, we turned our attention to the enantioselective preparation of **7** by an asymmetric reduction of corresponding ketone.[7] Therefore, the racemic chloro alcohol **7** was transformed to the corresponding chloroketone **8** in 90–91% yields by Swern oxidation according to the literature procedure.[5b] The commercially available reagent CBS was used for the enantioselective reduction. Under optimized conditions,[8] catalytic asymmetric reduction of

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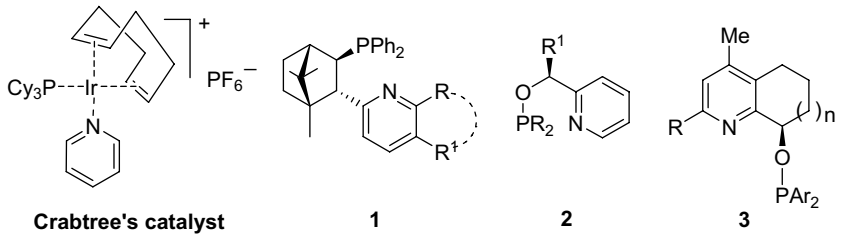
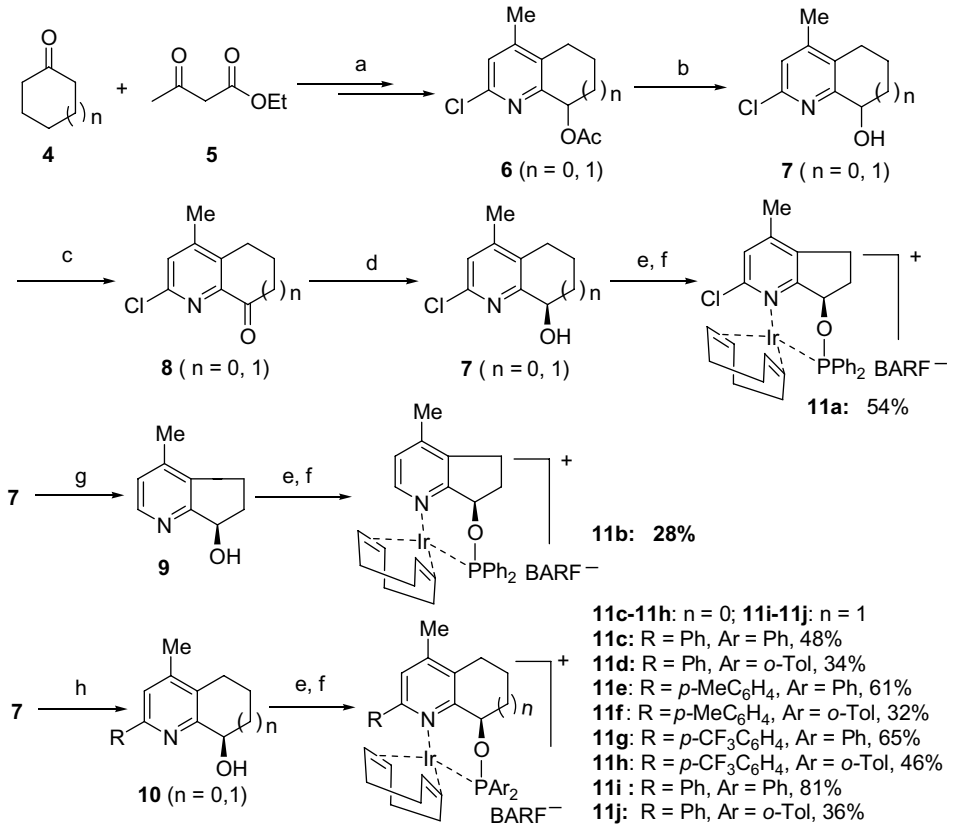


Figure 1.



Scheme 1. Synthesis of pyridyl phosphinite complexes **11a**–**j**. Reagents and conditions: (a) see Ref. 5; (b) K_2CO_3, methanol, rt, 2–6 h; (c) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, −78 °C to rt; (d) (*S*)-Me–CBS (0.1 equiv), BH_3·THF, 30 °C, 1.5–2 h, 87% ee ($n = 1$, 99% ee after crystallization) and 68% ee ($n = 2$, >99% ee after crystallization); (e) for Ar = Ph: Ph_2PNEt_2/imidazole/Et_3N, CH_2Cl_2, 10–24 h; for Ar = *o*-Tol: (*o*-Tol)$_2PNEt_2$/4,5-dichloroimidazole/Et_3N, $ClCH_2CH_2Cl$, reflux, 36 h; (f) $[Ir(COD)Cl]_2$, CH_2Cl_2, reflux, 1.5 h, then $NaBAr_F$, reflux, 30 min, H_2O, 10 min, BAr_F = (tetrakis[3,5-bis(trifluoromethyl)phenyl]borate); (g) Pd/C, 95% EtOH, H_2, rt, 4 h, 75%; (h) $Pd(PPh_3)_4$, $ArB(OH)_2$, Na_2CO_3/H_2O, EtOH, $MeOCH_2CH_2OMe$, reflux, 16 h.

chloroketone with (*S*)-Me–CBS–borane[9] provided (*R*)-chloro alcohol **7**[10] in quantitative yields and 87% ee ($n = 0$) or 68% ee ($n = 1$). For **7** ($n = 0$), the mother liquor of one recrystallization from the petroleum ether/Et_2O/EtOH was subsequently crystallized three times in *i*-PrOH/hexane to give the optically pure compound with 6% recovery. For **7** ($n = 1$), the mother liquor of three recrystallization from Et_2O was then crystallized once in hexane to give the optically pure compound with 55% recovery.

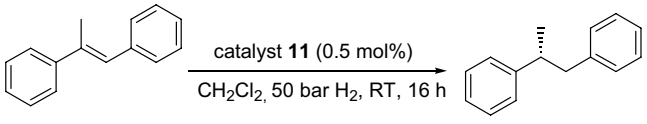
To study the influence of three modular centers of the ligands, a series of ligands were synthesized from the intermediate **7**. The chloro alcohol **7** was dechlorinated to afford **9** using Pd/C in 95% EtOH. Likewise, the chloro alcohol **7** was also subjected to a Suzuki coupling reaction with the corresponding arylboronic acid. The reactions proceeded smoothly in the presence of 3 mol % $Pd(PPh_3)_4$ and afforded the desired products **10** in high yields.

Deprotonation of the alcohol **7** with *n*-BuLi and subsequent reaction with the chlorodiphenylphosphine did not afford the desirable phosphinites **3**.[2d] However, reaction with *N*,*N*-diethyl aminodiphenylphosphanes in the presence of imidazole, the desired phosphinites were obtained at room temperature or reflux condition.[2d] For the steric hindered diethylaminodiarylphosphanes (Ar = *o*-Tol), no product was obtained under the above conditions even when 4,5-dichloroimidazole was used.

Nevertheless, the corresponding product was successfully obtained at reflux when a higher boiling point solvent 1,2-dichloroethane was used in the presence of 4,5-dichloroimidazole. The products namely, phosphinites **3** can be isolated by column chromatography under nitrogen in over 50% yields. However, these compounds are not stable, therefore, the reaction mixtures were subjected to a flash chromatography through a degassed silica gel in order to remove some impurities and directly used for the next step. The corresponding iridium complexes were made by a slightly modified standard literature procedure, and the resulting complexes are air stable foaming orange to red solid, which can be conveniently purified by chromatography.

Hydrogenation of (*E*)-1,2-diphenylpropene **12** was chosen as a model reaction to test potential catalysts. The hydrogenations were carried out at room temperature under 50 bar of hydrogen pressure using CH_2Cl_2 as the solvent. In this system, the selectivity and reaction reactivity were dependent on catalyst structure (Table 1). Firstly, for cyclopentanone derived catalysts (**11a–h**), excellent reactivity was observed except for **11b**. The enantioselectivity increased from 86% ee (R = H) to 98% ee (R = Ph) when the bulk of R group increased. The similar enantioselectivity was obtained when aryl group changed from electron-withdrawing group *p*-$CF_3C_6H_4$ to electron-donating *p*-$CH_3C_6H_4$. Secondly, upon the changing from five-member-ring to a six-member-ring derivative, the selectivity and reactivity of catalyst lowered significantly (entry 9 vs entry 3 and entry 10 vs entry 4). Thirdly, the enantioselectivities of the ligands with $(o\text{-Tol})_2P$ group was slightly superior to that of the corresponding ligands with Ph_2P group. Among the iridium complexes, the highest ee value (99%) was obtained with catalyst **11f**, which has a *p*-methylphenyl group on pyridine ring. It is noteworthy that the enantioselectivity with ligands **3** was comparable to that achieved with other chiral N,P ligands.[2] We have tested other two substrates ethyl 2-methylcinnamate **14** and allylic alcohol **15** with catalyst **11**, good enantioselectivities (88% ee and 86% ee) were also obtained, respectively.

Table 1. Iridium-catalyzed asymmetric hydrogenation of (*E*)-1,2-diphenylpropene **12**

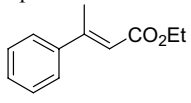


12 **13**

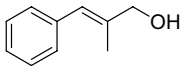
Entry	Catalyst	Conv (%)[a]	ee (%)[b]
1	**11a**	>99	86 (*R*)
2	**11b**	83	95 (*R*)
3	**11c**	>99	98 (*R*)
4	**11d**	>99	98 (*R*)
5	**11e**	>99	98 (*R*)
6	**11f**	>99	99 (*R*)
7	**11g**	>99	98 (*R*)
8	**11h**	>99	97 (*R*)
9	**11i**	32	86 (*R*)
10	**11j**	85	89 (*R*)

[a] The conversion was calculated based on the ratio of methyl group by ^1H NMR.

[b] Ee was measured by HPLC and absolute configuration of the product was determined by comparison of the sign of the optical rotation to reported data.



14



15

11f: 88% ee, >99% **11g:** 86% ee, >99%

In conclusion, we have developed a new class of modular conformationally rigid N,P-ligands for iridium-catalyzed asymmetric hydrogenation. Excellent reactivities and enantioselectivities were obtained in the hydrogenation of aryl alkenes. Further studies on optimized synthesis of the ligand and application to other asymmetric reactions are underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.111.

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