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Asymmetric Hydrogenation of Enamides, α-Enol and α-Enamido Ester Phosphonates Catalyzed by IndolPhos-Rh Complexes

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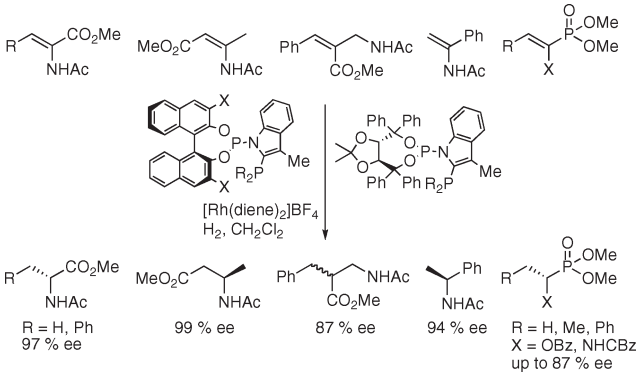

The scope of the IndolPhos-Rh-catalyzed asymmetric hydrogenation of enamides, α-enol and α-enamido ester phosphonates, has been investigated. In addition, Taddol-based IndolPhos ligands are introduced. High activities and good to excellent enantioselectivities up to 99% ee are obtained for a broad range of structurally diverse substrates, giving important chiral products such as α, β^2, and β^3 amino acid derivatives, arylamines, and amino and hydroxy phosphonates.

Asymmetric rhodium-catalyzed hydrogenation of prochiral olefins has been proven to be an attractive and efficient strategy for the introduction of chirality in many fine-chemical intermediates for the production of pharmaceuticals.[1] Being a mature field of research, a plethora of catalysts for this reaction have been developed in the last four decades, most frequently based on phosphorus ligands.[2] Therefore, improvement of these catalysts is challenging and only justified if two of the main challenges can be tackled, i.e., substrate specificity and availability of the chiral ligand. One approach to obtain a broad substrate scope utilizes combinatorial ligand synthesis[3] or supramolecular assembly of ligands,[4] which create large libraries of catalysts, and therefore increase the probability of finding an efficient catalyst for a given substrate. Alternatively, one can rely on privileged ligands that have proven to induce good enantioselectivities for a broad range of substrates.[5] Importantly, these ligands have to be synthesized in no more than one to three steps from cheap, commercially available starting materials to become applicable in this field.

Hybrid bidentate phosphine−phosphoramidite ligands are promising candidates for meeting the two challenges outlined above.[6,7] Specific substrate coordination, facilitated by two nonequivalent donor atoms, enables asymmetric hydrogenation of a broad range of prochiral olefins. Second, as the different donor atoms are often combined by means of a simple condensation, their synthesis is short and allows for easy modification. This concept was elegantly illustrated by Zheng and coworkers, who used hybrid phosphine−phosphoramidite, THNAPhos, for highly enantioselective hydrogenation of α-enol and α-enamido phosphonates, α-dehydroamino acid esters, α-arylenamides, and dimethyl itaconate.[8]

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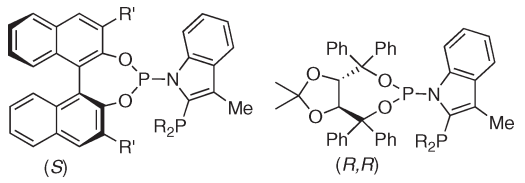


1a R = Ph; R' = H
1b R = ^{i}Pr; R' = H
1c R = Cy; R' = H
1d R = ^{o}Tol; R' = H
1e R = Ph; R' = $SiMe_3$
1f R = ^{i}Pr; R' = Me

2a R = Ph
2b R = ^{i}Pr

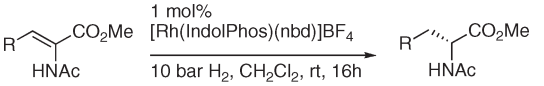
FIGURE 1. Structure of IndolPhos ligands **1a**−**f** and new Taddol derived ligands **2a**,**b**.

Our group contributed to this field with the development of IndolPhos (**1**), a readily available hybrid phosphine−phosphoramidite based on a rigid 3-methylindole backbone (Figure 1).[9] The use of a very rigid backbone connecting the inequivalent phosphorus donor atoms is proposed to be pivotal in order to achieve high selectivities over a broad range of substrates as it provides a constant chiral pocket, which is not affected greatly by the structure of the substrate. The potential of this ligand was demonstrated in asymmetric allylic alkylation,[10] hydroformylation, and hydrogenation of methyl 2-acetamidoacrylate, dimethyl itaconate, and 2-hydroxymethyl propionates.[11] However, a full demonstration of the broad applicability of **1** in asymmetric hydrogenation is lacking, but necessary in order to consider this ligand useful from an industrial point of view. We therefore report on the IndolPhos-Rh-catalyzed hydrogenation of enamides giving acces to enantiomerically enriched, protected α-, β^2-, and β^3-amino acid esters, and optically active arylamines. Furthermore, α-enol and α-enamido phosphonates are hydrogenated to their corresponding α-hydroxy and α-amino phosphonates. It should be noted that all of these products are of relevance to the pharmaceutical community as intermediates in drug synthesis.

To introduce more diversity in the IndolPhos library and increase the propensity of successful conversions, Taddol-based IndolPhos ligands **2** were introduced. Even though generally Taddol-derived phosphite and phosphoramidite ligands tend to give lower ee than their Binol derivatives, recent results from our laboratory have shown superior selectivity of Taddol-based phosphine−phosphites in the asymmetric hydroformylation of styrene.[12] The new ligands are prepared in similar fashion as the Binol-based IndolPhos ligands **1** (see the Supporting Information).

In our initial communication, we reported the hydrogenation of methyl 2-acetamidoacrylate (**3b**) with full conversion and up to 97% ee using an IndolPhos-Rh catalyst.[9] To study the effect of further substitution on the double bond, (*Z*)-methyl 2-acetamidocinnamate (**3a**) was hydrogenated with IndolPhos-Rh catalysts to yield the protected phenylalanine methyl ester (Table 1, entries 1−9). For comparison, the results obtained in the hydrogenation of **3b** are included as

TABLE 1. IndolPhos-Rh-Catalyzed Asymmetric Hydrogenation of Acyl-Protected (*Z*)-Dehydroamino Acid Methyl Esters 3[a]



3a: R = Ph
3b: R = H

entry	ligand	substrate	% conversion[b]	% ee (confign)[b]
1	**1a**	**3a**	59	24 (*R*)
2	**1b**	**3a**	100	91 (*R*)
3[c]	**1b**	**3a**	94	91 (*R*)
4	**1c**	**3a**	100	88 (*R*)
5	**1d**	**3a**	50	76 (*R*)
6	**1e**	**3a**	48	87 (*R*)
7	**1f**	**3a**	100	97 (*R*)
8	**2a**	**3a**	16	88 (*R*)
9	**2b**	**3a**	5	74 (*R*)
10	**1a**	**3b**	100	13 (*S*)
11	**1b**	**3b**	100	86 (*R*)
12	**1e**	**3b**	100	36 (*R*)
13	**1f**	**3b**	100	97 (*R*)
14[d]	**1f**	**3b**	100	98 (*R*)
15	**2a**	**3b**	100	91 (*R*)
16	**2b**	**3b**	100	83 (*R*)

[a]Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, 10 bar of H_2, at 25 °C for 16 h, using $[Rh(nbd)_2]BF_4$ as the metal precursor. [b]Conversion and ee were determined by chiral GC (Chiralsil DEX-CB). [c]S/C ratio = 5000:1; reaction time = 1.8 h. [d]S/C ratio = 10000:1; reaction time = 1.8 h.

well (entries 10−13). Catalysts were generated in situ from the corresponding ligand and $[Rh(nbd)_2]BF_4$. When using the diphenylphosphine ligand **1a**, low ee at moderate conversion is obtained. Good enantioselectivities are obtained for ditolylphosphine ligand **1d** and bulky 3,3′-bis-TMS-bisnaphthol-containing ligand **1e**, albeit at moderate conversion up to 50% only. Full conversion and high enantioselectivities are achieved when alkylphosphines are used. Introducing methyl groups in 3 and 3′ position on the bisnaphthol moiety, leads to an excellent ee of 97% for the catalyst based on ligand **1f**. The new Taddol derived ligands **2a**,**b** give good ee and low conversion for **3a**; however, full conversion and good ee up to 91% are obtained for **3b** (entries 15 and 16). Contrary to our earlier findings in the hydrogenation of **3b**, in which we observed a reversal of absolute configuration of the product when using ligand **1a**,[9] the hydrogenation of **3a** yields the *R*-enantiomer for all ligands. This result suggests that the same mechanism is operative for all IndolPhos-Rh catalysts.

When these results are compared to the results obtained for **3b**, which lacks the phenyl substituent on the double bond, it appears that the trisubstituted character of the double bond lowers the reactivity, as expected. Whereas full conversion was obtained for all ligands in the case of **3b**, only more electron-rich alkylphosphines give full conversion for **3a**. However, the activity and selectivity obtained with ligand **1f** are excellent for this benchmark substrate and identical with those obtained for **3b**. Therefore, for the best catalyst, there is no influence on the efficiency in the asymmetric hydrogenation from the introduction of a phenyl substituent on the double bond.

The high activity of the catalysts is further illustrated by the possibility to lower the catalyst concentration (Table 1, entries 3 and 14). For **3a**, 94% conversion is obtained after

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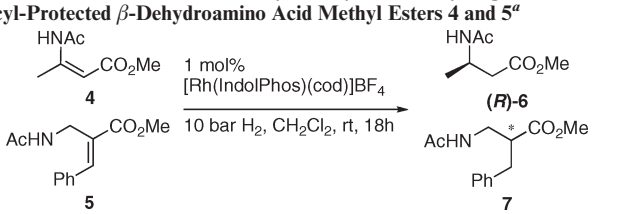
1.8 h without loss of enantioselectivity at a substrate/catalyst (S/C) ratio of 5000:1, using ligand **1b**. In the case of **3b**, full conversion is obtained within 1.8 h at an S/C ratio of 10000:1, using ligand **1f**. The ee even increases at this low catalyst loading to 98%. These numbers satisfy the criteria for commercial large-scale hydrogenation,[13] which is remarkable considering the simplicity of the ligand. Even though many highly selective catalysts have been reported for these benchmark substrates,[2] a thorough investigation of the activity in terms of turnover-frequency is often lacking, which hinders comparison of the high activities reported here to other systems.

After realizing that the IndolPhos-Rh catalysts were active in the asymmetric hydrogenation of trisubstituted olefins, we envisioned that also β^3-amino esters are feasible synthetic targets through hydrogenation of the corresponding β^3-acylamino acrylates. This reaction has recently gained much attention because the resulting β^3-amino acid derivatives are important building blocks for making chiral drugs.[14] Even though many ligands are effective in this transformation, only a few chiral ligands can provide the product in over 95% ee.[2] Hydrogenation of (*Z*)-methyl 3-acetamido-2-butenoate (**4**), using IndolPhos-Rh catalysts, gives acyl-protected β^3-alanine methyl ester (**6**) at 10 bar of H_2 (Table 2, entries 1−8). For the arylphosphine ligands, low to moderate conversion is obtained. Moderate conversion and high ee is achieved for TMS-substituted bisnaphthol derivative **1e**. On the other hand, high conversion and excellent ee values are obtained when using alkylphosphines. Isopropyl-substituted phosphines, in particular, give almost complete enantioselection and full conversion. These efficiencies are among the best reported to date for this transformation. The Taddol-based ligands give no or negligible activity and selectivity.

The synthesis of β^2-amino acid derivatives by means of asymmetric hydrogenation is far less explored to date, compared to their β^3 isomers.[15] This triggered our interest to utilize IndolPhos-Rh catalysts in the asymmetric hydrogenation of (*E*)-α-phenyl-β-(acetamidomethyl)acrylate (**5**), giving acyl-protected β^2-phenylalanine methyl ester (**7**) (Table 2, entries 9−16). All catalysts give good ee at moderate to low conversion, except for the ones generated from TMS-substituted ligand **1e** and Taddol-based ligand **2b**. Surprisingly, the highest ee of 87% was reached with the parent ligand **1a**, which gave poor results for the other substrates discussed above. In addition, the Taddol-based derivative **2a**, containing also a diphenylphosphine moiety, gives almost identical ee values at somewhat lower conversion. In terms of enantioselectivity, the performance of IndolPhos-Rh compares relatively well to the highest ee for this reaction of 96% ee, reported by our group.[41]

TABLE 2. IndolPhos-Rh-Catalyzed Asymmetric Hydrogenation of Acyl-Protected β-Dehydroamino Acid Methyl Esters 4 and 5[a]



entry	ligand	substrate	% conversion[b]	% ee[b]
1	**1a**	**4**	5	29
2	**1b**	**4**	95	98
3	**1c**	**4**	77	91
4	**1d**	**4**	11	10
5	**1e**	**4**	43	89
6	**1f**	**4**	100	99
7	**2a**	**4**	0	-
8	**2b**	**4**	10	17
9	**1a**	**5**	38	87
10	**1b**	**5**	26	73
11	**1c**	**5**	15	83
12	**1d**	**5**	44	73
13	**1e**	**5**	36	45
14	**1f**	**5**	24	81
15	**2a**	**5**	6	86
16	**2b**	**5**	1	40

[a]Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, 10 bar of H_2, at 25 °C for 18 h, using $[Rh(cod)_2]BF_4$ as the metal precursor. [b]Conversion and ee were determined by chiral GC (for **6**: Chiralsil DEX-CB; for **7**: Supelco *ss*-dex 225). The *R*-enantiomer was obtained in all cases for **6**. The absolute configuration for **7** was not determined.

Asymmetric hydrogenation of α-arylenamides is an attractive route toward optically pure arylamines, which are valuable intermediates in the synthesis of pharmaceuticals. As opposed to the substrates described earlier, these enamides do not contain an additional ester functionality, which may coordinate to the metal center. We conducted the hydrogenation of *N*-(1-phenylethenyl)acetamide (**8**) under standard conditions and obtained full conversion for all catalysts screened, except for **2a** (Table 3). A high ee of 92% is obtained for the catalyst generated from ligand **1a**. Parallel to the high selectivity obtained for substrate **5**, this efficiency is in stark contrast to the results obtained with this catalyst for the other enamide substrates, where low ee values up to only 24% were obtained. In general, all catalysts give good to high enantioselectivities up to 94%, except for ditolylphosphine ligand **1d** and the Taddol-derived ligands **2a**,**b**. The Taddol group as a source for chirality is clearly far less suited for this substrate. Interestingly, all catalysts give the *S* enantiomer as the major product, whereas for the other enamide substrates **2** and **4**, the *R* product is obtained. Such a reversal of absolute configuration has up to now only been reported for monophosphoramidite−rhodium catalysts.[16]

For the AH of α-arylenamides, selectivities up to 99% ee have been reported with bidentate phosphorus ligands.[2] However, when IndolPhos is compared to other ligands, which are prepared in a one- or two-step procedure, like MonoPhos, our

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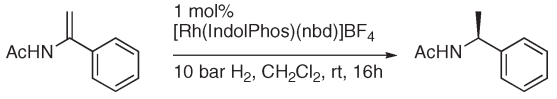
TABLE 3. IndolPhos-Rh-Catalyzed Asymmetric Hydrogenation of *N*-(1-Phenylethenyl)acetamide 8[a]

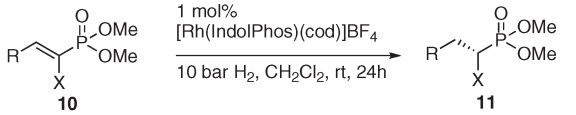


8 **(*S*)-9**

entry	ligand	substrate	% conversion[b]	% ee[b]
1	**1a**	**8**	100	92
2	**1b**	**8**	100	94
3	**1c**	**8**	100	88
4	**1d**	**8**	100	49
5	**1e**	**8**	100	91
6	**1f**	**8**	100	81
7	**2a**	**8**	32	17
8	**2b**	**8**	100	15

[a]Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, 10 bar of H_2, at 25 °C for 16 h, using $[Rh(nbd)_2]BF_4$ as the metal precursor. [b]Conversion and ee were determined by chiral GC (Chiralsil DEX-CB). The *S*-enantiomer was obtained in all cases.

TABLE 4. IndolPhos-Rh-Catalyzed Asymmetric Hydrogenation of α-Enamido and α-Enol Phosphonates 10a−d[a]



10 **11**

X = OBz, NHCbz
R = H, Me, Ph

entry	ligand	substrate	% conversion[b]	% ee (config)[b]
1	**1a**	**10a**: R = H, X = OBz	100	32 (*S*)
2	**1b**	**10a**: R = H, X = OBz	100	60 (*S*)
3	**1c**	**10a**: R = H, X = OBz	100	69 (*S*)
4	**1d**	**10a**: R = H, X = OBz	100	25 (*S*)
5	**1e**	**10a**: R = H, X = OBz	100	39 (*S*)
6	**1f**	**10a**: R = H, X = OBz	100	87 (*S*)
7	**2a**	**10a**: R = H, X = OBz	27	15 (*S*)
8	**2b**	**10a**: R = H, X = OBz	100	82 (*S*)
9	**2b**	**10b**: R = Me, X = OBz	30	46 (*S*)
10	**2b**	**10c**: R = Ph, X = OBz	5	40 (*S*)
11	**1a**	**10d**: R = H, X = NHCBz	100	55 (*S*)

[a]Reactions were performed in CH_2Cl_2, Rh/L = 1:1.1, Rh/substrate = 1:100, 10 bar of H_2, at 25 °C for 24 h, using $[Rh(cod)_2]BF_4$ as the metal precursor. [b]Conversion and ee were determined by chiral HPLC (see the Supporting Information for conditions).

system performs well. Feringa and co-workers report 86% ee at room temperature for the asymmetric hydrogenation of **8**.[16]

Chiral amino and hydroxy phosphonates are interesting synthetic targets, as they display enzyme inhibition, facilitated by their ability to mimic hydrolysis transition states.[17] Asymmetric hydrogenation of the corresponding enol or enamido phosphonates is an attractive route toward these optically active phosphonates, because the substrates can be obtained in two steps from the corresponding acyl chloride and trialkyl phosphite.[8,18] IndolPhos-Rh complexes provide active catalysts for the hydrogenation of α-enol and α-enamido phosphonates **10a**−**d** (Table 4). For the unsubstituted enol phosphonate **10a**, full conversion was obtained in all cases, except for ligand **2a**. Alkylphosphines provide catalysts giving higher ee up to 87%, compared to the arylphosphines. The good activity and selectivity of Taddol-derived ligand **2b** is remarkable, as this ligand gave an unsuccessful catalyst for the hydrogenation of most enamides. Indeed, also for substituted enol phosphonates **10b**,**c**, this ligand provided the highest ee up to 45%, whereas Binol-based ligands gave ee values not exceeding 20% (see the Supporting Information). For enamido phosphonate **10d**, full conversion and enantioselectivities up to 55% ee were obtained. Even though the reported enantioselectivities are promising, ee values over 95% have been reported for these substrates.[8,18]

The substrate scope presented in this study highlights the versatility of IndolPhos-Rh complexes in the hydrogenation of a variety of enamides and phosphonates. The ligands are especially suited for the hydrogenation of β^3-amino acid precursors with selectivities up to 99% ee. The ligand screening reveals that for IndolPhos ligands **1a**−**f**, alkylphosphines and in particular isopropyl-substituted phosphines give more active and selective catalysts for the majority of substrates. We are currently conducting mechanistic studies to explain these effects, which will be reported in due time. However, the observed trend does not hold in all cases and therefore demonstrates that screening of a ligand library is necessary for finding the optimal catalyst. The new Taddol-derived IndolPhos ligands **2** are less suited for the hydrogenation of enamides but show good activity and selectivity for enol phosphonates and even outperform the Binol-based ligands for substituted phosphonates. In the hydrogenation of α-dehydro amino acid esters, turnover numbers of over 10000 are found, which make IndolPhos-Rh catalysts suitable candidates for hydrogenations on industrial scale.

Experimental Section

General Hydrogenation Procedure. The hydrogenation experiments were carried out in a stainless steel autoclave (150 mL) charged with an insert suitable for 8 reaction vessels (including Teflon mini stirring bars) for conducting parallel reactions. In a typical experiment, the reaction vessels were charged with 1.0 μmol of $[Rh(diene)_2]BF_4$, 1.1 μmol of ligand, and 0.10 mmol of alkene substrate in 1.0 mL of CH_2Cl_2. Before starting the catalytic reactions, the charged autoclave was purged three times with 15 bar of dihydrogen and then pressurized at 10 bar of H_2. The reaction mixtures were stirred at 22 °C for the appropriate reaction time. After catalysis the pressure was reduced to 1.0 bar, and the conversion and enantiomeric purity were determined by chiral GC or HPLC.

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Supporting Information Available: General experimental methods, synthetic procedures, and characterization for ligands **2a**,**b**, additional catalyst screening results, and analyses of ee values of the hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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