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Asymmetric hydrogenation of α-arylacrylic and β-arylbut-3-enoic acids catalyzed by a Rh(I) complex of a monodentate secondary phosphine oxide ligand†

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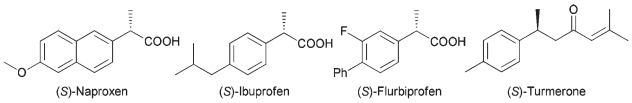
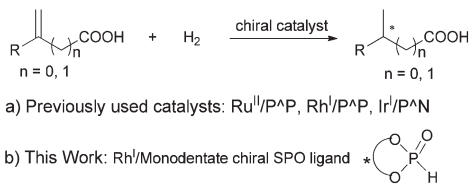
The Rh^I complexes of chiral secondary phosphine oxide ligands have been disclosed to be efficient for the catalytic asymmetric hydrogenation of α-arylacrylic and β-arylbut-3-enoic acids, providing the corresponding chiral α-arylpropanoic and β-arylbutanoic acids in excellent yields with up to 97% ee, including several anti-inflammatory drugs.

Optically active α-arylpropanoic or 3-arylbutanoic acids and their derivatives represent important classes of chiral chemicals that have found widespread pharmaceutical and synthetic applications. For example, α-arylpropanoic acids such as Naproxen and Ibuprofen are well-known non-steroid anti-inflammatory and analgesic drugs,[1]



while the 3-arylbutanoic acid derivatives such as chiral 3-arylbutanols can be used as important intermediates for the synthesis of aromatic sesquiterpenes of the bisabolane family.[2] Although a variety of methods for the asymmetric syntheses of the α-arylpropanoic acids[3] or 3-arylbutanoic acids[4] have been developed, catalytic asymmetric hydrogenation (AH) of the corresponding α-arylacrylic or β-arylbut-3-enoic acids represents the most straightforward and environmentally benign approach to these compounds. In the AH of α-arylacrylic acids, high enantioselectivities have been achieved with Ru^{II}/diphosphine,[5] Rh^I/diphosphine[6] or Ir^I/phosphine oxazoline catalysts.[5m,7] On the other hand, the AH of β-arylbut-3-enoic acids has been relatively less explored, with moderate to high enantioselectivities being achieved using Ru^{II}/diphosphine[5c,8] or Rh^I/diphosphine catalysts.[9] As far as we know, there is only a single example using a Rh^I complex of a monodentate chiral phosphine for AH of α-phenylacrylic acid with poor enantioselectivity (15% ee),[10] despite their ready preparation and good stability, among other salient features.[11] Herein, we report our results on the use of a chiral monodentate secondary phosphine oxide (SPO) ligand for the efficient Rh^I-catalyzed AH of a wide variety of α-arylacrylic or β-arylbut-3-enoic acids, to give the corresponding α-arylpropanoic and β-arylbutanoic acids in excellent yields with good to excellent enantioselectivities (up to 97% ee) (Scheme 1).



Scheme 1 Catalysts for AH of α-arylacrylic and β-arylbut-3-enoic acids.

Chiral SPOs are a type of readily accessible P ligands that are stable to air oxidation and inert to water, but their application in transition-metal-catalyzed asymmetric reactions has been relatively less explored.[12] Very recently, we have demonstrated that some chiral SPO compounds, either used alone or in combination with achiral triarylphosphines, are highly efficient chiral ligands for Rh^I-catalyzed AH of α-substituted ethenylphosphonic acids, β,β-diarylacrylic acids, and α- or β-trifluoromethyl acrylic acids.[13] Encouraged by these results, we sought to extend the Rh^I/SPO catalyzed AH methodology to the α-arylacrylic and β-arylbut-3-enoic acids. The study was initiated by surveying the effects of several reaction parameters, including chiral SPO ligands (**L1–L6**), Rh^I source, solvent, temperatures, as well as base additives, on the Rh^I-catalyzed AH of 2-(6-methoxynaphthalen-2-yl)acrylic acid (**1a**),

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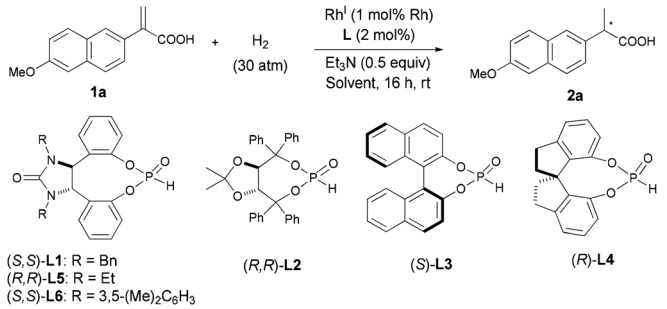
Table 1 Optimization of reaction conditions for Rh^I/SPO catalyzed AH of **1a**[a]



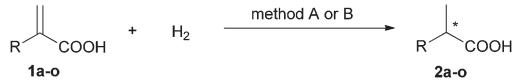
Entry	Rh^I	L	Solvent	ee[b] (%)
1	$[Rh(cod)_2]OTf$	(*S*,*S*)-**L1**	CH_2Cl_2	69 (*R*)
2	$[Rh(cod)_2]OTf$	(*R*,*R*)-**L2**	CH_2Cl_2	0
3	$[Rh(cod)_2]OTf$	(*S*)-**L3**	CH_2Cl_2	43 (*S*)
4	$[Rh(cod)_2]OTf$	(*R*)-**L4**	CH_2Cl_2	23 (*S*)
5	$[Rh(cod)_2]BF_4$	(*S*,*S*)-**L1**	CH_2Cl_2	72 (*R*)
6	$[Rh(nbd)_2]BF_4$	(*S*,*S*)-**L1**	CH_2Cl_2	71 (*R*)
7	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	CH_2Cl_2	81 (*R*)
8	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	$CHCl_3$	85 (*R*)
9	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	DCE	72 (*R*)
10	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	Et_2O	57 (*R*)
11	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	THF	86 (*R*)
12[d]	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	Dioxane	92 (*R*)
13	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	GDE	82 (*R*)
14	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	MTBE	80 (*R*)
15	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	Toluene	92 (*R*)
16	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	Acetone	60 (*R*)
17	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	EtOAc	84 (*R*)
18	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	CH_3OH	24 (*R*)
19	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	^{i}PrOH	5 (*R*)
20	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L1**	TFE	9 (*R*)
21	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*R*,*R*)-**L5**	Toluene	93 (*S*)
22	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*S*,*S*)-**L6**	Toluene	89 (*R*)
23[c]	$[Rh(\mu\text{-}Cl)(cod)]_2$	(*R*,*R*)-**L5**	Toluene	95 (*S*)

[a] Unless otherwise noted, all reactions were conducted under 30 atm of H_2 at rt for 16 h. [**1a**] = 0.1 M, [Rh^I] = 1.0 mM, [**L**] = 2.0 mM, solvent = 2.5 mL. All conversions were >99% as determined by ^{1}H NMR analysis. [b] Determined by HPLC on a chiral AD-H column after esterification with CH_2N_2, and the absolute configuration was assigned by comparison of the $[\alpha]_D^{20}$ with that reported in the literature.[7b] [c] Method A: the reaction is carried out in toluene under 50 atm of H_2 at 0 °C for 24 h. [d] Method B: the reaction is carried out in dioxane under 30 atm of H_2 at rt for 16 h.

a precursor for Naproxen. The reactions were generally conducted at rt for 16 h under 30 atm of hydrogen, and the results are shown in Table 1. Though full conversions of **1a** were achieved in all cases, the enantioselectivity of the product **2a** varied to a considerable extent depending on the detailed conditions. For the screening of the SPO ligands **L1–L4**, the reactions were run in CH_2Cl_2 with 0.5 equiv. of Et_3N as the additive, and the catalyst was generated *in situ* by mixing 1 mol% $[Rh(cod)_2]OTf$ (cod = cycloocta-1,5-diene, OTf^- = $CF_3SO_3^-$) with the SPO ligand in a 1 : 2 molar ratio. Clearly, 1,2-diphenylethylenediamine-derived[14] SPO **L1** appears to be the most promising (69% ee) among the tested ligands (entries 1–4), which was thus used in further optimization studies. With (*S*,*S*)-**L1** as the chiral ligand, the cationic $[Rh(cod)_2]OTf$, $Rh(cod)_2BF_4$ or $Rh(nbd)_2BF_4$ afforded similar enantioselectivities of **2a** (69–72% ee, entries 1, 5, and 6), whereas the $[Rh(\mu\text{-}Cl)(cod)]_2$ led to a substantial enhancement of ee value to 81% (entry 7). The solvents also demonstrated a profound effect on the enantioselectivity of the reaction (entries 7–20). While the reactions performed well in aprotic solvents [CH_2Cl_2, $CHCl_3$, DCE (dichloroethane), THF, Et_2O, dioxane, GDE (glycol dimethyl ether), MTBE (methyl *tert*-butyl ether), toluene, and EtOAc] to give **2a** in moderate to high enantioselectivities (entries 8–17), the protic solvents [CH_3OH, ^{i}PrOH, and TFE (CF_3CH_2OH)] only resulted in substantially decreased ee values (entries 18–20) under otherwise identical reaction conditions. Toluene and dioxane turned out to be optimal, affording **2a** in excellent enantioselectivities (92% ee, entries 12 and 15). A number of organic or inorganic bases have also been examined as additives for $[Rh(\mu\text{-}Cl)(cod)]_2$/(*S*,*S*)-**L1** catalyzed AH of **1a**, among which Et_3N was found to be optimal in terms of enantioselectivity (for details, see Tables S1 and S2 in ESI†). SPO ligands **L5** and **L6** with a backbone similar to that of **L1** have also been examined in the AH of **1a**, to give the product **2a** with 93% and 89% ee, respectively (entries 21 and 22). Finally, lowering the reaction temperature to 0 °C led to a further improvement of ee value to 95% for the $[Rh(\mu\text{-}Cl)(cod)]_2$/**L5** catalyzed reaction, albeit in this case the reaction was run under slightly modified conditions (50 atm of H_2, 24 h, entry 23). Thus, two sets of optimized conditions for AH of **1a** were found using either $[Rh(\mu\text{-}Cl)(cod)]_2$/(*R*,*R*)-**L5** (defined as method A shown in entry 23) or $[Rh(\mu\text{-}Cl)(cod)]_2$/(*S*,*S*)-**L1** (defined as method B shown in entry 12) as the catalyst, both affording **2a** with high ee values albeit slightly varied conditions were used.

With these results in hand, we proceeded to examine the substrate scope of the protocol in the AH of α-substituted acrylic acids **1a–o**. The reactions were carried out with $[Rh(\mu\text{-}Cl)(cod)]_2$/(*R*,*R*)-**L5** or $[Rh(\mu\text{-}Cl)(cod)]_2$/(*S*,*S*)-**L1** as the catalyst under the conditions specified by method A (entry 23, Table 1) or method B (entry 12, Table 1), respectively, and the results are summarized in Table 2. Full conversions of the substrates and good to excellent enantioselectivities (83–96% ee) of α-arylpropanoic acids **2a–n** were achieved for the AH of various α-arylacrylic acids **1a–n**, indicating the less significant stereoelectronic influence of the substituents on the reactions involving this type of substrate (entries 1–14). On the other hand, AH of α-benzylacrylic acid **1o** was less satisfactory, with a moderate ee value of **2o** being attained using either method A or B (entry 15). Generally speaking, similar levels of enantioselectivity were achieved for most of the substrates using the reaction conditions of methods A and B, but method B showed superior outcomes to method A for some specific substrates (**1i–k**, **1m–n**), indicating mutual complementation of two methods. Especially noteworthy is that several non-steroid anti-inflammatory drugs were synthesized in high optical purities by using this approach. Apart from Naproxen (95% ee, entry 1), Flurbiprofen (90% ee, entry 11), Ibuprofen (93% ee, entry 12), Ketoprofen (90% ee, entry 13) and Suprofen (83% ee,

Table 2 Rh^I/SPO catalyzed AH of α-substituted acrylic acids **1a–o**[a]



1a-o **2a-o**

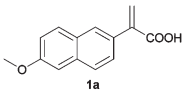
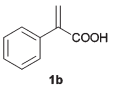
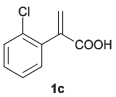
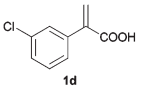
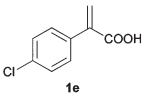
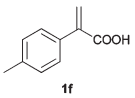
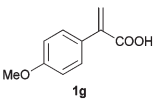
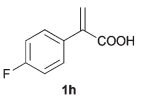
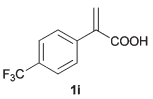
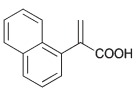
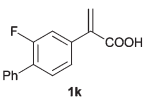
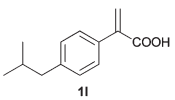
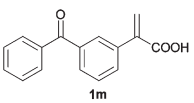
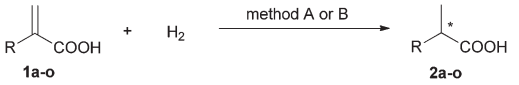
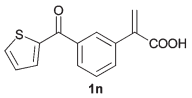
Entry	Substrate (**1a–o**)	A/B	Conv.[b] (%)	ee[c] (%)
1[d]	 **1a**	A	>99	95 (*S*)
		B	>99	92 (*R*)
2	 **1b**	A	>99	96 (*S*)
		B	>99	93 (*R*)
3	 **1c**	A[e]	>99	91 (*S*)
		B	>99	92 (*R*)
4	 **1d**	A	>99	94 (*S*)
5	 **1e**	A	>99	94 (*S*)
6	 **1f**	A	>99	93 (*S*)
7	 **1g**	A	>99	94 (*S*)
8	 **1h**	A	>99	94 (*S*)
9	 **1i**	A	>99	81 (*S*)
		B	>99	90 (*R*)
10	 **1j**	A	50	60 (*S*)
		B	>99	92 (*R*)
11[d]	 **1k**	A	>99	86 (*S*)
		B	>99	90 (*R*)
12[d]	 **1l**	A	>99	93 (*S*)
13[d]	 **1m**	A	>99	86 (*S*)
		B	>99	90 (*R*)

Table 2 *(Contd.)*



1a-o **2a-o**

Entry	Substrate (**1a–o**)	A/B	Conv.[b] (%)	ee[c] (%)
14[d]	 **1n**	A	>99	78 (+)
		B	>99	83 (−)
15	 **1o**	A	50	43 (*S*)
		B	>99	54 (*R*)

[a] Unless otherwise noted, all reactions were conducted using either method A or B with [**1**] = 0.1 M, [[Rh(μ-Cl)(cod)]$_2$] = 0.5 mM, and 0.5 molar equiv. of Et_3N. Conditions for method A: P_{H2} = 50 atm, [(*R*,*R*)-**L5**] = 2.0 mM, toluene (2.5 mL), 0 °C, 24 h. Conditions for method B: P_{H2} = 30 atm, [(*S*,*S*)-**L1**] = 2.0 mM, dioxane (2.5 mL), rt, 16 h. [b] Determined by ^{1}H NMR. [c] Determined by a chiral HPLC column after esterification with CH_2N_2, and the absolute configurations were assigned by comparison of their optical rotations with reported values (see the ESI). [d] The products are non-steroid anti-inflammatory agents. [e] 2 mol% Rh^I was used.

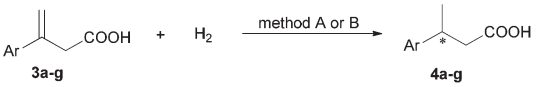
entry 14) were all readily accessible in a straightforward manner *via* this AH protocol.

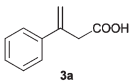
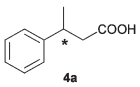
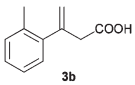
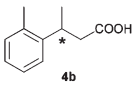
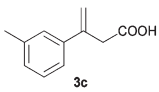
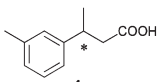
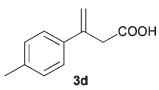
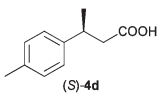
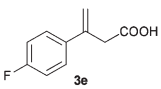
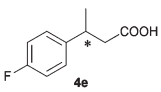
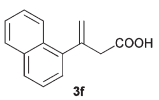
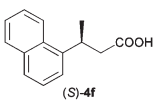
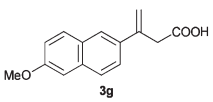
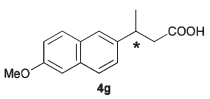
The Rh^I/SPO catalyzed protocol has also been extended to the AH of β-arylbut-3-enoic acids **3a–g**, a class of less explored olefinic substrates. As shown in Table 3, in most cases the [Rh(μ-Cl)(cod)]$_2$/(*S*,*S*)-**L1** catalyst system was demonstrated to be highly enantioselective for the AH of these substrates, providing the corresponding chiral β-arylbutanoic acids **4a**, **4c–e**, and **4g** in full substrate conversions with excellent enantioselectivities (94–97% ee, entries 1, 3–5, and 7). Exceptions are found for AH of the *o*-methyl substituted substrate **3b** and 3-(1-naphthyl)but-3-enoic acid **3f**, wherein substantially declined ee values for **4b** (entry 2) and **4f** (entry 6) were obtained, probably as a result of unfavourable steric interactions of the *o*-substituent with the catalyst, although we are unable to give a clear scenario of the actual interaction mode at the moment.

Conclusions

A class of Rh^I complexes of monodentate chiral SPO ligands were found to be highly enantioselective in the AH of α-arylacrylic acids and β-arylbut-3-enoic acids, affording the corresponding enantioenriched α-arylpropanoic acids and β-arylbutanoic acids, respectively, in full substrate conversions and generally good to excellent enantioselectivities (up to 97% ee). Especially noteworthy is that several non-steroid anti-inflammatory drugs are readily accessible in high enantiopurities by using this AH protocol, which thus may demonstrate

Table 3 Rh^{I}/SPO catalyzed AH of β-arylbut-3-enoic acids **3a–g**[a]



Entry	Substrate (**3a–g**)	A/B	Product (**4a–g**)	ee[b] (%)
1[c]		A B		77 (*R*) 94 (*S*)
2		B		16 (+)
3		B		95 (+)
4		B		94 (*S*)
5		B		94 (+)
6		B		59 (*S*)
7		B		97 (+)

[a] For reaction conditions, see footnote a in Table 2. All conversions were >99% as determined by ^{1}H NMR. [b] Determined by HPLC on a chiral column after esterification with CH_2N_2. The absolute configurations were assigned by comparison of their optical rotations with reported values (see the ESI). [c] AH of (*E*)-3-phenylbut-2-enoic acid (the isomer of **3a**) using method B afforded only 15% conversion and 51% ee of **4a**; thus the possibility of isomerization–hydrogenation can be ruled out.

further potential in asymmetric synthesis of bioactive compounds.

Experimental

General procedures for Rh^{I}/SPO catalyzed asymmetric hydrogenation of α-arylacrylic acids or β-arylbut-3-enoic acids

Method A. The chiral monodentate secondary phosphine oxide (SPO) ligand (*R*,*R*)-**L5** (1.9 mg, 0.005 mmol) and $[Rh(\mu\text{-}Cl)(cod)]_2$ (0.62 mg, 0.00125 mmol) were dissolved in toluene (1.0 mL) in a vial under an argon atmosphere, and the resulting solution was stirred for 10 min at rt to afford the precatalyst solution. To a Schlenk tube containing a solution of the substrate (0.25 mmol) in toluene (1.5 mL) was added Et_3N (17 μL, 0.125 mmol), and the resulting solution was stirred at rt for 10 min. This solution was transferred into the vial containing the precatalyst solution as described above, and the vial was transferred into a Parr steel autoclave in a glove box. The autoclave was sealed and purged three times with hydrogen, before finally being pressurized to 50 atm pressure of hydrogen. The reaction mixture was stirred at 0 °C for 24 h. The hydrogen gas was released in a hood, and the conversion of the substrate was determined by ^{1}H NMR analysis of the mixture. The ee value of the hydrogenation product was determined by HPLC on a chiral column after esterification with CH_2N_2, and the absolute configuration was assigned by comparison of the $[\alpha]_D^{20}$ of the purified product with that reported in the literature.

Method B. The procedure is similar to that described above for method A, except for using (*S*,*S*)-**L1** (2.5 mg, 0.005 mmol) as the ligand and dioxane as the solvent under 30 atm of H_2 at rt for 16 h.

Gram-scale procedure based on method B. The chiral monodentate secondary phosphine oxide (SPO) ligand (*R*,*R*)-**L1** (100 mg, 0.2 mmol) and $[Rh(\mu\text{-}Cl)(cod)]_2$ (25 mg, 0.05 mmol) were dissolved in dioxane (10 mL) in a 50 mL vial under an argon atmosphere, and the resulting solution was stirred for 20 min at rt to afford the precatalyst solution. To a Schlenk tube containing a solution of substrate **1b** (1.48 g, 10 mmol) in dioxane (10 mL) was added Et_3N (0.68 mL, 5 mmol), and the resulting solution was stirred at rt for 10 min. This solution was transferred into the vial containing the precatalyst solution as described above, and the glass vial was transferred into a Parr steel autoclave in a glove box. The autoclave was sealed and purged three times with hydrogen, before finally being pressurized to 30 atm. The reaction mixture was stirred at rt for 16 h. After the hydrogen gas was released slowly in a hood, the conversion of **1b** was determined by ^{1}H NMR analysis of the reaction mixture to be >99%. The reaction mixture was acidified with dilute hydrochloric acid (1 M, 20 mL) and extracted with EtOAc (3 × 50 mL). After removal of the solvent *in vacuo*, the residual was purified by flash column chromatography on silica gel (PE/EA = 3/1) to afford the acid (*S*)-**2b** as a yellowish solid (1.470 g) in 98% isolated yield. The ee value of the resulting (*S*)-**2b** product was determined to be 93% by HPLC on a chiral column after esterification with CH_2N_2.

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