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New chiral ferrocene/indole-based diphosphine ligands for Rh-catalyzed asymmetric hydrogenation of functionalized olefins

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ABSTRACT

Convenient synthesis of a new family of chiral ferrocene/indole-based diphosphine ligands, (R_c,R_p)-IndoFerroPhos (**L**), from (S_c,R_p)-PPFA and 2-(diphenylphosphino)indole has been described. These new ligands exhibited high efficiency in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins including α-dehydroamino acid esters, α-enamides and dimethyl itaconate, in which up to >99% yield and 98% ee were achieved.

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Chiral diphosphine ligands played a pivotal role in the transition-metal-catalyzed asymmetric reaction [1]. In the past decades, a large amount of structurally diverse and efficient diphosphine ligands have been developed, and successfully applied in various catalytic asymmetric reactions. However, no ligand proves to be universal in asymmetric catalysis, and many bidentate P-chelate ligands reported so far suffered from either a lengthy synthesis or the use of an expensive chiral starting material, and some of them have poor thermal and air stability [2]. As a result, the exploration of more efficient and practical chiral diphosphine ligands in terms of excellent reactivity and stereoselectivity, good air- and moisture-stability, and ease of preparation remains a subject of longstanding interest to organic chemistry.

In this context, the planar-chiral ferrocene framework based on Ugi's amine (*N*,*N*-dimethyl-1-ferrocenylethylamine) represents a privileged backbone for ligand development [3]. A recently emerging strategy for the development of new ligands is the incorporation of a heterocycle into the α-ferrocenylmethyl position of ferrocene framework. The presence of a heterocyclic group on the ferrocene system could significantly improve the structure of the chiral ferrocene scaffold, thus creating new chiral ligands for use in those catalytic reactions that are less successful with conventional ligands. Based on this strategy, many ferrocene/heterocycle-based P,P-, P,N- and P,S-ligands have been developed and successfully employed in various asymmetric catalytic reactions such as allylic alkylation, hydrogenation, cycloaddition, hydroboration and so on [4]. As our ongoing program in the development of highly efficient chiral diphosphine ligands [5] for asymmetric catalysis, herein we wish to report a new class of ferrocene/indole-based diphosphine ligands [6], (R_c,R_p)-IndoFerroPhos (**L**) (Fig. 1), featuring easy accessibility and derivatization as well as excellent air- and moisture-stability. More importantly, these new chiral diphosphine ligands displayed excellent enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins, in which up to >99% yield and 98% ee were achieved.

Initially, we attempted the preparation of the targeted ferrocene/indole-based (R_c,R_p)-IndoFerroPhos **L** *via* a synthetic route as shown in Scheme 1. The synthesis started from *N*,*N*-dimethyl (S_c)-1-[(R_p)-(2-diphosphino)ferrocenyl]ethylamine **1** [7], which was treated with Ac_2O at 100 °C to give (S_c,R_p)-**2**. Nucleophilic substitution of (S_c,R_p)-**2** with indoles led to the ferrocene/indole compounds (R_c,R_p)-**4** [8]. However, subsequent phosphination of **4** with *n*-BuLi and $ClPPh_2$ failed, and very low yield of the targeted products was detected even after many attempts in different conditions. In the case of (R_c,R_p)-**4** with an N–H group, a *N*-phosphinated diphosphine compound (R_c,R_p)-**5** was separated in high yield. The search for another synthetic approach to these new ferrocene/indole-based diphosphine ligands is therefore required. We envisioned that a direct Friedel-Craft alkylation of 2-(diphenylphosphino)-1*H*-indole **6** with (S_c,R_p)-**2** should readily prepare the targeted ligand (R_c,R_p)-**L1** (Scheme 2). After the extensive reaction condition screening, we delightedly found that the

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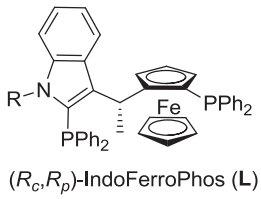
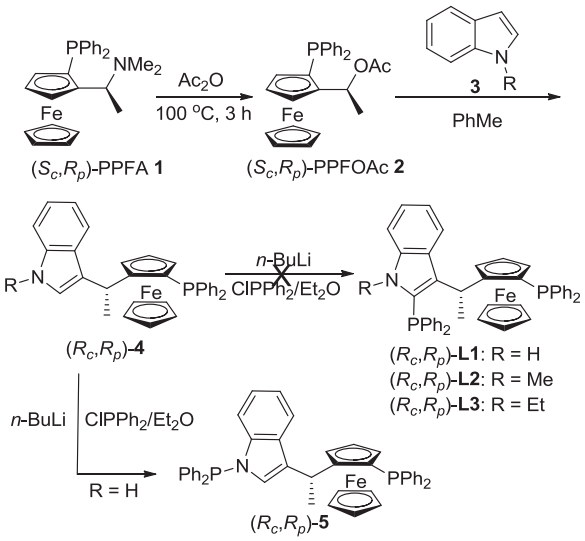
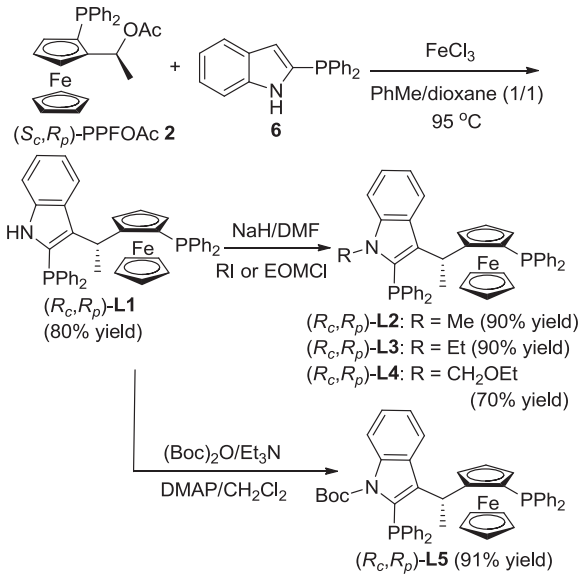


Fig. 1. New chiral ferrocene/indole-based diphosphine ligands (R_c,R_p)-IndoFerroPhos (**L**).



Scheme 1. Initial attempt for the synthesis of chiral ferrocene/indole-based diphosphine ligands.



Scheme 2. Synthesis of new chiral ferrocene/indole-based diphosphine ligands, (R_c, R_p)-IndoFerroPhos (**L**).

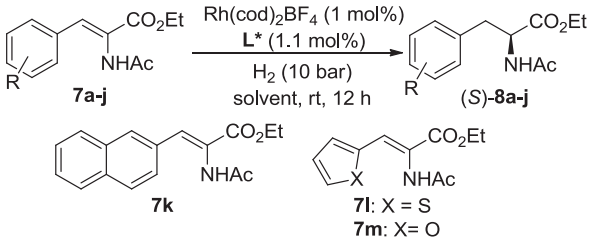
nucleophilic substitution of (S_c,R_p)-**2** on the ferrocenylmethyl position with 2-(diphenylphosphino)-1*H*-indole (**6**) could be performed smoothly in a 1:1 mixture of toluene and 1,4-dioxane at 95 °C in the presence of $FeCl_3$, thus leading to the desired ligand (R_c,R_p)-**L1** in good yield. The derivatization of (R_c,R_p)-**L1** by the treatment with NaH in DMF followed with iodomethane, iodoethane or chloromethyl ethyl ether afforded the corresponding ligands (R_c,R_p)-**L2**-**L4** in reasonable yields respectively**.** *N*-Boc protected ligand (R_c,R_p)-**L5** was also prepared in high yield by the reaction of (R_c,R_p)-**L1** with $(Boc)_2O$ in CH_2Cl_2 in the presence of DMAP and triethylamine at room temperature**.** Besides the easy preparation, another salient and practical feature of these diphosphine ligands is their excellent air- and moisture-stability. Even after being held at ambient temperature in open air for more than one month, ligand (R_c,R_p)-**L4** did not show any changes in its ^1H or ^{31}P NMR spectra and exhibited the same activity and enantioselectivity in catalytic hydrogenation.

In the first set of experiments, we used the Rh-catalyzed asymmetric hydrogenation of a variety of ethyl (*Z*)-acetamidocinnamates **7** to benchmark the potential of these newly developed diphosphine ligands in the asymmetric catalysis [9], and the results are summarized in Table 1. Hydrogenation was conducted in $ClCH_2CH_2Cl$ at room temperature under a H_2 pressure of 10 bar in the presence of 1.0 mol% of catalyst prepared *in situ* from $Rh(COD)_2BF_4$ and 1.1 equiv of (R_c,R_p)-IndoFerroPhos **L**. To our delight, these new ligands showed high efficiency in the hydrogenation of ethyl (*Z*)-2-acetamido-3-phenylacrylate **7a** (entries 1–5). In all cases, full conversions were observed with good to high enantioselectivities. Among them, (R_c,R_p)-IndoFerroPhos **L4** displayed the best result (>99% yield and 96% ee). In comparison, *N*-phosphinated diphosphine ligand (R_c,R_p)-**5** led to only moderate enantioselectivity of 63% ee (entry 6).

We next evaluated the effect of the solvent on the reaction outcome. In all solvents tested, hydrogenations led to good performance. However, no result was superior to that in $ClCH_2CH_2Cl$ (entries 7–10). Under the optimized conditions (entry 4), we hydrogenated a variety of ethyl (*Z*)-acetamidocinnamates **7** to obtain the corresponding α-amino acid esters. The substitution pattern of the substituent on the phenyl ring had no obvious influence on the hydrogenation performance. Thus, all three substrates with a chloro group at the *ortho*, *meta* or *para* position gave the satisfactory results (entries 11–13). The electronic property of *para*-substituent on the phenyl ring less affected the hydrogenation outcome, and all substrates exhibited high yields and enantioselectivities (entries 13–19). 2-Naphthyl substrate **7k** also served well, leading to the hydrogenation product **8k** in 93% yield and with 93% ee (entry 20). Heteroaromatic 2-thienyl substrate **7l** was well tolerated, giving the product **8l** in >99% yield and with 93% ee (entry 21). However, 2-furyl substrate **7m** led to the unsatisfactory enantioselectivity of 59% ee (entry 22).

To further show the synthetic utility of (R_c,R_p)-IndoFerroPhos, we then investigated their efficiency in the Rh-catalyzed asymmetric hydrogenation of α-enamides **9**. Good enantioselectivities were also observed in this reaction, and the results are summarized in Table 2. Different with the hydrogenation of ethyl (*Z*)-acetamidocinnamates **7**, (R_c,R_p)-**L1** displayed better enantioselectivity than (R_c,R_p)-**L4** in some cases. For example, in the hydrogenation of *N*-(1-phenylvinyl)acetamide **9a**, 98% ee was achieved with (R_c,R_p)-**L1** (entry 1), while only 90% ee was observed with (R_c,R_p)-**L4** (entry 2). The substitution pattern of the substituent on the phenyl ring had some influence on the hydrogenation (entries 3–5). Thus, *para*-substituted **9d** led to lower enantioselectivity in comparison with its *orthro*- and *meta*-analogues (**9b** and **9c**). The electronic property of *para*-substituent also affected the hydrogenation outcome (entries 5–10). 4-MeO-substituted substrate **9f** gave a decreased enantioselectivity of only 82% ee (entry 7). 2-Naphthyl substrate **9j** worked well, giving the hydrogenation product **10j** in 92% yield and with 91% ee (entry 11). Heteroaromatic 2-thienyl substrate **9k** was not so compatible with the hydrogenation, leading to the product **10k** in 85% yield and with 81% ee (entry 12).

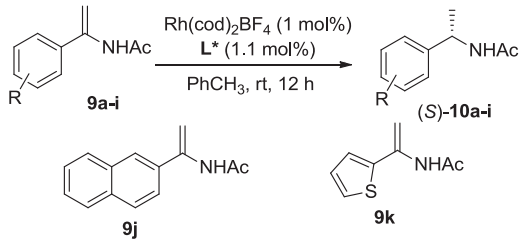
Table 1
Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid esters **7**.[a]



Entry	L*	Substrate **7**	Solvent	Yield[b] (%)	ee[c] (%)
1	(R_c,R_p)-**L1**	**7a**: R = H	$ClCH_2CH_2Cl$	>99	81
2	(R_c,R_p)-**L2**	**7a**: R = H	$ClCH_2CH_2Cl$	>99	95
3	(R_c,R_p)-**L3**	**7a**: R = H	$ClCH_2CH_2Cl$	>99	96
4	(R_c,R_p)-**L4**	**7a**: R = H	$ClCH_2CH_2Cl$	>99	96
5	(R_c,R_p)-**L5**	**7a**: R = H	$ClCH_2CH_2Cl$	>99	92
6	(R_c,R_p)-**5**	**7a**: R = H	$ClCH_2CH_2Cl$	>99	63
7	(R_c,R_p)-**L4**	**7a**: R = H	MeOH	88	91
8	(R_c,R_p)-**L4**	**7a**: R = H	THF	92	95
9	(R_c,R_p)-**L4**	**7a**: R = H	toluene	94	96
10	(R_c,R_p)-**L4**	**7a**: R = H	CH_2Cl_2	96	93
11	(R_c,R_p)-**L4**	**7b**: R = 2-Cl	$ClCH_2CH_2Cl$	97	93
12	(R_c,R_p)-**L4**	**7c**: R = 3-Cl	$ClCH_2CH_2Cl$	96	96
13	(R_c,R_p)-**L4**	**7d**: R = 4-Cl	$ClCH_2CH_2Cl$	96	95
14	(R_c,R_p)-**L4**	**7e**: R = 4-Br	$ClCH_2CH_2Cl$	>99	97
15	(R_c,R_p)-**L4**	**7f**: R = 4-F	$ClCH_2CH_2Cl$	>99	96
16	(R_c,R_p)-**L4**	**7g**: R = 4-Me	$ClCH_2CH_2Cl$	>99	94
17	(R_c,R_p)-**L4**	**7h**: R = 4-OMe	$ClCH_2CH_2Cl$	98	93
18	(R_c,R_p)-**L4**	**7i**: R = 4-NO_2	$ClCH_2CH_2Cl$	>99	95
19	(R_c,R_p)-**L4**	**7j**: R = 4-Ph	$ClCH_2CH_2Cl$	>99	96
20	(R_c,R_p)-**L4**	**7k**	$ClCH_2CH_2Cl$	93	93
21	(R_c,R_p)-**L4**	**7l**	$ClCH_2CH_2Cl$	>99	93
22	(R_c,R_p)-**L4**	**7m**	$ClCH_2CH_2Cl$	99	59

[a] All reactions were carried out with a $Rh(COD)_2BF_4$/(R_c,R_p)-IndoFerroPhos **L**/**7** (0.2 mmol) ratio of 1:1.1:100 in 2 mL of solvent at room temperature under a H_2 pressure of 10 bar for 12 h.
[b] Yield of isolated product.
[c] Determined by HPLC using a chiral stationary phase.

Table 2
Rh-catalyzed asymmetric hydrogenation of α-enamides **9**.[a]



Entry	L*	Substrate **9**	Yield[b] (%)	ee[c] (%)
1	(R_c,R_p)-**L1**	**9a**: R = H	90	98
2	(R_c,R_p)-**L4**	**9a**: R = H	96	90
3	(R_c,R_p)-**L4**	**9b**: R = 2-Cl	91	97
4	(R_c,R_p)-**L4**	**9c**: R = 3-Cl	91	96
5	(R_c,R_p)-**L4**	**9d**: R = 4-Cl	92	88
6	(R_c,R_p)-**L1**	**9e**: R = 4-Me	92	94
7	(R_c,R_p)-**L4**	**9f**: R = 4-OMe	96	82
8	(R_c,R_p)-**L1**	**9g**: R = 4-F	96	90
9	(R_c,R_p)-**L4**	**9h**: R = 4-Br	94	94
10	(R_c,R_p)-**L4**	**9i**: R = 4-NO_2	91	97
11	(R_c,R_p)-**L4**	**9j**	92	91
12	(R_c,R_p)-**L4**	**9k**	85	81

[a] All reactions were carried out with a $Rh(COD)_2BF_4$/(R_c,R_p)-IndoFerroPhos **L**/**9** (0.2 mmol) ratio of 1:1.1:100 in 2 mL of toluene at room temperature under a H_2 pressure of 10 bar for 12 h.
[b] Yield of isolated product.
[c] Determined by HPLC using a chiral stationary phase.

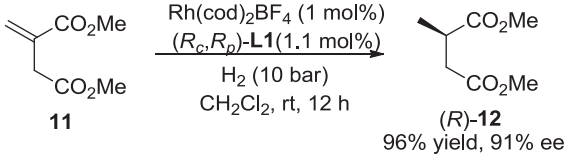


Fig. 2. Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate.

Remarkable enantioselectivity and catalytic activity were also observed in the hydrogenation of dimethyl itaconate **11** (Fig. 2). The most efficient ligand was (R_c,R_p)-**L1**, which provided the hydrogenation product **12** in 91% ee.

In conclusion, we have developed a new family of chiral diphosphine ligands (R_c,R_p)-IndoFerroPhos **L**, by combining a ferrocene backbone and an indole fragment. Excellent levels of enantioselectivity in the Rh-catalyzed hydrogenation of ethyl (*Z*)-acetamidocinnamate, α-enamides, and dimethyl itaconate have been achieved. Their ease of preparation, extraordinary stability toward air and moisture, and tolerance of various hydrogenation conditions make this new family of chiral diphosphine ligands highly practical for general laboratory preparations, as well as scale-up operations. Further investigations of other catalytic asymmetric reactions with these diphosphine ligands are underway.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151860.

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