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Rh_2(*S*-PTTL)$_3$TPA—A Mixed Ligand Dirhodium(II) Catalyst for Enantioselective Reactions of α-Alkyl-α-Diazoesters

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Abstract

Herein we report the synthesis of the mixed ligand paddlewheel complex dirhodium(II) tris[*N*-phthaloyl-(*S*)-tert-leucinate] triphenylacetate, Rh_2(*S*-PTTL)$_3$TPA, the structure of which bears similarity to the chiral crown complex Rh_2(*S*-PTTL)$_4$. Rh_2(*S*-PTTL)$_3$TPA engages substrate classes (aliphatic alkynes, silylacetylenes, α-olefins) that are especially challenging in intermolecular reactions of α-alkyl-α-diazoesters, and catalyzes enantioselective cyclopropanation, cyclopropenation, and indole C-H functionalization with yields and enantioselectivities that are comparable or superior to Rh_2(*S*-PTTL)$_4$. Mixing ligands on paddlewheel complexes offers a versatile handle for diversifying catalyst structure and reactivity. The results described herein illustrate how mixed ligand catalysts can create new opportunities for the optimization of catalytic asymmetric processes.

Rh(II)-carboxylate catalysts supported by *N*-phthaloyl- and *N*-naphthaloyl amino acid ligands are robust tools for asymmetric synthesis.[1] These catalysts were pioneered by Hashimoto,[2] and in recent years have opened new modes of reactivity including highly enantioselective cyclopropanation[3], cyclopropenation[4], and C-H functionalization[5] of α-alkyl-α-diazoesters; cyclopropanation and C-H functionalization of α-aryl- and α-vinyl- α-diazoesters[6]; cyclopropanation of PMP-α-diazoketones,[7] and cycloadditions of β-keto-α-diazoesters[8].

We recently reported that dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-tert-leucinate], Rh_2(*S*-PTTL)$_4$ (Fig. 1), gives high enantioselectivity in the cyclopropanation reactions of α-alkyl-α-diazoesters.[3] The model for enantioselectivity was explained by a “chiral crown” structure, in which all four *N*-phthalimide groups are presented on the same face of the catalyst in an α, α, α, α conformation.[9] Charette also proposed that the α, α, α, α conformation is important for Rh-catalysts supported by *N*-phthaloyl amino acid ligands in cyclopropanation reactions of α-4-methoxyphenyl-α-diazoketones.[7] Crystallographic support for the chiral crown structure in bimetallic paddlewheel complexes has been established in subsequent study[10], which includes work on Rh_2(*S*-NTTL)$_4$ catalyzed cyclopropanation by Ghanem,[11] Rh_2(*S*-TBPTTL)$_4$ catalyzed cyclopropenation[4] by Hashimoto, and Rh_2(*S*-NTTL)$_4$ catalyzed C-H functionalization of indoles by our group.[5]

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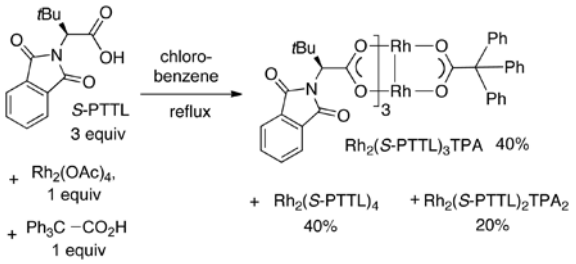

(1)

The chiral crown structure offers a unique platform for catalyst design. Inspection of transition state models involving chiral crown catalysts implies that non-covalent ligand-substrate interactions contribute to the induction of asymmetry.[3,5,7] We hypothesized that the chiral pocket would still be maintained in structures where one of the chiral carboxylate ligands of Rh_2(*S*-PTTL)$_4$ was replaced by an achiral ligand. We further reasoned that introducing a ligand with a large aromatic surface area could have a beneficial influence on the yield and enantioselectivity in intermolecular reactions. Herein, we report the mixed ligand catalyst dirhodium(II) tris [*N*-phthaloyl-(*S*)-tert-leucinate] triphenylacetate, Rh_2(*S*-PTTL)$_3$TPA (Eq 1). Computational and crystallographic studies show that Rh_2(*S*-PTTL)$_3$TPA adopts a structure in which the *N*-phthaloyl groups are presented on the same face of the catalyst. For a number of recalcitrant substrates, Rh_2(*S*-PTTL)$_3$TPA is shown to give results in enantioselective cyclopropanation, cyclopropenation, and indole C-H functionalization that are superior to the parent catalyst, Rh_2(*S*-PTTL)$_4$.

While studies on chiral bimetallic rhodium (II) complexes have been extensive,[12] there has been relatively little study on bimetallic Rh(II) complexes bearing different ligand types. Corey reported that Rh_2(DPTI)$_3$(OAc), which is capable of achieving high enantioselectivity in cyclopropenation and cyclopropanation reactions of ethyl diazoacetate.[13] Doyle has reported immobilized Rh(II) mixed ligand carboxamidates as useful catalysts for intramolecular cyclopropanation and C-H insertion reactions,[13] and Hashimoto has reported a polymer-supported analogue of Rh_2(*S*-PTTL)$_4$ as a useful recyclable catalyst for C-H insertion reactions.[13] Concurrent with the work being reported here, Charette and coworkers have developed chiral Rh-catalysts bearing mixed *N*-phthaloyl amino acid ligands that give excellent enantioselectivity in the cyclopropanation reaction of α-nitro-α-diazo-*p*-methoxyacetophenone with styrene.[14]

As shown in Eq. 1, the unsymmetrical complex Rh_2(*S*-PTTL)$_3$TPA can be synthesized in 40% yield by simply combining *N*-phthaloyl-(*S*)-tert-leucinate (3 equiv), triphenylacetic acid (1 equiv) and $Rh_2(OAc)_4$ (1 equiv). Also formed in the reaction are Rh_2(*S*-PTTL)$_4$ (40%) and isomers of Rh_2(*S*-PTTL)$_2$TPA$_2$ (20%).

We began work on Rh_2(*S*-PTTL)$_3$TPA with computational and crystallographic studies. Crystals of Rh_2(*S*-PTTL)$_3$TPA were grown from ethanol. Rh_2(*S*-PTTL)$_3$TPA adopts a conformation in the solid state in which all of the phthaloyl groups are displayed on the α-face (Fig 1a–b). When DFT calculations (B3LYP/LAN2DZ) were used to computationally optimize the crystallographic coordinates, the lowest energy structure displayed in Fig 1c was found. An energetically and structurally similar structure to the one displayed in Fig 1c was also found as the result of a conformational search.[15] Starting from several different conformations, Rh_2(*S*-PTTL)$_3$TPA was subjected to molecular dynamics-based conformational (LowModeMD[16]), and the lowest energy structures were optimized using DFT calculations (B3LYP/LAN2DZ).

The largest difference between the computed and solid state structures of Rh_2(*S*-PTTL)$_3$TPA is the ψ-angle for one the PTTL ligands, which is −11.1° in the x-ray structure (Fig 1b), but 44.0° in the calculated structure (Fig 1a). This clockwise ψ-angle twist[17] in the crystal structure may be a result of attractive intramolecular (2.456 Å) and intermolecular (2.512 Å) interactions between the phthalimide carbonyl and a nearby aromatic hydrogen from the TPA ligand. However, there is an overall good agreement between the predicted and crystallized structure of Rh_2(*S*-PTTL)$_3$TPA.

As shown in table 1, the reaction to produce Rh_2(*S*-PTTL)$_3$TPA also produced isomers of Rh_2(*S*-PTTL)$_2$TPA$_2$ (20%). The *cis*-isomer crystallized from a solution of CD_3CN. In the x-ray structure of *cis*-Rh_2(*S*-PTTL)$_2$TPA$_2$, both phthalimido groups are projected on the same face of the catalyst.

As reported previously, the Rh_2(*S*-PTTL)$_4$ catalyzedcyclopropanation of styrene by ethyl-α-diazobutanoate was not particularly enantioselective, providing **1** in 79% ee. As shown in Table 1, a number of Rh-catalysts were surveyed, including Rh_2(*S*-NTTL)$_4$, the most useful catalyst from our prior work on indole C-H functionalization,[5] and Rh_2(*S*-TBPTTL)$_4$, a catalyst recently reported by Hashimoto to be useful in cyclopropenation[4] and also reported to be useful in the cyclopropanation of α-diazopropionates.[18] Of the catalysts surveyed, Rh_2(S-PTTL)$_3$TPA gave the best enantioselectivity in hexanes with 88% ee (Table 1).[19]

To determine if Rh_2(*S*-PTTL)$_3$TPA could also improve the selectivity for other cyclopropanation reactions, we surveyed a range of substrates as shown in Scheme 1. In addition to cyclopropane **1**, significant improvements in enantioselectivity were observed in the cases of cyclopropanation products **2**–**6** when Rh_2(S-PTTL)$_3$TPA was used instead of Rh_2(S-PTTL)$_4$. Slight enantioselectivity improvements were also noted for **7** and **8**, and results comparable to Rh_2(S-PTTL)$_4$ were observed in the case of cyclopropanation product **9**. In general, yields and diastereoselectivities were comparable for the reactions studied. A notable exception was 3-methoxystyrene, where the diastereoselectivity to form **2** increased from 83:17 with Rh_2(*S*-PTTL)$_4$ to 99:1 with Rh_2(*S*-PTTL)$_3$TPA.

In prior studies on intermolecular cyclopropanation with α-alkyl-α-diazoesters, it was noted that α-olefins are particularly challenging substrates. The reaction between 1-octene and ethyl α-diazobutanoate did not yield cyclopropane products with Rh_2TPA_4, a catalyst that is effective in cyclopropanation reactions of α-alkyl-α-diazoesters with styrenes or vinyl ethers.[20] Very recently, Hashimoto reported the cyclopropanation of diazopropionate with 1-hexene.[18] Still unknown, however, is α-olefin cyclopropanation by α-*n*-alkyl-α-diazocarbonyl compounds, which contain weaker β-C-H bonds. As shown in Scheme 3, the reaction between 1-hexene and isobutyl α-diazobutanoate (5 equiv.) is successful with with Rh_2(*S*-PTTL)$_4$, but gives cyclopropane **10** in only 33% yield. With Rh_2(*S*-PTTL)$_3$TPA, cyclopropane **10** can be obtained in a more useful 64% yield, albeit with modest dr (72:28) and enantiomeric excess (72% ee and 65% ee for the major and minor diasteroemers, determined by reduction to **10a**). This represents the first example of an α-olefin cyclopropanation with an α-*n*-alkyl-α-diazocarbonyl compound that is selective over β-hydride elimination. We previously reported a method to access cyclopropenation products of α-alkyl-α-diazoesters using low reaction temeperatures and Rh_2Piv_4 as a catalyst.[20] Very recently, Hashimoto reported an elegant method for enantioselective cyclopropenation using α-alkyl-α-diazoesters.[4] Despite these advances, considerable challenges remain. Silylacetylenes had not proven effective substrates for cyclopropenation reactions with α-alkyl-α-diazoesters. Avoiding β-elimination in cyclopropenation of aliphatic alkynes had also been limited to α-methyl-α-diazocarbonyls, which possess strong bonds to β-hydrogens.[22] Unknown were cyclopropenation reactions between aliphatic alkynes and diazo compounds with weaker β-C-H bonds. Previously, we reported that the scope of

cyclopropenation could be extended to α-*n*-alkyl-α-diazoesters by using Rh_2Piv_4 at low temperature.[21] These conditions were successful with aromatic alkynes and enynes. However, cyclopropenation products were not observed with 1-hexyne.

As shown in Scheme 4, Rh_2(*S*-PTTL)$_3$TPA successfully catalyzes the reactions of α-*n*-alkyl-α-diazoesters with trimethylsilylacetylene and 1-hexyne. Compared to other catalysts that were surveyed, Rh_2(*S*-PTTL)$_3$TPA was superior both in terms of yield and in terms of enantioselectivity. Products of β-elimination dominated the reactions with Rh_2(*S*-PTTL)$_4$, Rh_2(*S*-NTTL)$_4$ and Rh_2(*S*-TCPTTL)$_4$. With Rh_2(*S*-PTTL)$_3$TPA, cyclopropenation product **11** was produced from ethyl α-diazobutanoate and trimethylsilylacetylene in 82% yield and 91% ee. For Rh_2(*S*-PTTL)$_4$, the next best catalyst, the yield (22%) and enantioselectivity (racemic) were sharply reduced. Similar trends in yield were noted in the cyclopropenation reactions of 1-hexyne to form **12** and **13**, with comparable enantioselectivity to Rh_2(*S*-PTTL)$_4$ being noted in Rh_2(*S*-PTTL)$_3$TPA-catalyzed formation of **12** and superior enantioselectivity to Rh_2(*S*-PTTL)$_4$ being noted in Rh_2(*S*-PTTL)$_3$TPA-catalyzed formation of **13**.

We recently described a Rh_2(*S*-NTTL)$_4$ catalyzed method for enantioselective C-H functionalization of indoles.[5] Hashimoto and coworkers described the use of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-triethylalaninate [Rh_2(*S*-PTTEA)$_4$] to be useful in the C-H functionalization of indoles by α-diazopropionates.[23] Despite a good scope of reactivity, a number of substrate types have thus far proven problematic, including 4-substituted indoles, which have a nucleus prevalent in biologically active natural products. To date, only Hashimoto has achieved the enantioselective C-H functionalization of a 4-substituted indole: the Rh_2(*S*-PTTEA)$_4$ catalyzed reaction of *N*-methoxymethyl-4-methylindole with 2,4-dimethyl-3-pentyl-α-diazopropionate in 69% ee.

As shown in Table 2, 4-methyl-*N*-phenylindole **14** reacts poorly with excess ethyl α-diazobutanoate under Rh_2(*S*-NTTL)$_4$ catalyzed conditions, leading to product **15** in only 5% yield and 40% ee (Table 2). With an excess of ethyl α-diazobutanoate, Rh_2(*S*-PTTL)$_3$TPA gave **15** in superior yield (79%) and enantioselectivity (81% ee) relative to Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-NTTL)$_4$.

Conclusions

In summary, we have described a mixed ligand catalyst, Rh_2(*S*-PTTL)$_3$TPA, which displays all of the *N*–phthalimide groups on one face in structural similarity to the chiral crown complex Rh_2(S-PTTL)$_4$. Rh_2(*S*-PTTL)$_3$TPA engages substrate classes (aliphatic alkynes, silylacetylenes, α-olefins) that are especially challenging in intermolecular reactions of α-alkyl-α-diazoesters, and catalyzes enantioselective cyclopropanation, cyclopropenation, and indole C-H functionalization with yields and enantioselectivities that are comparable or superior to Rh_2(S-PTTL)$_4$. The use of mixed ligand catalysts offers new opportunities for the optimization of catalytic processes that are catalyzed by bimetallic paddlewheel complexes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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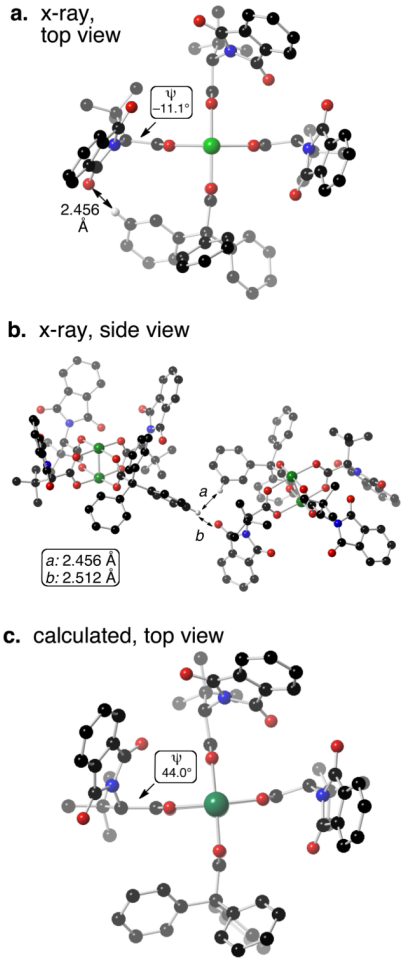
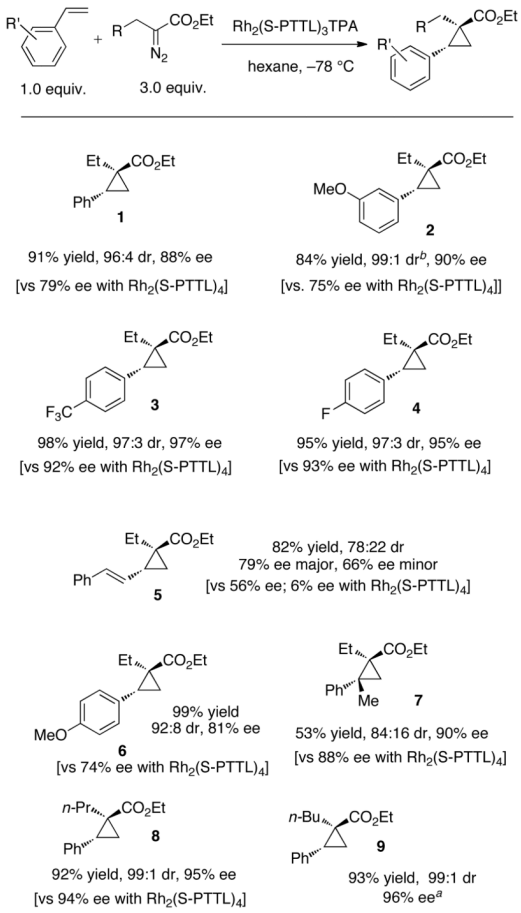


Fig. 1.

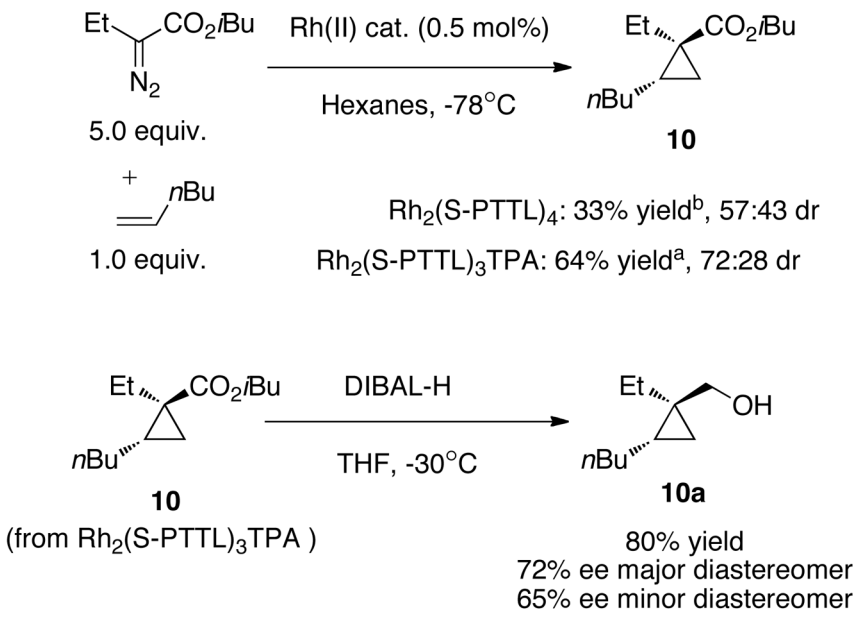
(a) Top view and (b) side view of crystal structure of Rh_2(*S*-PTTL) $_3$TPA. Axial ethanol ligands are not displayed. (c) Lowest energy conformation of Rh_2(*S*-PTTL) $_3$TPA from DFT calculation.



Scheme 1.

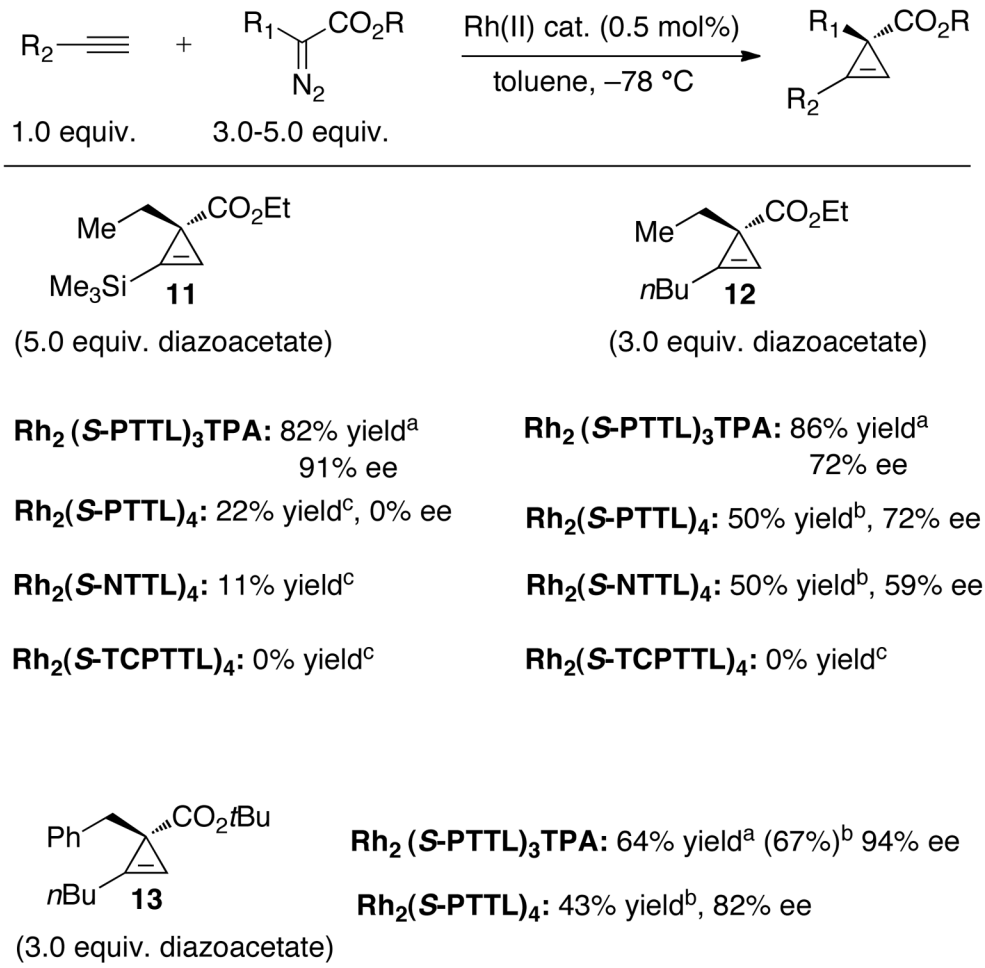
Rh_2(*S*-PTTL)$_3$TPA catalyzed cyclopropanation of styrene derivatives with α-alkyl diazoesters

[a] The enantioselectivity with Rh_2(*S*-PTTL)$_4$ was the same as that observed for Rh_2(*S*-PTTL)$_3$TPA. [b] The dr with Rh_2(*S*-PTTL)$_4$ was only 83:17



Scheme 3.

Diastereoselective Rh_2(*S*-PTTL)$_3$TPA catalyzed cyclopropanation of 1-hexene. a) Isolated yield. b) Yield by ^{1}H NMR

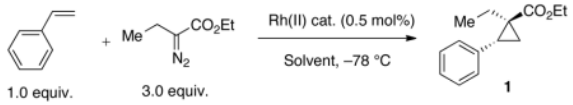


Scheme 4.

Enantioselective cyclopropenation of aliphatic alkynes 1-hexene and trimethylsilylacetylene. Rh_2(*S*-TCPTTL)$_4$= dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate]; a) Isolated yield. b) Yield by ^{1}H NMR. c) Yield by GC.

Table 1

Catalyst screening for enantioselective cyclopropanation of styrene with ethyl α-diazobutanonate: Rh_2(*S*-BPTTL)$_4$= dirhodium(II) tetrakis[*N*-2,3-naphthaloyl-(*S*)-*tert*-leucinate]; Rh_2(*S*-NTTL)$_4$= dirhodium(II) tetrakis[*N*-1,8-naphthaloyl-(*S*)-*tert*-leucinate]; Rh_2(*S*-TBPTTL)$_4$= dirhodium(II) tetrakis[*N*-tetrabromophthaloyl-(*S*)-*tert*-leucinate];



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Rh(II) Catalyst	Solvent	%yd[a]	dr[b]	%ee[c]
Rh_2(*S*-PTTL)$_4$	Hexanes	95	92:8	79
Rh_2(*S*-BPTTL)$_4$	Toluene	80	88:12	73
Rh_2(*S*-NTTL)$_4$	Toluene	61	75:25	45
Rh_2(*S*-TBPTTL)$_4$	CH_2Cl_2	6	97:3	11
Rh_2(*S*-TBPTTL)$_4$	Toluene	10	88:12	16
Rh_2(*S*-TBPTTL)$_4$	Hexanes	23[d]	84:16	16
Rh_2(TPA)(*S*-PTTL)$_3$	Toluene	66	95:5	81
Rh_2(TPA)(*S*-PTTL)$_3$	Hexanes	91	96:4	88

[a] Isolated yields.

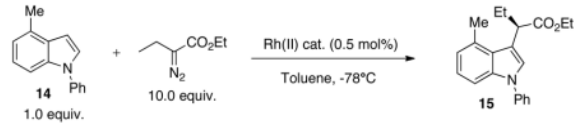
[b] Measured by GC.

[c] Measured by chiral HPLC.

[d] Run at −60 °C for 2 hours. No reaction occurred at −78 °C.

Table 2

C-H functionalization of 4-substituted indoles.



Rh(II) Catalyst	%yd[a]	%ee[b]
Rh_2(*S*-NTTL)$_4$	5	40
Rh_2(*S*-PTTL)$_4$	43	64
Rh_2 (*S*-PTTL)$_3$(TPA)	80	81

[a] Isolated yields.

[b] Measured by chiral HPLC