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Asymmetric Addition of Dimethylzinc to *N*-Tosylarylimines Catalyzed by a Rhodium–Diene Complex toward the Synthesis of Chiral 1-Arylethylamines

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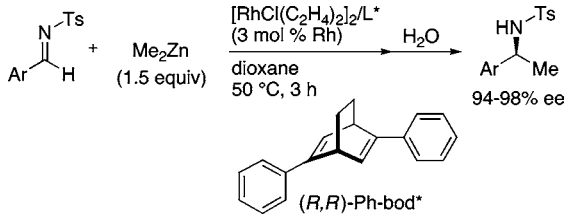
ABSTRACT



A rhodium complex coordinated with a chiral diene, (*R*,*R*)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (Ph-bod*), catalyzed the asymmetric addition of dimethylzinc to *N*-tosylarylimines to give high yields of chiral 1-aryl-1-ethylamines with high enantioselectivity (94–98% ee).

The enantioselective preparation of α-chiral amines is one of the most important objectives in organic synthesis because they are known to play important roles for their bioactivity in several chiral drugs and natural products.[1] Of several approaches recently developed for the synthesis of α-chiral amines, the catalytic enantioselective alkylation of imines using dialkylzinc reagents is most attractive if high enantioselectivity as well as high catalytic activity is realized.[2−8] In this context, most of the studies reported so far are on the catalytic ethylation of imines using diethylzinc because of its high reactivity and selectivity. On the other hand, efficient methods for the asymmetric methylation of imines are still few in number due to the lower reactivity of dimethylzinc, where a large amount of dimethylzinc is often used in order to obtain the methylation product in high yield. The leading studies of the asymmetric methylation of imines with dimethylzinc have been developed by Hoveyda/Snapper,[2] Tomioka,[3] and Charette.[8] They reported promising results, for example, in copper-catalyzed asymmetric methylation of *N*-tosylimines with an amidophosphine ligand (Tomioka)[3b] and of *N*-phosphinoylimines with a chiral bis(phosphine) monoxide ligand (Charette)[8b] and in the methylation-catalyzed by a Lewis acid complexed with chiral amino acid based ligands (Hoveyda/Snapper).[2d]

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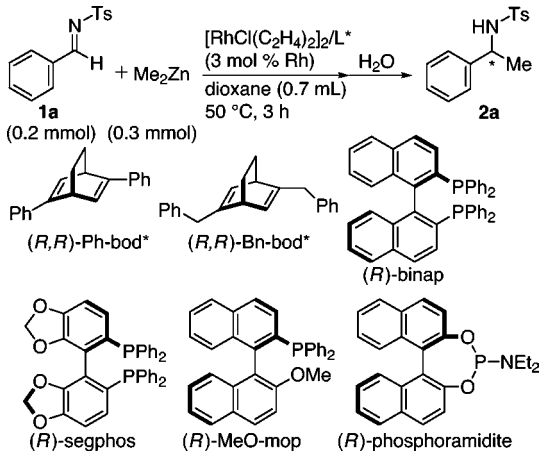
Recently, it has been disclosed that rhodium complexes coordinated with chiral diene ligands are highly active and enantioselective catalysts for the asymmetric addition of arylboronic acids to imines[9,10] as well as to α,β-unsaturated carbonyl compounds.[11] Here, we report that the asymmetric methylation of *N*-tosylimines with dimethylzinc proceeds with high enantioselectivity in the presence of a chiral diene/rhodium catalyst to give high yields of the corresponding amines of 94−98% ee. To the best of our knowledge, this is the first example of a rhodium-catalyzed methyl-transfer reaction.

Our initial attempts to use methylboronic acid for the asymmetric methylation of imines failed. Thus, the reaction of *N*-tosylimine of benzaldehyde **1a** with methylboronic acid in the presence of a rhodium catalyst containing binap or a chiral diene ligand under the reaction conditions similar to those used for the asymmetric arylation using arylboronic acids[9a] resulted in low yields (<10%) of the methylation product. It was found that the use of dimethylzinc as a methylating reagent in the presence of a chiral diene rhodium catalyst greatly improved the asymmetric methylation (Scheme 1, Table 1).

Scheme 1



Thus, the reaction of **1a** with dimethylzinc in the presence of 3 mol % of a chiral rhodium catalyst, generated in situ from $[RhCl(C_2H_4)_2]_2$ and a C_2-symmetric chiral diene ligand (*R*,*R*)-Ph-bod*,[9a,11d] in dioxane at 50 °C for 3 h gave, after hydrolysis, 82% yield of *N*-tosyl-1-phenylethylamine (**2a**) which is 97% ee (entry 1). The absolute configuration was determined to be *S* by comparison of its specific rotation with the reported value.[12] It should be noted that this rhodium-catalyzed methylation smoothly proceeded using only 1.5 equiv of dimethylzinc. The use of another chiral diene ligand (*R*,*R*)-Bn-bod*[9a,11d] leads to lower enantioselectivity (62% ee) (entry 2). The higher catalytic activity of the chiral diene-rhodium complexes than phosphine-rhodium complexes is demonstrated by the results obtained with some chiral phosphine ligands under similar conditions. The yields of **2a** are very low with (*R*)-binap,[13] (*R*)-segphos,[14] (*R*)-MeO-mop,[15] and (*R*)-phosphoramidite[16] (entries 3−6).

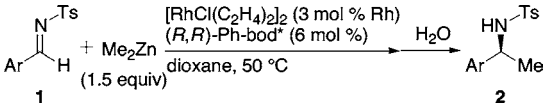
The data in Table 2 illustrate that the methylation of several *N*-tosylarylimines having different substituents on the aromatic nuclei can be performed to afford the *N*-tosylamines (**2a**−**j**) in good yields with high enantioselectivity. The

Table 1. Effects of Ligands on the Asymmetric Addition of Dimethylzinc to **1a**[a]

entry	ligand	yield[b] (%)	ee[c] (%)
1	(*R*,*R*)-Ph-bod*	82	97 (*S*)
2	(*R*,*R*)-Bn-bod*	65	62 (*S*)
3	(*R*)-binap	14	52 (*R*)
4	(*R*)-segphos	4	4 (*S*)
5	(*R*)-MeO-mop	<1	
6	(*R*)-phosphoramidite	6	5 (*S*)

[a] The reaction of **1a** with Me_2Zn (1.0 M in hexane, 1.5 equiv) was carried out in dioxane at 50 °C for 3 h in the presence of 3 mol % of rhodium catalyst generated from $[RhCl(C_2H_4)_2]_2$ and ligands (6 mol % of diene ligands, 3.3 mol % of bisphosphine ligands, and 6 mol % of monophosphine ligands, respectively). [b] Isolated yield after column chromatography on silica gel. [c] Determined by HPLC. Absolute configuration of **2a** was determined by comparison of its specific rotation with the reported one (ref 3b).

Table 2. Rhodium-Catalyzed Asymmetric Methylation of **1**



entry	imine	time (h)	isolated yield (%)	ee[a] (%)
1	**1a**: C_6H_5	3	**2a**: 82	97 (*S*)
2	**1b**: 4-ClC_6H_4	3	**2b**: 84	96 (*S*)
3	**1c**: 3-ClC_6H_4	3	**2c**: 83	96 (*S*)
4	**1d**: 4-FC_6H_4	3	**2d**: 84	98 (*S*)
5	**1e**: 4-$CF_3C_6H_4$	3	**2e**: 83	94 (*S*)
6	**1f**: 3-$MeOC_6H_4$	6	**2f**: 91	97 (*S*)
7	**1g**: 4-MeC_6H_4	6	**2g**: 81	98 (*S*)
8	**1h**: 3-MeC_6H_4	6	**2h**: 82	98 (*S*)
9[b]	**1i**: 2-MeC_6H_4	12	**2i**: 61	96 (*S*)
10[b]	**1j**: 2-naphthyl	12	**2j**: 75	98 (*S*)

[a] The absolute configurations were assigned by consideration of the stereochemical pathway. [b] 5 mol % of Rh with the ligand (10 mol %) was used.

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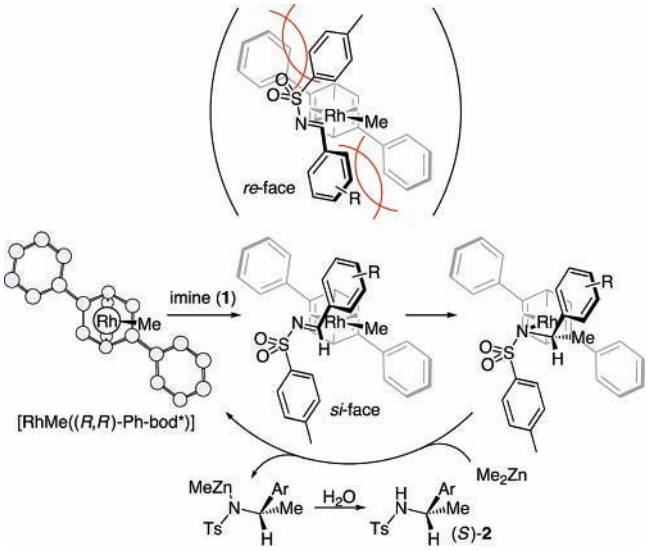
aromatic imines having electron-withdrawing substituents, such as chloro, fluoro, and trifluoromethyl groups, smoothly gave the corresponding amines **2** in high yields (83−84%) with high ee values (94−98% ee) (entries 2−5). On the other hand, in the reaction of imines with electron-donating substituents, a longer reaction time (6 h) was required to complete the reaction. Nevertheless, the corresponding amines **2f**−**h** were obtained in good yields with high enantioselectivity (entries 6−8). The methylation of imines with an ortho substituent (**1i)** and 2-naphthylimine **1j** was sluggish, and the increase of the catalyst loading was needed to acquire the corresponding products sufficiently (entries 9 and 10). The *p*-toluenesulfonyl group was readily removed from the 1-aryl-1-ethylamines by the standard method.[10d] For example, treatment of **2a** with lithium in liquid ammonia at −78 °C gave (*S*)-1-phenylethylamine in 79% yield without loss of its enantiomeric purity.

The present rhodium-catalyzed methylation may proceed via a methylrhodium species,[17] which is formed by the reaction of [RhCl(diene)] with dimethylzinc. Addition of the methylrhodium to C═N bond forms an aminorhodium species, which undergoes the *σ*-bond metathesis with Me_2Zn to regenerate the methylrhodium species and to produce the methylated product as a zinc amide. The *S* configuration of the product **2a** obtained with (*R*,*R*)-Ph-Bod* is rationalized by the coordination of imine **1a** to a rhodium

Scheme 2



with its *si*-face as shown in Scheme 2, which is similar to the arylation of imine that we previously reported.[9a]

In summary, asymmetric synthesis of 1-aryl-1-ethylamines with high enantioselectivity (94−98% ee) was accomplished by use of a chiral diene ligand (Ph-bod*) for the rhodium-catalyzed enantioselective methylation of *N*-tosylarylimines with dimethylzinc.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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