Asymmetric Catalysis

Rhodium-Catalyzed Asymmetric 1,6-Addition of Aryl Zinc Reagents to Dienones**

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The catalytic asymmetric 1,4-addition of organometallic reagents to electron-deficient olefins is one of the most important methods of forming stereogenic centers in carboncarbon bond-forming reactions.^[1] In this field, attention has focused on asymmetric 1,4-additions catalyzed by copper,^[2,3] rhodium,^[4-8] palladium,^[9] and nickel^[10] complexes. On the other hand, asymmetric 1,6-addition to extended conjugate systems has developed less rapidly.^[11] Although several reports have appeared on diastereoselective 1,6-additions,^[12] the use of a chiral catalyst for this asymmetric transformation remains to be studied. Herein, we report the first example of a catalytic asymmetric 1,6-addition to 2,4-dien-1-ones, in which a stereogenic center at the C5 position is also formed; this reaction is realized by a rhodium-catalyzed addition of aryl zinc reagents to dienones in the presence of chlorotrimethylsilane.

To investigate conjugate addition to 3-((E)-hexenyl)-2cyclohexenone (1), several phenyl organometallic reagents that had been successfully used in rhodium-catalyzed asymmetric 1,4-addition reactions to electron-deficient alkenes^[4-7] were examined for their reactivity and selectivity (Scheme 1 and Table 1). When the reaction was carried out with phenylboronic acid under reaction conditions that have been shown to be very efficient for asymmetric 1,4-additions



Scheme 1. Rhodium-catalyzed addition of phenyl organometallic reagents (PhM) to dienone **1**.

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Table 1: Rhodium-catalyzed asymmetric 1,6-addition to 1 forming products $3a-e^{[a]}$

Entry	PhM (equiv)	Conditions ^[b]	Yield $[\%]^{[c]}$	ee [%] ^[d]
1	PhB(OH) ₂ (2.5)	A	0 ^[e]	-
2	$PhTi(O/Pr)_3$ (1.6)	В	0 ^[f]	-
3	PhTi(O/Pr)₄Li/Me₃SiCl	С	78 (3 a)	88
	(1.5/2.0)			
4	PhZnCl ^[g] (1.4)	D	18 (3 a)	96
5	PhZnCl ^[g] /Me₃SiCl (1.4/1.5)	D	99 (3 a)	96
6	PhZnX ^[h] /Me₃SiCl (1.4/1.5)	D	94 (3 a)	94
7	4-FC ₆ H ₄ ZnX ^[h] /Me ₃ SiCl	D	90 (3 b)	98
	(1.4/1.5)			
8	4-MeOC ₆ H₄ZnCl ^[g] /Me₃SiCl	D	94 (3 c)	91
	(1.4/1.5)			
9	3-MeOC ₆ H₄ZnCl ^[h] /Me₃SiCl	D	86 (3 d)	86
	(1.4/1.5)			
10	2-naphthylZnCl ^[h] /Me₃SiCl	D	85 (3e)	91
	(1.4/1.5)			

[a] The reactions were carried out with 0.30 mmol of 1 in the presence of 3 mol% of the rhodium catalyst. [b] Conditions A: [{Rh(OH)[(S)-binap]}_2], dioxane/H₂O (10:1), 50 °C, 3 h. Conditions B: [{Rh(OH)[(S)-binap]}_2], THF, 30 °C, 1 h; hydrolysis with dilute HCl. Conditions C: [{RhCl[(S)-binap]}_2], THF, 20 °C, 0.5 h; hydrolysis with dilute HCl. Conditions D: [{RhCl[(S)-binap]}_2], THF, 20 °C, 0.5 h; hydrolysis with dilute HCl. Conditions D: [{RhCl[(S)-binap]}_2], THF, 20 °C, 0.5 h; hydrolysis with dilute HCl. Conditions D: [{RhCl[(S)-binap]}_2], THF, 20 °C, 2 h; hydrolysis with dilute HCl. [c] Yield of product isolated by column chromatography on silica gel (hexane/ethyl acetate, 4:1). [d] Determined by HPLC analysis with a chiral stationary-phase column (chiralpak OJ: hexane/2-propanol, 95:5); *ee* value for *R* enantiomer. [e] Dienone 1 was recovered. [f] A 1,2-addition product 2 was formed in 70% yield. [g] Generated from ArLi and ZnCl₂. [h] Generated from ArMgBr and ZnCl₂.

 $(3 \text{ mol }\% \text{ (Rh) of } [\{\text{Rh}(\text{OH})[(S)-\text{binap}]\}_2] \text{ (binap = 2,2'-bis-$ (diphenylphosphanyl)-1,1'-binaphthyl) as the catalyst in dioxane/H₂O (10:1) at 50 °C for 3 h),^[5b] the starting dienone 1 was recovered quantitatively (Table 1, entry 1). The use of the phenyltitanium reagent PhTi(OiPr)3 in the presence of $[{Rh(OH)[(S)-binap]}_2]$ in THF at 30 °C, which gives titanium enolates as 1,4-addition products with high enantioselectivities from α,β -unsaturated ketones,^[6a] does not react in the same way with the present substrate 1. Instead, titanium reagent reacted to give the tertiary alcohol 2 (70% yield; Table 1, entry 2) by a noncatalyzed 1.2-addition. The lithium titanate reagent PhTi(OiPr)₄Li (1.5 equiv), used in the chlorotrimethylsilane presence of (2.0 equiv)and [{RhCl[(S)-binap]]₂] (3 mol% Rh) in THF at 20°C, proved more promising.^[6c] The 1,6-addition product (R)-3-(2-phenylhexyl)-2-cyclohexenone (3a) was afforded after acidic hydrolysis in 78% yield and with 88% ee (Table 1, entry 3). The zinc reagent PhZnCl (1.4 equiv), which has been recently found to be more efficient than boron or titanium reagents in rhodiumcatalyzed asymmetric 1,4-addition reactions to enones,^[7] gave the 1,6-addition product 3a with higher enantioselectivity (96% ee(R)), although its yield was as low as 18% (Table 1, entry 4).

We have found, therefore, that chlorotrimethylsilane greatly accelerates^[13] the rhodium-catalyzed 1,6-addition of aryl zinc reagents to dienone **1**. Thus, **1** was treated with PhZnCl (1.4 equiv; generated from PhLi and ZnCl₂ in THF) in the presence of chlorotrimethylsilane (1.5 equiv) and [{RhCl[(*S*)-binap]}₂] (3 mol % Rh) in THF at 20 °C for 2 h, and the phenylation product (*R*)-**3a** was obtained in a

quantitative yield with 96% *ee* after acidic hydrolysis (Scheme 2; Table 1, entry 5). The 1,6-addition product before hydrolysis was a 1,3-dienyl silyl ether **4** (Z/E = 4:1). The high yield of the addition product may be ascribed to the



 $\it Scheme \ a.$ Rhodium-catalyzed asymmetric 1,6-addition of ArZnCl to dienone 1 in the presence of Me_3SiCl.

activation of **1** by the chlorosilane acting as a Lewis acid,^[13] which accelerates the addition of **1** to a phenylrhodium species in the catalytic cycle (see below). The asymmetric addition of aryl zinc reagents generated from 4-FC₆H₄MgBr, 4-MeOC₆H₄Li, 3-MeOC₆H₄MgBr, and 2-naphthylMgBr also gave the corresponding 1,6-addition products **3b**-e, respectively, in high yields and with high enantioselectivities (Table 1, entries 7–10). The formation of any 1,4- or 1,2-addition products was not detected in the reaction of **1** under the current conditions.

The absolute configuration of the 1,6-addition product **3a** was determined to be *R* after its conversion into (*R*)-1,2-diphenylhexane^[14] (**5d**). The key step in the synthetic pathway to **5d** is the oxidation of the cyclohexenone moiety in **3a** into the methoxyphenyl group in **5a** (Scheme 3).^[15]



Scheme 3. Determination of the absolute configuration of the 1,6-addition product **3 a.** a) I₂, MeOH, reflux (99%); b) BBr₃, CH₂Cl₂, room temperature (90%); c) Tf₂O, pyridine, ClCH₂CH₂Cl, room temperature (99%); d) H₂, Pd/C, EtOH, EtN(*i*Pr)₂, room temperature (86%). Tf=trifluoromethanesulfonyl.

Communications

The treatment of the linear dienone 4-methylundeca-3,5dien-2-one (6) with PhZnCl and chlorotrimethylsilane in the presence of the Rh/(S)-binap (3 mol % Rh) catalytic system also proceeded with perfect 1,6-selectivity to give the phenylation product in high yield (Scheme 4). Hydrolysis with



Scheme 4. Rhodium-catalyzed asymmetric 1,6-addition of PhZnCl to dienone **6** in the presence of Me_3SiCl .

hydrochloric acid afforded α,β -unsaturated ketone **7** and β,γ unsaturated ketone **8** as a mixture of olefinic isomers in a ratio of 21:79. Treatment of the mixture with sodium bicarbonate in ethanol at reflux for 48 h shifted the ratio of **7/8** to 67:33. Both **7** and **8** were found to be *R* enantiomers in 95% *ee*. The configuration was determined by correlation with (*R*)-3phenylnonen-2-one^[5a] ((*R*)-**9**), which was obtained by oxidative cleavage of the double bond in **7**.

The selectivity of the 1,6-addition was not as high in the reaction of hepta-3,5-dien-2-one (10); the 1,4-addition product was formed as a by-product because 10 lacks a substituent at the β position. Thus, the addition of PhZnCl to 10 in the presence of chlorotrimethylsilane under similar conditions gave the 1,6-addition products 11 (77% *ee*) and 12 in a combined yield of 58% together with the 1,4-addition product 13 in 25% yield (Scheme 5).

The catalytic cycle proposed for the rhodium-catalyzed 1,4-addition of aryl titanates in the presence of chlorotrime-thylsilane^[6c] can be applied to the 1,6-addition of aryl zinc



Scheme 5. Rhodium-catalyzed asymmetric addition of PhZnCl to dienone 10 in the presence of Me₃SiCl.

reagents (Scheme 6), as this mechanism involves the reaction of an oxo- π -allyl rhodium intermediate with chlorosilane to afford a chlororhodium complex and a silyl enolate as the product. With a dienone as the substrate, insertion of its γ , δ -double bond into the phenyl-rhodium bond in **A** is slow



Scheme 6. The catalytic cycle for the rhodium-catalyzed 1,6-addition reaction. $[Rh] = [Rh{(S)-binap}]$.

compared with the insertion of the α , β -double bond of an α , β unsaturated ketone; therefore, insertion of the dienone γ , δ double bond takes place more smoothly with the assistance of a chlorosilane as a Lewis acid. An alkyl rhodium intermediate **B** is formed by the insertion reaction and undergoes isomerization to a thermodynamically stable oxo- π -allyl rhodium complex **C**. A silylation reaction of **C** with chlorotrimethylsilane yields a chlororhodium species **D** and a silyl dienyl ether as the 1,6-addition product. Transmetalation between **D** and PhZnCl regenerates the phenylrhodium species **A**.

The absolute configuration R of the 1,6-addition product **3**, obtained with (*S*)-binap as a chiral ligand, was rationalized by using the stereochemical pathway shown in Scheme 7. At the insertion step, coordination of the γ , δ -double bond at the *Re* face is more favorable than coordination at the *Si* face because of the steric repulsions between one of the phenyl rings of the binap ligand and the cyclohexene moiety.

In summary, catalytic asymmetric 1,6-additions to 2,4dien-1-ones has been realized with up to 98% *ee* using a chiral



Scheme 7. The stereochemical pathway in the rhodium-catalyzed asymmetric 1,6-addition reaction.

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bisphosphine/rhodium catalyst, aryl zinc reagents, and a chlorosilane. Further studies on the scope and limitations of this new catalytic asymmetric carbon–carbon bond-forming reaction are underway.

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