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Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryltitanium Reagents Generating Chiral Titanium Enolates: Isolation as Silyl Enol Ethers

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A growing attention has been paid to rhodium-catalyzed addition of organoboronic acids to alkenes[1] and alkynes[2] and its application to catalytic asymmetric synthesis.[3,4,5] Recently it has been reported that some organosilicon compounds can participate in the rhodium-catalyzed reaction.[6] The catalytic cycle has been revealed for the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones catalyzed by a rhodium−binap complex.[7] One of the key steps is the hydrolysis of an (oxa-π-allyl)rhodium intermediate giving a β-arylated ketone and a hydroxorhodium species. It follows that the reaction must be carried out in the presence of water or a proton source, and as a result, the 1,4-addition products are obtained not as boron enolates but as the hydrolyzed products. It would be better to isolate chiral metal enolates generated regiospecifically by the rhodium-catalyzed asymmetric 1,4-addition and to use them for further transformations.[8,9] We found that the use of aryltitanium triisopropoxides ($ArTi(OPr\text{-}i)_3$) as arylating reagents for the rhodium-catalyzed asymmetric 1,4-addition in nonprotic solvent realizes the formation of titanium enolates as the 1,4-addition products which are versatile intermediates for the synthesis of enantiomerically enriched compounds by the reaction with electrophiles.

The reaction of 2-cyclohexenone (**1a**) with $PhTi(OPr\text{-}i)_3$[10,11] (**2m**) in the presence of 3 mol % of $[Rh(OH)((S)\text{-binap})]_2$[7] in THF-$d_8$ was monitored by ^1H NMR at 20 °C. Within 10 min, the ^1H resonances for the enone **1a** disappeared and were replaced by new signals attributable to titanium enolate **3am**.[12,13] On addition of methanol, protonolysis of the enolate took place to give a high yield (85%) of 3-phenylcyclohexanone (**4am**), which is an *S* isomer of 99.5% ee. Attempts to isolate the enolate as a silyl enol ether by silylation of the titanium enolate **3am** with a chlorotrialkylsilane were not successful. We found that addition of lithium isopropoxide to titanium enolate **3am** in THF followed by silylation of the resulting titanate[14] with chlorotrimethylsilane leads to silyl enol ether **5am** in a high yield (84%).[15] The results obtained for the rhodium-catalyzed asymmetric 1,4-addition of aryltitanium reagents **2m**−**p** to α,β-unsaturated ketones **1a**−**e**, which was carried out in THF at 20 °C (Scheme 1), are summarized in Table 1. The asymmetric 1,4-addition products were isolated as trimethylsilyl enol ethers **5** after the silylation by way of the titanates generated by the addition of lithium isopropoxide to titanium enolates **3**.

The asymmetric 1,4-addition forming a chiral titanium enolate was also successful with the titanium reagents containing 4-substituted phenyl ($ArTi(OPr\text{-}i)_3$, **2n,o**) (entries 2−3). They gave the corresponding silyl enol ethers **5an** and **5ao** with over 99% enantioselectivity. The catalytic asymmetric titanium enolate formation also proceeded with high enantioselectivity for 2-cyclopentenone (**1b**) and 2-cycloheptenone (**1c**) (entries 5−6). Linear α,β-unsaturated ketones **1d** and **1e** are good substrates for the present 1,4-addition, giving the corresponding silyl enol ethers **5dm** and **5em** with high enantioselectivity (entries 7−8).

Scheme 1

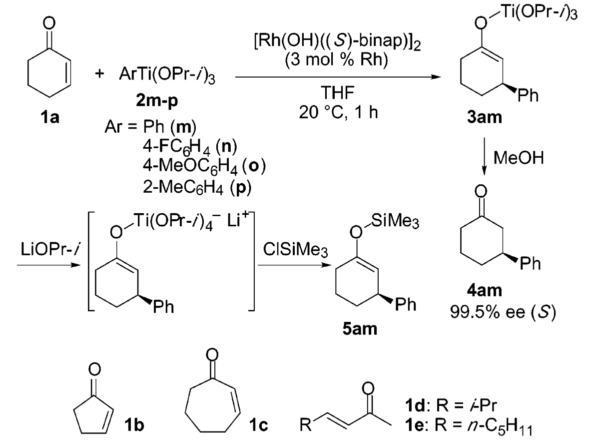

Table 1. Asymmetric 1,4-Addition of Aryltitanium Triisopropoxide **2** to Enone **1** Catalyzed by $[Rh(OH)((S)\text{-binap})]_2$; Isolation as Silyl Enol Ether **5**[a]

entry	enone 1	$ArTi(OPr\text{-}i)_3$ 2	silyl ether **5** yield (%)[c]		% ee of **4**[b] (config)	
1	**1a**	**2m**	**5am**	84	99.5	(*S*)
2	**1a**	**2n**	**5an**	68	99.0	(*S*)
3	**1a**	**2o**	**5ao**	84	99.8	(*S*)
4	**1a**	**2p**[d]	**5ap**	63	94	(*S*)
5[e]	**1b**	**2m**	**5bm**	62[f]	99.8	(*S*)
6[g]	**1c**	**2m**	**5cm**	89	98	(*S*)
7	**1d**	**2m**	**5dm**[h]	77	99.8	(*S*)
8	**1e**	**2m**	**5em**[i]	84	97	(*R*)

[a] The rhodium-catalyzed 1,4-addition was carried out with enone **1** (1.00 mmol) and $ArTi(OPr\text{-}i)_3$ **2** (1.60 mmol) in 5.0 mL of THF in the presence of 3 mol % (Rh) of $[Rh(OH)((S)\text{-binap})]_2$ at 20 °C for 1 h. To the reaction mixture, were added LiOPr-*i* (1.60 mmol) and $ClSiMe_3$ (2.00 mmol). [b] Determined by HPLC analysis of ketone **4** with chiral stationary phase columns (Chiralcel OD-H (**4am**, **4ap**, **4cm**, **4dm**, **4em**), AD (**4an**, **4ao**), and OB-H (**4bm**)). [c] Isolated yield by bulb-to-bulb distillation. [d] $2\text{-}MeC_6H_4Ti(OPr\text{-}i)_3$ (**2p**) was generated in situ from $2\text{-}MeC_6H_4Li$ and $ClTi(OPr\text{-}i)_3$. [e] Reaction for 5 min. [f] Contaminated with ca. 6% of **4bm** (hydrolyzed product). [g] Reaction for 15 min. [h] A mixture of *E* and *Z* isomers (10/9). [i] A mixture of *E* and *Z* isomers (10/11).

Although the silyl enol ethers such as those isolated here are well-documented to be very useful as synthetic intermediates[16] which are readily converted into various kinds of enantiomerically enriched compounds, the titanium enolates generated by the rhodium-catalyzed asymmetric 1,4-addition can be used, not by way of the silyl enol ethers, for alkylation with alkyl halides (Scheme 2). Thus, the titanium enolate **3am** was allowed to react with lithium isopropoxide and allyl bromide to give 82% yield of (2*R*,3*S*)-*trans*-3-phenyl-2-allylcyclohexanone (**6**) as a single diastereomeric isomer, whose enantiomeric purity is over 99%. In the reaction of the enol

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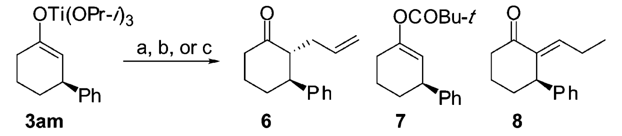
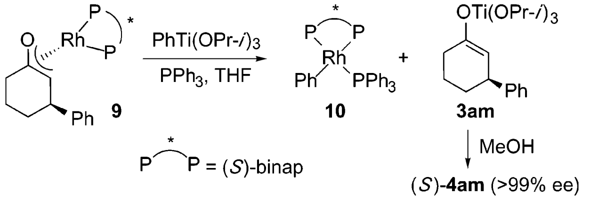
Scheme 2 [a]

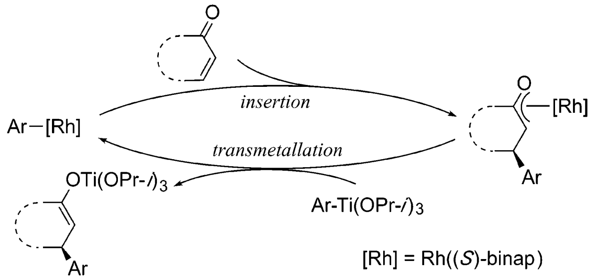


[a] (a) BrCH$_2$CH=CH$_2$, LiOPr-i , THF, 82% (**6**); (b) ClCOBu-t, LiOPr-i, THF, 79% (**7**); (c) EtCHO, THF, 45% (**8**).

Scheme 3



Scheme 4



titanate with pivaloyl chloride, O-acylation took place selectively to give a high yield of enol ester **7**. Treatment of **3am** with propanal resulted in the formation of (E)-enone **8**[17] by the aldol addition and elimination.

^{31}P NMR studies showed that addition of the phenyltitanium reagent PhTi(OPr-i)$_3$ (**2m**) to the (oxa-π-allyl)((S)-binap)rhodium complex **9**[7,18] in the presence of triphenylphosphine in THF generated the phenylrhodium complex coordinated with (S)-binap and triphenylphosphine **10**.[7] Protonolysis of the resulting THF solution with methanol gave a high yield of (S)-3-phenylcyclohexanone (**4am**) (Scheme 3). These results indicate that the catalytic cycle of the present 1,4-addition consists of two steps (Scheme 4): One is transmetalation of the aryl group from titanium to the (oxa-π-allyl)rhodium intermediate, forming an arylrhodium species and the titanium enolate. The other is insertion of an enone into the arylrhodium species, forming the (oxa-π-allyl)rhodium complex, this step having been established during our studies on the rhodium-catalyzed 1,4-addition of arylboronic acids.[7]

To summarize, the rhodium-catalyzed asymmetric 1,4-addition forming chiral titanium enolates with high enantioselectivity was realized for the first time by the use of ArTi(OPr-i)$_3$. The chiral titanium enolates can be isolated as silyl enol ethers by way of titanate-type enolates generated by the addition of lithium isopropoxide to the titanium enolates. The catalytic cycle has been established by a stoichiometric reaction of an (oxa-π-allyl)rhodium complex.

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

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(12) ^{1}H NMR (THF-d_8): δ 1.27 (br d, J = 5.5 Hz, 18H), 1.37−1.49 (br m, 1H), 1.60−1.72 (br m, 1H), 1.74−1.86 (br m, 1H), 1.86−2.00 (br m, 1H), 2.14−2.43 (br m, 2H), 3.47−3.58 (br m, 1H), 4.38−4.75 (br m, 3H), 4.91−5.11 (br m, 1H), 7.11 (t, J = 7.2 Hz, 1H), 7.21 (t, J = 7.2 Hz, 2H), 7.25 (d, J = 7.2 Hz, 2H).

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(17) Contaminated with ca. 8% of its isomer.

(18) The (oxa-π-allyl)rhodium complex **8** was generated in the NMR sample tube by addition of 2-cyclohexenone to phenylrhodium **9** (ref 7).

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