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Rhodium-Catalyzed Asymmetric 1,6-Addition of Aryltitanates to Enynones Giving Axially Chiral Allenes

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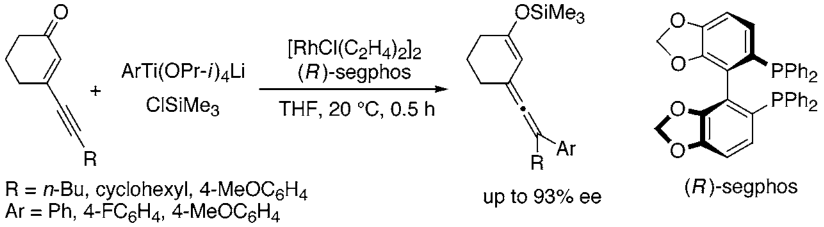
ABSTRACT



The addition of aryltitanate reagents ArTi(OPr-*i*)$_4$Li to 3-alkynyl-2-en-1-ones in the presence of chlorotrimethylsilane and a rhodium-(*R*)-segphos as a catalyst proceeded in a 1,6-fashion to give a high yield of axially chiral allenylalkenyl silyl enol ethers with up to 93% ee.

Enantiomerically enriched allenes whose chirality is due to their allene axis are known to be useful as chiral building blocks in synthetic organic chemistry.[1] Although growing attention has been paid to their asymmetric synthesis,[2] synthesis by means of asymmetric catalysis has not been well developed. To the best of our knowledge, there have been reported only two types of catalytic methods: (1) palladium-catalyzed asymmetric hydroboration[3] and hydrosilylation[4] of but-1-en-3-ynes and rhodium- or nickel-catalyzed asymmetric double hydrosilylation of butadiynes[5] and (2) palladium-catalyzed asymmetric substitution of 2-bromobuta-1,3-dienes and allenylmethyl phosphonates.[6] One of the reactions, presumably applicable to the catalytic asymmetric synthesis of axially chiral allenes, is the 1,6-addition of organometallic reagents to 3-alkynyl-2-en-1-ones, which has been reported by Hulce[7] and Krause[8] to proceed by means of organocopper reagents; however, its catalytic asymmetric version has not been reported. Here we wish to report that the catalytic asymmetric 1,6-addition giving axially chiral allenes was realized for the first time by rhodium-catalyzed addition of aryltitanate reagents in the presence of chlorotrimethylsilane.

For the 1,6-addition to 3-(1-hexynyl)-2-cyclohexenone (**1a**), which is readily accessible from 1,3-cyclohexanedione,[9] we examined several reaction conditions, including those

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[1] For reviews: (a) *The Chemistry of the Allenes*; Landor, S. R., Ed.; Academic Press: London, 1982. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis;* Wiley: New York, 1984. (c) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (d) Krause, N.; Hoffmann-Röder, A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002, p 145.

[2] For a relevant review on the enantioselective synthesis of allenes: Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933.

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[5] (a) Tillack, A.; Michalik, D.; Koy, C.; Michalik, M. *Tetrahedron Lett.* **1999**, *40*, 6567. (b) Tillack, A.; Koy, C.; Michalik, D.; Fischer, C. *J. Organomet. Chem.* **2000**, *603*, 116.

[6] (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089. (b) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217. (c) Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S.-I. *Chem. Lett.* **2002**, 140.

[7] (a) Fredrick, M. A.; Hulce, M. *Tetrahedron* **1997**, *53*, 10197 and references therein. (b) Cheng, M.; Hulce, M. *J. Org. Chem.* **1990**, *55*, 964. (c) Hulce, M. *Tetrahedron Lett.* **1988**, *29*, 5851.

[8] (a) For a relevant review: Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1. (b) Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 1644 and references therein. (c) Krause, N. *Chem. Ber.* **1990**, *123*, 2173.

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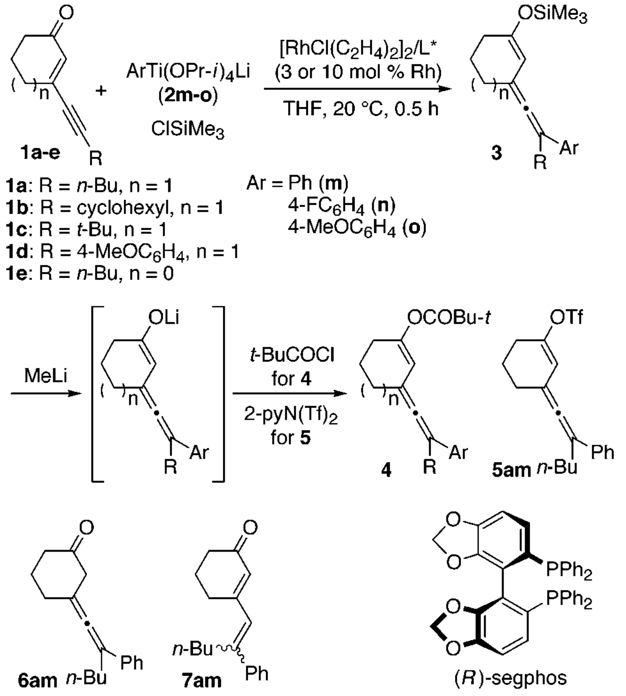
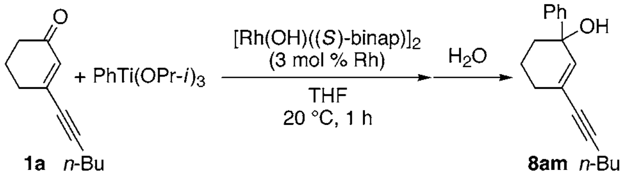
reported previously for the rhodium-catalyzed asymmetric 1,4-addition to electron-deficient olefins.[10−13] It was found that a new reaction system consisting of an aryltitanate reagent, chlorotrimethylsilane, and a chiral phosphine−rhodium catalyst gives a high yield of allenylalkenyl silyl ether as a 1,6-addition product (Scheme 1). Thus, to a solution of enynone **1a** (0.30 mmol), chlorotrimethylsilane (0.63 mmol), [RhCl(C$_2$H$_4$)$_2$]$_2$ (0.0045 mmol, 3 mol % Rh), and (*R*)-segphos[14] (0.014 mmol) in THF was added a THF solution of titanate PhTi(OPr-*i*)$_4$Li (**2m**) (0.45 mmol), generated by the addition of Ti(OPr-*i*)$_4$ to aryllithium or by the addition of LiOPr-*i* to ArTi(OPr-*i*)$_3$, and the mixture was stirred at 20 °C for 0.5 h. Addition of a small amount of water followed by removal of precipitates by filtration through a short Celite/MgSO$_4$ pad gave a crude 3-alkenylidene-1-(trimethylsilyloxy)cyclohexene **3am** in a high yield. Because the silyl ether **3am** is not stable enough for the determination of its enantiomeric purity by the HPLC analysis with a chiral stationary phase column, it was converted into the more stable pivalate ester **4am** by treatment with methyllithium in ether and then with pivaloyl chloride. The pure ester **4am** was isolated in 86% yield (from **1a**) by a silica gel PTLC (hexane/ethyl acetate = 20/1), and its enantiomeric purity was determined to be 90% ee (Chiralcel OD-H, hexane). Isolation of the allene as triflate **5am** (82%) was also possible by treatment of the lithium enolate with ArN(Tf)$_2$ (Ar = 2-pyridyl).[7b] On protonation of the lithium enolate by treatment with pivalic acid, the formation of allenyl ketone **6am** was observed, but it readily underwent isomerization into dienyl ketone **7am** on silica gel chromatography.

Scheme 1



The use of the titanate reagent (PhTi(OPr-*i*)$_4$Li (**2m**)) and chlorotrimethylsilane at the same time is important for the present 1,6-addition reaction to proceed.[15] The 1,6-addition is not observed in the absence of chlorotrimethylsilane. The rhodium-catalyzed reaction of **1a** with titanium reagent PhTi(OPr-*i*)$_3$[11] brought about 1,2-addition to carbonyl, giving tertiary alcohol **8am** as a major product (Scheme 2).

Scheme 2



As a chiral ligand, (*R*)-segphos was more enantioselective than other phosphine ligands we examined. In the reaction of **1a** with **2m**, (*R*)-binap, (*S*)-(*R*)-PPF-P(Bu-*t*)$_2$, and (*R*)-MeO-MOP gave **4am** in 80, 14, and 0 % ee, respectively. Because the 1,6-addition proceeds slowly in the absence of the rhodium catalyst,[16] the use of a larger amount (10 mol % Rh) of the catalyst resulted in a slightly higher enantioselectivity. The results obtained with the rhodium/(*R*)-segphos catalyst for some other enynones **1** and titanates **2** (Scheme 1) are summarized in Table 1. The chemoselectivity in giving allenes and the enantioselectivity were dependent on the substituent at the alkyne terminus of **1**. The yields of allenes **3** were lower for the sterically more bulky substituents **1c** and **1d**, and the enantioselectivity was higher for the sterically less bulky substituents, *n*-butyl **1a** and cyclohexyl **1b**, giving higher selectivity than *tert*-butyl **1c**. Aryltitanate reagents **2n** and **2o**, which contain fluoro and methoxy groups at the 4-position of the phenyl, respectively, gave essentially the same results as phenyltitanate **2m**.

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(15) Reaction of **1a** with phenylboronic acid under the conditions used for the asymmetric 1,4-addition to enones (3 mol % Rh(acac)(C$_2$H$_4$)$_2$/(*R*)-binap in dioxane/H$_2$O (10/1), 100 °C, 3 h) (see ref 10) gave only a small amount (7%) of the dienyl ketone **7am**.

(16) Reaction of **1a** with **2m** and ClSiMe$_3$ in the absence of the rhodium catalyst at 20 °C for 0.5 h gave ca. 70% yield of the silyl ether **3am**.

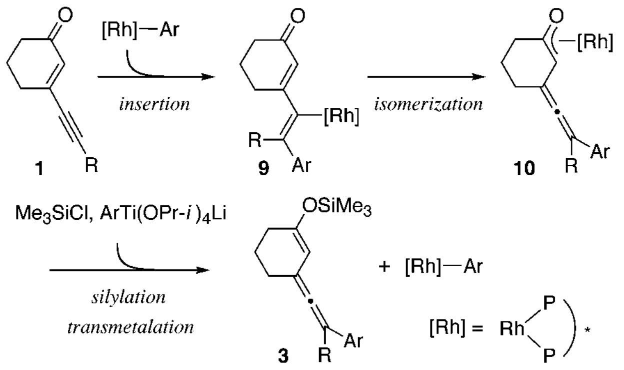
Table 1. Asymmetric 1,6-Addition of Aryltitanate Reagent **2** to Enynone **1** Catalyzed by $[RhCl(C_2H_4)_2]_2$/(*R*)-Segphos and Isolation as Pivalate Ester **4**[a]

entry	enynone **1** (R)	titanate **2** (Ar)	silyl ether **3** yield (%)[b]	pivalate **4** yield (%)[c]	% ee[d]
1[e]	**1a** (*n*-Bu)	**2m** (Ph)	**3am** >99	**4am** 86	90
2	**1a** (*n*-Bu)	**2m** (Ph)	**3am** >99	**4am** 85	92
3	**1a** (*n*-Bu)	**2n** ($4\text{-}FC_6H_4$)	**3an** >99	**4an** 85	91
4	**1a** (*n*-Bu)	**2o** ($4\text{-}MeOC_6H_4$)	**3ao** >99	**4ao** 83	93
5	**1b** (*c*-Hex)	**2m** (Ph)	**3bm** >99	**4bm** 91	70
6	**1b** (*c*-Hex)	**2o** ($4\text{-}MeOC_6H_4$)	**3bo** >99	**4bo** 80	80
7	**1c** (*t*-Bu)	**2m** (Ph)	**3cm** 61	**4cm** 44	26
8	**1d** ($4\text{-}MeOC_6H_4$)	**2m** (Ph)	**3dm** 60	**4dm** 56	75
9[e]	**1e** (*n*-Bu)	**2m** (Ph)	**3em** >99	**4em** 80[f]	70

[a] To a solution of enynone **1** (0.30 mmol), chlorotrimethylsilane (0.63 mmol), $[RhCl(C_2H_4)_2]_2$ (0.015 mmol, 10 mol % Rh), and (*R*)-segphos (0.033 mmol) in THF was added a THF solution of titanate $ArTi(OPr\text{-}i)_4Li$ (**2**) (0.45 mmol), generated by the addition of $Ti(OPr\text{-}i)_4$ to aryllithium or by the addition of LiOPr-*i* to $ArTi(OPr\text{-}i)_3$, and the mixture was stirred at 20 °C for 0.5 h. For the isolation of silyl enol ether **3** and pivalate ester **4**, see the text and Supporting Information. [b] Yield of **3** determined by NMR analysis of the crude product. [c] Isolated yield of **4** by silica gel chromatography. [d] Determined by HPLC analysis of pivalate **4** with a chiral stationary phase column, Chiralcel OD-H. [e] With 3 mol % rhodium and 4.5 mol % (*R*)-segphos. [f] Contaminated with ca. 20% dienyl ketone.

The present 1,6-addition giving the allenylalkenyl silyl ethers **3** is considered to proceed through the catalytic cycle shown in Scheme 3, which is analogous to the rhodium-catalyzed 1,4-addition.[10h,11a] Thus, insertion of the carbon–carbon triple bond of enynone **1** into the rhodium-aryl bond forms alkenylrhodium **9**,[17] which isomerizes into thermodynamically more stable oxa-π-allylrhodium intermediate **10**.[10h] At this isomerization, the stereochemical outcome of the asymmetric 1,6-addition should be determined. The final step is the silylation and transmetalation of **10**, giving allenylalkenyl silyl ether **3** and the aryl-rhodium intermediate.[18]

Scheme 3



In summary, catalytic asymmetric 1,6-addition to 3-alkynyl-2-en-1-ones giving enantiomerically enriched axially chiral allenes (up to 93% ee) was realized for the first time by use of a chiral bisphosphine-rhodium catalyst and aryltitanate reagents and a chlorosilane. The axially chiral allenes were produced as silyl enol ethers and can be converted into enol pivalate esters or enol triflates. Studies on the scope and limitation of this new catalytic asymmetric transformation reaction are underway.

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

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(18) It was observed that treatment of an (oxa-π-allyl)rhodium complex with chlorotrimethylsilane and titanate, $PhTi(OPr\text{-}i)_4Li$ (**2m**), gives silyl enol ether and phenyl-rhodium species (see also ref 11a).