Novel Method for the Preparation of Enantiomerically Pure Propargylic Substituted Compounds

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Summary: We have found a novel method for the preparation of enantiomerically pure propargylic alkylated compounds from an achiral propargylic alcohol assisted by a ruthenium complex bearing BINAP as a chiral ligand. It is noteworthy that products bearing completely opposite configurations are obtained with an almost 100% ee.

In sharp contrast to the enantioselective allylic substitution reaction of allylic alcohol derivatives with nucleophiles catalyzed by transition-metal complexes, which is one of the most successful and reliable methods in asymmetric synthesis,[1] the enantioselective propargylic substitution reaction of propargylic alcohol derivatives catalyzed by transition-metal complexes has not yet been developed. We have recently disclosed that the ruthenium-catalyzed propargylic substitution reaction of propargylic alcohols with a variety of heteroatom- and carbon-centered nucleophiles afforded the corresponding functionalized propargylic compounds in high yields with complete regioselectivity.[2] It is noteworthy that the reactions are catalyzed by thiolate-bridged diruthenium complexes[3] such as $[Cp^*RuCl(\mu_2\text{-}SR)]_2$ ($Cp^* = \eta^5\text{-}C_5Me_5$; R = Me, ^{n}Pr, ^{i}Pr) and $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*(OH_2)]OTf$ ($OTf = OSO_2CF_3$) but not by various monoruthenium complexes.[2] More recently, we have prepared several diruthenium complexes bearing chiral thiolate-bridged ligands and applied them as catalysts to the catalytic enantioselective propargylic alkylation of propargylic alcohols with acetone, which resulted in the formation of the propargylic alkylated compounds in good yields, but with only a moderate enantioselectivity (up to 35% ee).[4]

Nicholas and co-workers reported the stereospecific propargylic alkylation of chiral propargylic alcohols by using a stoichiometric amount of $[Co_2(CO)_5L]$ (L = phosphite), but several reaction steps as well as two separation procedures of the produced diastereoisomers were necessary on the way to obtaining the enantiomerically rich propargylic alkylated compounds.[5] As an alternative Nicholas reaction, Gimeno and co-workers developed a ruthenium-assisted stoichiometric and stepwise method for the preparation of propargylic alkylated compounds from propargylic alcohols via ruthenium−allenylidene complexes as key intermediates.[6] High diastereoselectivities were achieved in the reactions of the ruthenium−allenylidene complexes with lithium enolates.[7,8] Independently, Müller and co-workers reported the highly diastereoselective substitution reaction of propargylic alcohol derivatives with various nucleophiles via propargyl cations stabilized by a chromium carbonyl arene moiety, $(arene)Cr(CO)_3$.[9] Thus, successful examples of asymmetric propargylic substitu-

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(3) (a) The thiolate-bridged diruthenium complexes were found to provide a unique bimetallic reaction site for activation and transformation of various terminal alkynes; see: Nishibayashi, Y.; Yamanashi, M.; Wakiji, I.; Hidai, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2909 and references therein. (b) Nishibayashi, Y.; Imajima, H.; Onodera, G.; Hidai, M.; Uemura, S. *Organometallics* **2004**, *23*, 26. (c) Nishibayashi, Y.; Imajima, H.; Onodera, G.; Inada, Y.; Hidai, M.; Uemura, S. *Organometallics* **2004**, *23*, 5100. (d) The methanethiolate-bridged diruthenium complexes $[Cp^*RuCl(\mu_2\text{-}SMe)]_2$ and $[Cp^*RuCl(\mu_2\text{-}SMe)_2RuCp^*(OH_2)](OTf)$ are commercially available from Wako Pure Chemical Industries (Japan) as met-DIRUX (*met*hanethiolate-bridged *diru*thenium comple*x*) (130-14581) and met-DIRUX-OTf (132-14781).

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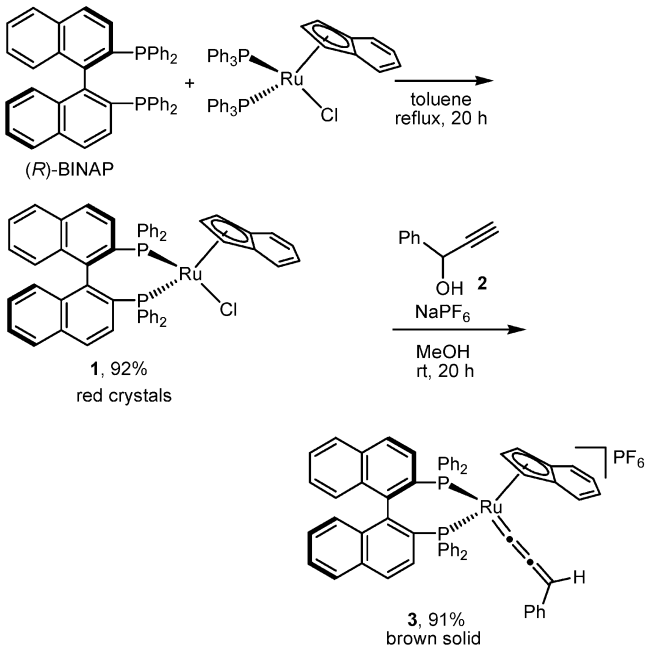
Scheme 1



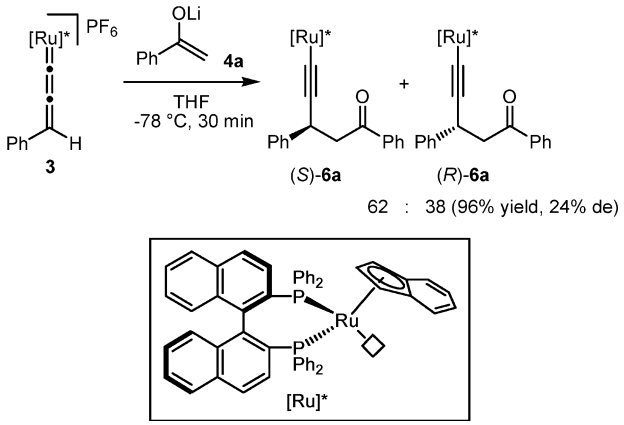
tion reactions have only been limited to the diastereoselective reactions by using stoichiometric amounts of transition-metal complexes.

As an extension of our ongoing study on enantioselective propargylic substitution reactions, we have now found a novel method for the preparation of enantiomerically pure propargylic alkylated compounds from an achiral propargylic alcohol assisted by a ruthenium complex bearing BINAP[10] as a chiral ligand. This methodology is considered to be the first synthetic approach to the highly enantioselective propargylic substitution reactions. Preliminary results are described here.

Treatment of [Ru(η^5-C_9H_7)Cl((*R*)-BINAP)][11] (**1**), which was newly prepared from the reaction of [Ru(η^5-C_9H_7)-Cl(PPh_3)$_2$] with (*R*)-BINAP in toluene at reflux temperature for 20 h, with racemic 1-phenyl-2-propyn-1-ol (**2**) in the presence of $NaPF_6$ in MeOH at room temperature for 20 h gave the corresponding allenylidene complex [Ru{=C=C=CHPh}(η^5-C_9H_7)((*R*)-BINAP)]PF_6 (**3**) in 91% yield as a single isomer (Scheme 1). The formation of **3** was confirmed by elemental analysis and IR and NMR (^{1}H, ^{13}C{^{1}H}, and ^{31}P{^{1}H}) spectroscopy.

The reaction of **3** with the lithium enolate **4a**, which was generated in situ from the corresponding silyl enol ether **5a** and MeLi at 0 °C, in tetrahydrofuran (THF) at −78 °C for 30 min gave the corresponding σ-alkynyl complex [Ru{C≡CC(CH_2COPh)HPh}(η^5-C_9H_7)((*R*)-BINAP)] (**6a**) as a mixture of two diastereoisomers in quantitative yield (Scheme 2). Only moderate diastereoselectivity was observed, even when the reaction was

Scheme 2



carried out at −100 °C. It is noteworthy that the diastereoisomers of the σ-alkynyl complex ((*S*)- and (*R*)-**6a**) can be easily separated by using column chromatography on SiO_2. As a result, the σ-alkynyl complex bearing an *S* configuration on the alkynyl ligand ((*S*)-**6a**) was isolated in 55% yield with >99% de, while the σ-alkynyl complex bearing an *R* configuration on the alkynyl ligand ((*R*)-**6a**) was isolated in 28% yield also with >99% de. This result indicates that each σ-alkynyl complex can be obtained in diastereomerically pure form.

Protonation of each of the diastereomerically pure σ-alkynyl complexes ((*S*)- and (*R*)-**6a**) with HBF_4·Me_2O in diethyl ether at −20 °C for 30 min gave the corresponding vinylidene complexes [Ru{=C=CHC(CH_2-COPh)HPh}(η^5-C_9H_7)((*R*)-BINAP)]BF_4 ((*R*)- and (*S*)-**7a**, respectively) in high yield and in an enantiomerically pure form (Scheme 3). Treatment of the vinylidene complex bearing an *R* configuration on the vinylidene ligand ((*R*)-**7a**) with acetonitrile at reflux temperature for 30 min afforded (*R*)-1,3-diphenyl-4-pentyn-1-one[12] ((*R*)-**8a**) in 89% yield with >99% ee, together with the formation of [Ru(N≡CMe)(η^5-C_9H_7)((*R*)-BINAP)]BF_4 (**9**) (Scheme 4). Similarly, transformation of another vinylidene complex bearing an *S* configuration on the vinylidene ligand ((*S*)-**7a**)) proceeded smoothly to give (*S*)-1,3-diphenyl-4-pentyn-1-one ((*S*)-**8a**) in enantiomerically pure form also, together with **9**. This stepwise reaction provides both propargylic alkylated products in enantiomerically pure form.

When the reactions of the allenylidene complex **3** with other lithium enolates (**4b**,**c**) were investigated under the same reaction conditions, the corresponding σ-alkynyl complexes [Ru{C≡CC(CH_2COAr)HPh}(η^5-C_9H_7)-((*R*)-BINAP)] (**6b** (Ar = *p*-F-C_6H_4) and **6c** (Ar = 1-naphthyl)) were formed as a mixture of two diastereoisomers quantitatively with only a low diastereoselectivity (Scheme 5). Fortunately, in both cases, the σ-alkynyl complexes could be easily separated by column chromatography on SiO_2 in diastereomerically pure form. Protonation of the isolated σ-alkynyl complexes ((*S*)-**6b** and (*S*)-**6c**) followed by the ligand exchange reaction of the vinylidene complexes produced ((*R*)-**7b** and (*R*)-**7c**) with acetonitrile resulted in the formation of propargylic

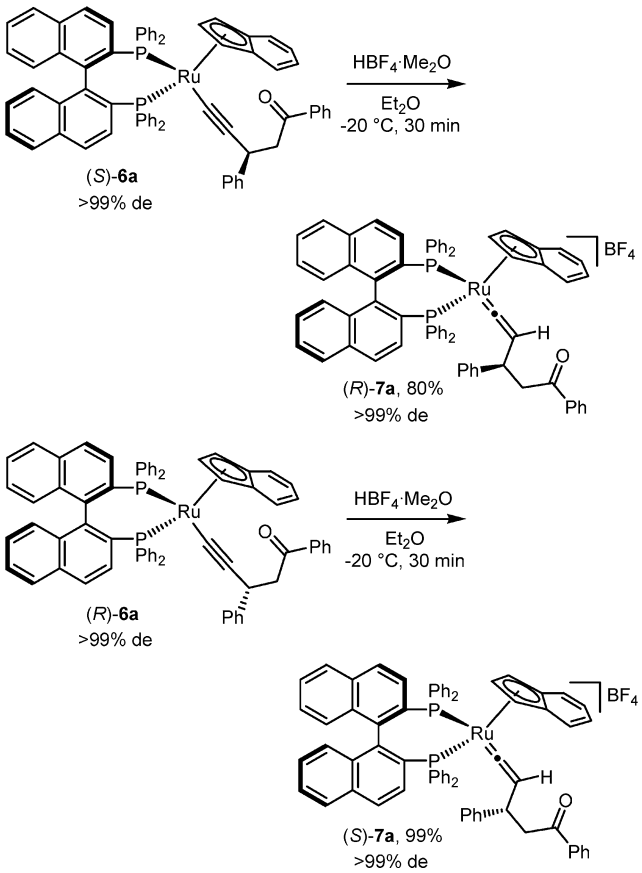
(9) Netz, A.; Polborn, K.; Müller, T. J. J. *J. Am. Chem. Soc*. **2001**, *123*, 3441.

(10) For a recent review, see: Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

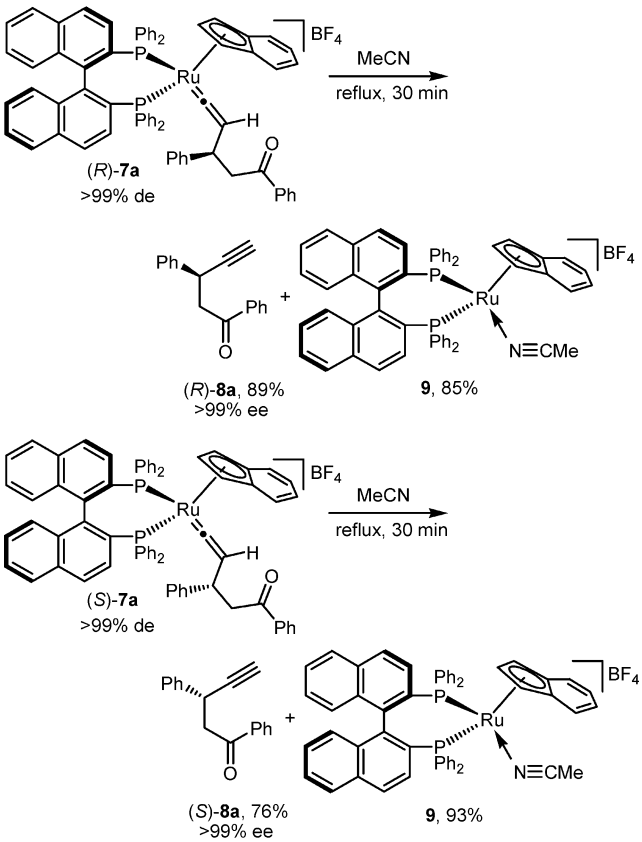
(11) The molecular structure of **1** has been unambiguously clarified by X-ray analysis. Crystal data for **1**: $C_{53}H_{39}ClPRu$, M_r = 874.36, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 10.7043(9) Å, b = 16.348(1) Å, c = 23.4626(5) Å, V = 4105.7(2) Å^3, Z = 4, μ(Mo Kα) = 5.62 cm^{-1}, 8788 reflections measured, 6997 unique reflections, which were used in all calculations. Final R1 = 0.036 and wR2 = 0.094 (all data).

(12) (a) Hydrogenation of (*R*)-**8a** afforded (+)-(*S*)-PhCH(CH_2C(O)-Ph)CH_2CH_3. (b) Alexakis, A.; Benhaim, C.; Rosset, S.; Human, M. *J. Am. Chem. Soc*. **2002**, *124*, 5262. (c) Shintani, R.; Fu, G. C. *Org. Lett*. **2002**, *4*, 3699.

Scheme 3

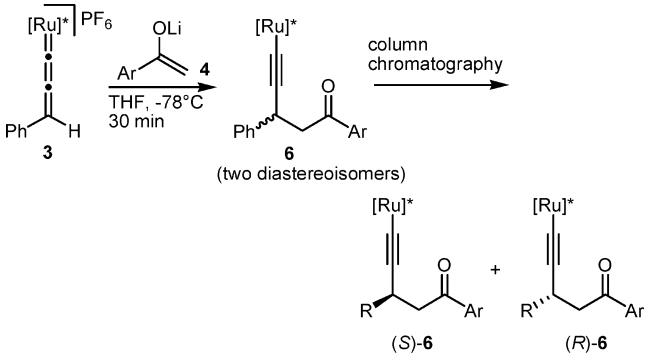


Scheme 4



alkylated compounds ((*R*)-**8b** and (*R*)-**8c**) in enantiomerically pure form (Scheme 6). The ruthenium complex

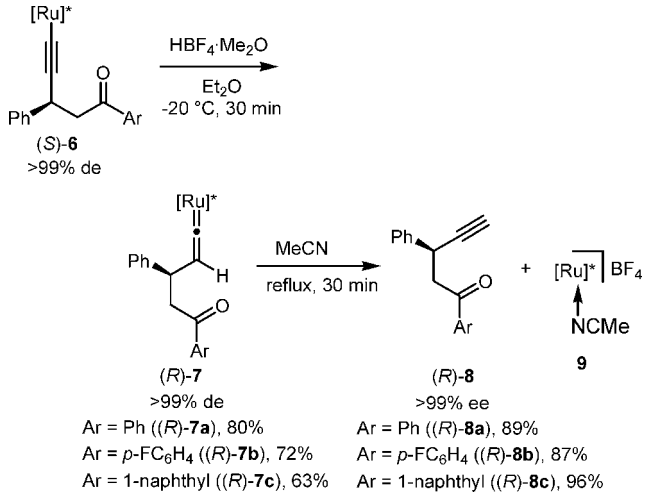
Scheme 5



entry	Ar	yield of **6** (%)	de of **6** (%)[a]	isolated yield (%)[b] [de (%)] (*S*)-**6**	(*R*)-**6**
1	Ph (**4a**)	96	25	55 [>99]	28 [>99]
2	*p*-FC_6H_4 (**4b**)	90	14	41 [>99]	24 [>99]
3	1-naphthyl (**4c**)	93	1	42 [>99]	26 [>99]

[a] Determined by ^{1}H NMR. [b] After column chromatography.

Scheme 6



9 can be converted into the original ruthenium−BINAP complex **1** by ligand exchange. In fact, we confirmed the quantitative formation of **1** in the reaction of **9** with an excess amount of KCl in the presence of 18-crown-6.[13] Thus, a synthetic cycle for the formation of enantiomerically pure propargylic alkylated compounds from an achiral propargylic alcohol has been accomplished by starting from the ruthenium−BINAP complex **1** (Scheme 7). In this pseudo-catalytic cycle, the ruthenium−BINAP complex can be recovered and reused for this asymmetric synthetic reaction. The overall process has the potential to be a general synthetic protocol to obtain propargylic-substituted compounds with complete enantioselectivity.

In summary, we have found a novel method for the preparation of enantiomerically pure propargylic alkylated compounds from an achiral propargylic alcohol assisted by a ruthenium complex bearing BINAP as a chiral ligand. Although four reaction steps and the column chromatographic separation of two diastereoisomers are necessary to obtain the expected com-

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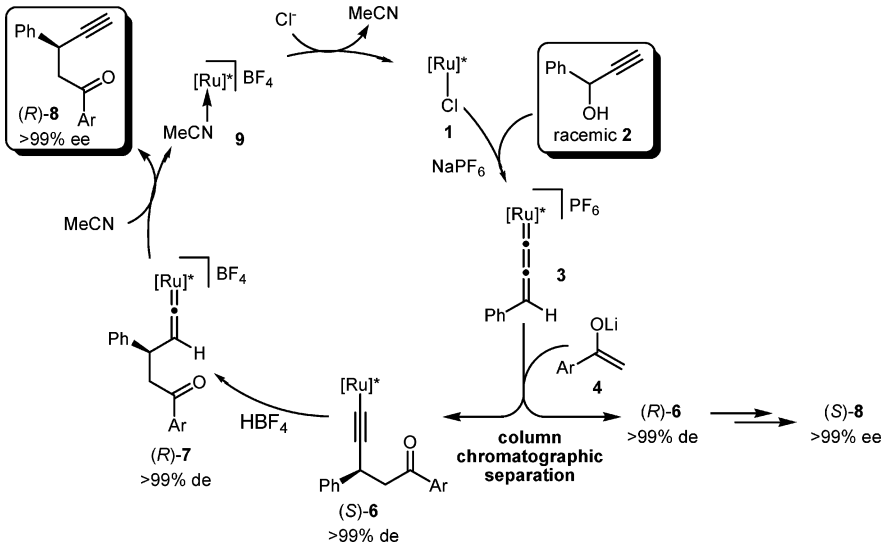
Scheme 7



pounds, this stepwise reaction provides the first synthetic approach to highly enantioselective propargylic substitution reactions. It is also noteworthy that products bearing completely opposite configurations are obtained with almost 100% ee. Further work is currently in progress to improve the diastereoselectivity in the reaction of the ruthenium allenylidene complexes with lithium enolates and to broaden the scope of this enantioselective propargylic substitution reaction by using other nucleophiles.

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Supporting Information Available: Text giving experimental procedures and ^{1}H, ^{13}C, and ^{31}P NMR spectral data for **1**, **3**·0.5CH_2Cl_2, and **6**–**8** and a table and figure giving crystallographic details for **1**; crystallographic data for **1** are also available as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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