Synthetic Methods

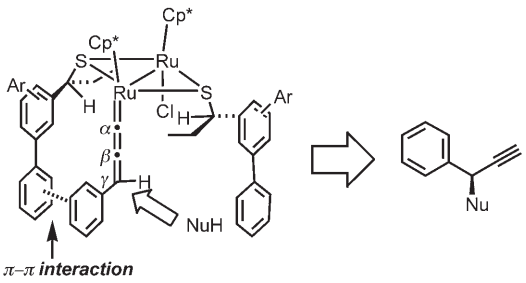
DOI: 10.1002/anie.200502981

Ruthenium-Catalyzed Asymmetric Propargylic Substitution Reactions of Propargylic Alcohols with Acetone**

Youichi Inada, Yoshiaki Nishibayashi, and Sakae Uemura*

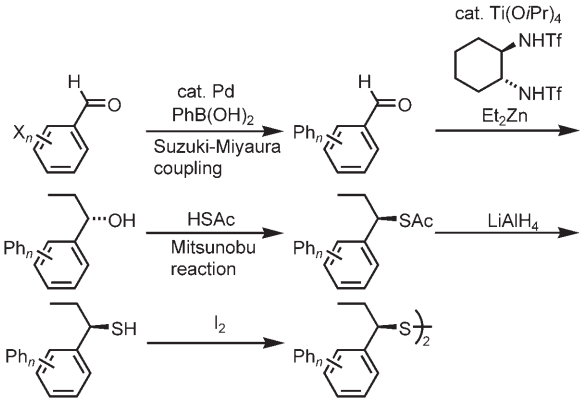
In sharp contrast to enantioselective allylic substitution reactions of allylic alcohol derivatives with nucleophiles catalyzed by transition metal complexes,[1] its propargylic version has not yet been developed. We recently disclosed that ruthenium-catalyzed propargylic substitution reactions of propargylic alcohols with a variety of heteroatom- and carbon-centered nucleophiles affords the corresponding functionalized propargylic compounds in high yields with complete regioselectivity.[2] The reactions were catalyzed only 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] and they proceeded via allenylidene complexes[4] as key intermediates under the synergistic effect of the two ruthenium atoms in the diruthenium complexes.[2]

More recently, we have prepared several diruthenium complexes bearing chiral thiolate bridging ligands and applied them as catalysts in the catalytic enantioselective propargylic alkylation of propargylic alcohols with acetone, which resulted in the formation of the propargylic alkylated compounds in good yields, but only with moderate enantioselectivity (up to 35% *ee*).[5] To achieve higher enantioselectivity, a different concept than steric repulsion between substrates and chiral ligands, which was considered in our previous system,[5] would be needed. Therefore, we envisaged a new type of chiral ligands with a phenyl ring that might interact with a phenyl ring of ruthenium–allenylidene complexes by π–π interaction.[6] In this system, nucleophilic attack of nucleophiles at the C_γ atom of the allenylidene ligand should occur from the side that is not blocked by the chiral ligand (Scheme 1). Indeed, high enantioselectivity was observed in catalytic propargylic alkylation with the second-generation catalyst (up to 82% *ee*). Preliminary results are described here.



Scheme 1. Nucleophilic attack of acetone on the C_γ atom of the allenylidene complex.

A new class of chiral disulfides was prepared from the corresponding aldehydes (Scheme 2).[7] Treatment of 1-phenyl-2-propyn-1-ol (**2a**) with acetone in the presence of a catalytic amount of chiral thiolate-bridged diruthenium com-



Scheme 2. Preparation of chiral disulfides.

[*] Prof. Dr. Y. Nishibayashi
Institute of Engineering Innovation
The University of Tokyo
Bunkyo-ku, Tokyo, 113-8656 (Japan)
Fax: (+81) 3-5841-1175
E-mail: ynishiba@sogo.t.u-tokyo.ac.jp
Y. Inada, Prof. Dr. S. Uemura
Department of Energy and Hydrocarbon Chemistry
Graduate School of Engineering
Kyoto University
Nishikyo-ku, Kyoto, 615-8510 (Japan)

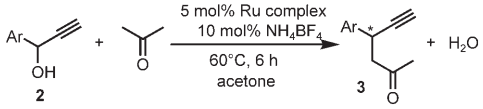
[**] This work was supported by a Grant-in-Aid for Scientific Research for Young Scientists (A) (No.15685006) to Y.N. from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. Y.I. is a recipient of the JSPS Predoctoral Fellowships for Young Scientists.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

plexes, which were prepared in situ from the tetranuclear ruthenium(II) complex and the corresponding chiral disulfides in THF at room temperature for 12 h,[3,5] and NH_4BF_4 at reflux temperature for 6 h afforded the propargylic alkylated product 4-phenyl-5-hexyn-2-one (**3a**) in moderate yields with complete regioselectivity (Scheme 3). The enantiomeric excess of the product was determined by GLC on a chiral capillary column. Compared with our previous result,[5] the introduction of a phenyl group in the *meta* position of the phenyl ring of a chiral disulfide (**1a**) increased the enantioselectivity from 11 to 37% *ee*. Interestingly, introduction of a further phenyl group into the phenyl ring (**1f** and **1g**) greatly increased the enantioselectivity to 43 and 64% *ee*, respectively, but the enantioselectivity decreased when the positions of the phenyl rings were not appropriate (**1b**–**1e**). Finally, the use of a chiral disulfide (**1h**) bearing three phenyl groups on a phenyl ring achieved the highest enantioselectivity (74% *ee*).[7] Unfortunately, the introduction of a *p*-methylphenyl or *p*-*tert*-butylphenyl group on the phenyl ring of a chiral disulfide (**1i** and **1j**) did not improve the enantioselectivity. The use of **1h** as chiral ligand at lower reaction temperature did not influence the enantioselectivity. Other additives such as NH_4PF_6 did not affect the enantioselectivity. In the absence of additives such as NH_4BF_4 and NH_4PF_6, no reaction occurred. When other simple ketones such as 2-butanone and 3-methyl-2-butanone were used in place of acetone, the catalytic reactions did not proceed smoothly.

Next, the catalytic alkylation of propargylic alcohols **2** was investigated using **1h** as chiral ligand. Typical results for various alcohols **2** are shown in Table 1. The presence of substituents such as methyl, methoxy, and chloro in the benzene ring of the propargylic alcohols did not greatly affect the enantioselectivity for the products (Table 1, entries 2–4). Enantioselectivity at the same level was observed in the reactions of 1-naphthyl-2-propyn-1-ols (**2e** and **2f**) with acetone under the same reaction conditions (Table 1, entries 5 and 6). Although the reaction of propargylic alcohol bearing a phenyl group in the benzene ring (**2g**) with acetone gave the same enantioselectivity (Table 1, entry 7), the introduction of two phenyl groups at the *meta* positions of the benzene ring of the propargylic alcohols further increased the enantioselectivity to 82% *ee* (Table 1, entry 8).

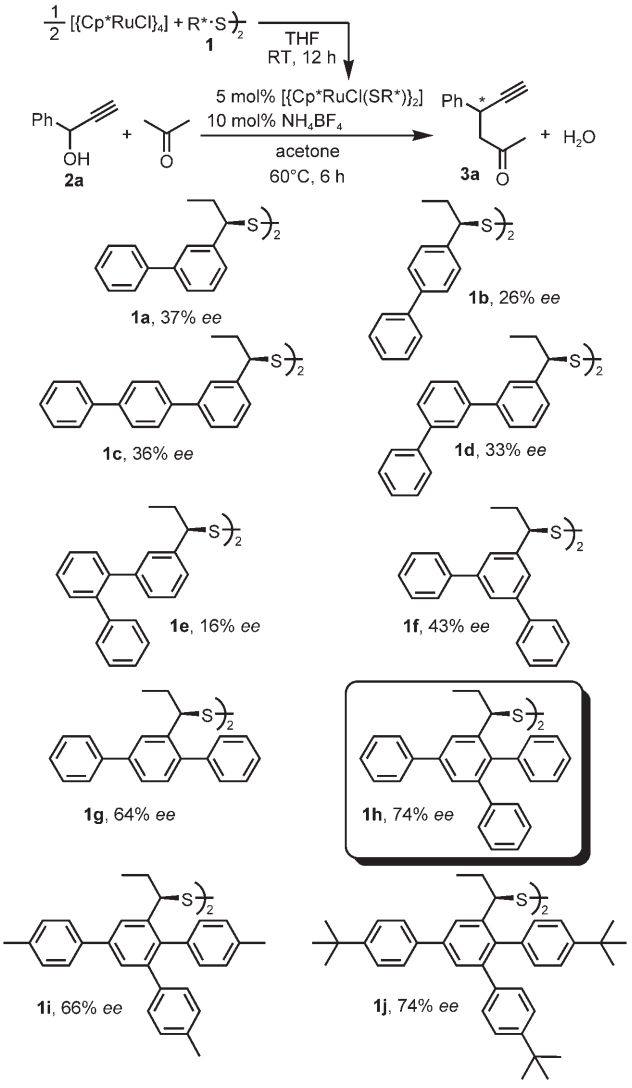
Table 1: Ruthenium-catalyzed asymmetric propargylic alkylation of propargylic alcohols (**2**) with acetone.[a]



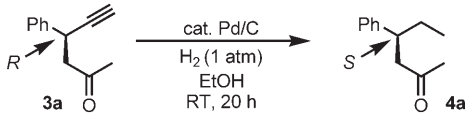
Entry	**2**, Ar	**3**, yield [%][b]	*ee* of **3** [%][c]
1	**2a**, Ph	**3a**, 56	74
2	**2b**, *o*-MeC_6H_4	**3b**, 61	72
3	**2c**, *p*-$MeOC_6H_4$	**3c**, 14	68[d]
4	**2d**, *p*-ClC_6H_4	**3d**, 57	68[d]
5	**2e**, 1-naphthyl	**3e**, 42	70
6	**2f**, 2-napthyl	**3f**, 50	70
7	**2g**, *p*-PhC_6H_4	**3g**, 50	70
8	**2h**, 3,5-$Ph_2C_6H_3$	**3h**, 58	82

[a] All reactions of **2** (0.300 mmol) with acetone were carried out in the presence of ruthenium complex (0.015 mmol, generated in situ from $[\{Cp^*RuCl\}_4]$ and **1h**) and NH_4BF_4 (0.030 mmol) in acetone (4.5 mL) at 60°C for 6 h. [b] Yield of isolated product. [c] Determined by HPLC. [d] Determined by GLC.

To obtain more information on the propargylic alkylation, the stereochemistry of the alkylated product **3a** in the reaction with **1h** as a chiral ligand was determined. Hydrogenation of the alkylated product in the presence of a catalytic amount of Pd/C under 1 atm of H_2 at room temperature for 20 h gave (*S*)-4-phenyl-2-hexanone (**4a**)[7,8] quantitatively (Scheme 4), that is, the original alkylated product **3a** has an *R* absolute configuration. This result is consistent with our proposed reaction pathway (Scheme 1), and the π–π interaction[6] of phenyl rings between the ligand and allenylidene moieties might be considered to be one of the reasons for achievement of high enantioselectivity.



Scheme 3. Reactions of 1-phenyl-2-propyn-1-ol (**2a**) with acetone in the presence of chiral thiolate-bridged diruthenium complexes generated in situ from $[\{Cp^*RuCl\}_4]$ and chiral disulfides.



Scheme 4. Palladium-catalyzed hydrogenation of **3a**.

In summary, we have developed a diruthenium complex-catalyzed, highly enantioselective propargylic substitution reaction of propargylic alcohols with acetone to give the propargylic alkylated products with up to 82% *ee*. Here, π–π interaction of phenyl rings between the ligand and allenylidene moieties is considered to play a crucial role in achieving such a high selectivity. The method presented is in sharp contrast to the so-far-known highly diastereoselective and enantioselective propargylic substitution reactions, which use a stoichiometric amount of transition metal complexes.[9] Further work is currently in progress to improve the enantioselectivity and to broaden the scope of this enantioselective propargylic substitution reaction by using other nucleophiles.[10]

Experimental Section

Typical experimental procedure for the reaction of **2a** with acetone: [{Cp*RuCl}$_4$] (8.2 mg, 0.0075 mmol) and **1h** (11.4 mg, 0.015 mmol) were placed in a 20 mL round-bottomed flask under N_2. Anhydrous THF (1.0 mL) was added, and then the mixture was magnetically stirred for 12 h at room temperature. The solvent was evaporated in vacuo. NH_4BF_4 (3.1 mg, 0.030 mmol) and anhydrous acetone (4.5 mL) were added under N_2, and then the mixture was magnetically stirred at room temperature. After the addition of **2a** (39.7 mg, 0.30 mmol), the reaction flask was kept at 60 °C for 6 h. The solvent was concentrated under reduced pressure by an aspirator, and then the residue was purified by column chromatography (SiO_2) with hexane and AcOEt to give **3a** as a pale yellow oil (30.3 mg, 0.18 mmol, 56% yield, 74% *ee*); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta =$ 2.13 (s, 3H), 2.26 (s, 1H), 2.80 (dd, 1H, $J = 16$, 5.2 Hz), 3.00 (dd, 1H, $J = 16$, 8.4 Hz), 4.20 (br, 1H), 7.22–7.39 ppm (m, 5H); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta = 30.4$, 32.4, 51.5, 71.0, 84.8, 127.1, 127.2, 128.6, 140.1, 205.4 ppm. The optical purity of **3a** was determined by HPLC analysis (column: Daicel, OD; eluent: hexane/2-propanol 97:3).

Received: August 22, 2005
Published online: October 27, 2005

Keywords: asymmetric catalysis · nucleophilic substitution · ruthenium · S ligands · synthetic methods

[1] For recent reviews, see a) J. Tsuji, *Palladium and Catalysts*, Wiley, New York, **1995**, p. 290; b) B. M. Trost, D. L. VanVranken, *Chem. Rev.* **1996**, *96*, 395; c) B. M. Trost, C. Lee in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, chap. 8E.

[2] a) Y. Nishibayashi, I. Wakiji, M. Hidai, *J. Am. Chem. Soc.* **2000**, *122*, 11019; b) Y. Nishibayashi, I. Wakiji, Y. Ishii, S. Uemura, M. Hidai, *J. Am. Chem. Soc.* **2001**, *123*, 3393; c) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 11846; d) Y. Nishibayashi, M. D. Milton, Y. Inada, M. Yoshikawa, I. Wakiji, M. Hidai, S. Uemura, *Chem. Eur. J.* **2005**, *11*, 1433; e) S. C. Ammal, N. Yoshikai, Y. Inada, Y. Nishibayashi, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 9428.

[3] The thiolate-bridged diruthenium complexes have been found to provide unique bimetallic reaction sites for activation and transformation of various terminal alkynes: a) Y. Nishibayashi, M. Yamanashi, I. Wakiji, M. Hidai, *Angew. Chem.* **2000**, *112*, 3031; *Angew. Chem. Int. Ed.* **2000**, *39*, 2909, and references therein; b) Y. Nishibayashi, H. Imajima, G. Onodera, M. Hidai, S. Uemura, *Organometallics* **2004**, *23*, 26; c) Y. Nishibayashi, H. Imajima, G. Onodera, Y. Inada, M. Hidai, S. Uemura, *Organometallics* **2004**, *23*, 5100.

[4] For recent examples of catalytic reactions via allenylidene complexes, see a) B. M. Trost, J. A. Flygare, *J. Am. Chem. Soc.* **1992**, *114*, 5476; b) S. M. Maddock, M. G. Finn, *Angew. Chem.* **2001**, *113*, 2196; *Angew. Chem. Int. Ed.* **2001**, *40*, 2138; c) K.-L. Yeh, B. Liu, C.-Y. Lo, H.-L. Huang, R.-S. Liu, *J. Am. Chem. Soc.* **2002**, *124*, 6510; d) S. Datta, C.-L. Chang, K.-L. Yeh, R.-S. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 9294.

[5] Y. Nishibayashi, G. Onodera, Y. Inada, M. Hidai, S. Uemura, *Organometallics* **2003**, *22*, 873.

[6] For a review, see E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244; *Angew. Chem. Int. Ed.* **2003**, *42*, 1210.

[7] See Supporting Information for experimental details.

[8] M.-J. Brienne, C. Ouannes, J. Jacques, *Bull. Soc. Chim. Fr.* **1967**, 613.

[9] a) A. J. M. Caffyn, K. M. Nicholas, *J. Am. Chem. Soc.* **1993**, *115*, 6438; b) V. Cadierno, S. Conejero, M. P. Gamasa, J. Gimeno, *Dalton Trans.* **2003**, 3060; c) Y. Nishibayashi, H. Imajima, G. Onodera, S. Uemura, *Organometallics* **2005**, *24*, 4106.

[10] We have already investigated the reaction of **2a** with *p*-chloroaniline in the presence of our second generation catalyst, but good enantioselectivity was not observed.

