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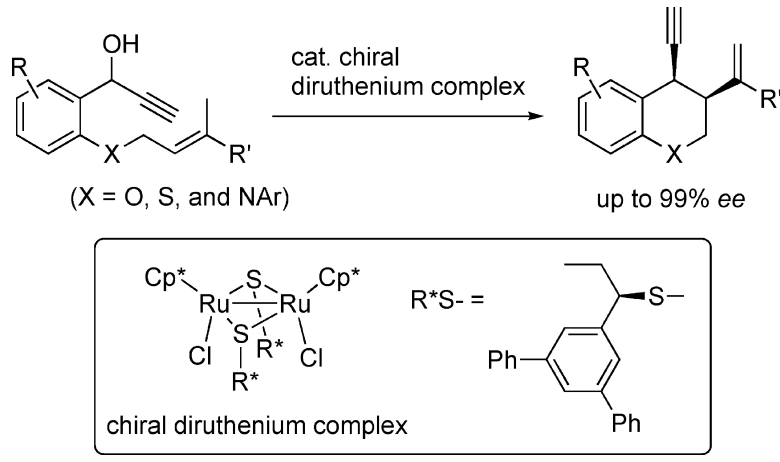

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Ruthenium-Catalyzed Enantioselective Carbon−Carbon Bond Forming Reaction via Allenylidene-Ene Process: Synthetic Approach to Chiral Heterocycles Such As Chromane, Thiochromane, and 1,2,3,4-Tetrahydroquinoline Derivatives

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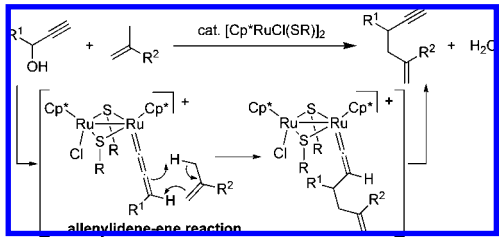
Heterocycles containing oxygen, sulfur, and nitrogen atoms such as chromane, thiochromane, and 1,2,3,4-tetrahydroquinoline derivatives are widely found in many natural and biologically active compounds.[1] In addition to classical synthetic approaches to these heterocycles, a variety of preparative methods catalyzed by transition metal complexes have been reported including its asymmetric version for the optically active heterocycles.[1,2]

We have recently disclosed the ruthenium-catalyzed inter- and intramolecular carbon−carbon bond forming reactions between propargylic alcohols and alkenes which proceeded via an allenylidene[3]-ene type pathway (Scheme 1).[4] We have now envisaged the application of this reaction system to the preparation of a variety of optically active heterocycles via an intramolecular cyclization of propargylic alcohols bearing an alkene moiety at a suitable position. In fact, we have succeeded in obtaining chiral chromanes, benzochromenes, thiochromanes, and 1,2,3,4-tetrahydroquinolines in good to high yields with up to 99% ee. Preliminary results are described here.

Scheme 1



Heating of propargylic alcohol bearing an (*E*)-alkene moiety (**1a**) in $ClCH_2CH_2Cl$ at 60 °C for 6 h in the presence of 5 mol % of an optically active thiolate-bridged diruthenium complex [Cp*RuCl(μ_2-SR*)]$_2$ (Cp* = η^5-C_5Me_5, -SR* = (*R*)-SCH(Et)$C_6H_3Ph_2$; **2a**)[5] and 10 mol % of NH_4BF_4 gave 4-ethynyl-3-(1-phenylethenyl)chromane (**3a**) in 85% isolated yield as a mixture of two diastereoisomers, the *syn*-isomer with 93% ee being the major (*syn*-**3a**/*anti*-**3a** = 17/1) (Scheme 2).[6] Use of the complex bearing other optically active sulfur ligands (**2b** and **2c**) did not afford satisfactory results in both reactivity and selectivity. We have previously found that **2c** promoted enantioselective propargylic substitution reactions[7] and propargylation of aromatic compounds[8] with a high enantioselectivity, but it did not work effectively for the present type of carbon−carbon bond forming reaction.

Scheme 2

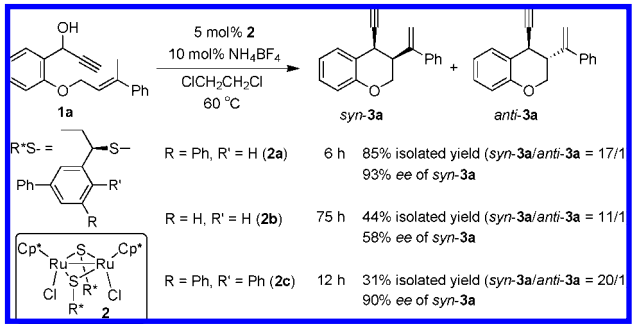


Table 1. Ru-Catalyzed Formation of Chiral Chromanes (**3**)[a]

run	1	time (h)	yield of 3[b] (%)	*syn*-3/*anti*-3[c]	ee of *syn*-3[d]
1	R = Ph (**1a**)	6	85 (**3a**)	17/1	93
2	R = ^{t}Bu (**1b**)	18	87 (**3b**)	>99/<1	76
3	R = Me (**1c**)	6	85 (**3c**)	10/1	33
4	**1d**	5	87 (**3d**)	7/1	47
5		48	65 (**3a**)	1/2.5	33[e]

[a] All reactions of **1** (0.20 mmol) were carried out in the presence of **2a** (0.01 mmol) and NH_4BF_4 (0.02 mmol) at 60 °C in $ClCH_2CH_2Cl$ (5 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. [e] Enantiomeric excess of *anti*-isomer.

With **2a** as a catalyst, the nature of a substituent on an alkene moiety of the starting compound **1** was revealed to be the most important factor to achieve a high enantioselectivity. Typical results are shown in Table 1. The introduction of an unsymmetrical (*E*)-alkene moiety to the starting compound (**1a**−**1d**) generally gave satisfactory results in both product yield and diastereoselectivity as well as enantioselectivity of the major isomer (Table 1, runs 1−4). In contrast, the reaction of propargylic alcohol bearing a (*Z*)-alkene moiety (**1e**) proceeded quite slowly under the same reaction conditions to give the corresponding product **3a**, in 65% yield, where the *anti*-isomer (*syn*-**3a**/*anti*-**3a** = 1/2.5) was mainly obtained with 33% ee (Table 1, run 5).

Intramolcular cyclization of a variety of propargylic alcohols bearing an (*E*)-alkene moiety (**1**) was investigated using **2a** as a catalyst. Typical results are shown in Table 2. The presence of a substituent such as a methyl moiety on the benzene backbone of propargylic alcohols (**1f**−**1g**) did not affect much the enantioselectivity of the produced chromanes (Table 2, runs 2 and 3). However, the introduction of a chloro moiety to the 4-position of the benzene ring (**1h**) decreased the reactivity (Table 2, run 4), a larger amount of **2a** (10 mol %) being necessary to obtain the cyclic product (**3h**) in high yield. The nature of an aryl group in the alkene part (**1i**) gave some effects on the diastereomeric ratio, but not on the enantioselectivity of the major isomer (Table 2, run 5). On the other hand, reactions of propargylic alcohols bearing a naphthyl backbone (**1j**−**1l**) were sluggish under identical conditions, and a prolonged reaction time and/or a larger amount of **2a** were necessary to obtain the corresponding benzochromanes (**3j**−**3l**) in good yields with a high enantioselectivity (Table 2, runs 6−8). The highest enantioselectivity (99% ee) was achieved in the case of **1k**. After one recrystallization of crude cyclic product, the enantio- as well as diastereomerically pure **3k** was isolated, and its absolute configuration [(3*S*,4*S*)][6] was determined by X-ray analysis.

Results of a theoretical study on the reaction of propargylic alcohol with 1,3-conjugated diene indicated that the allenylidene-ene reaction

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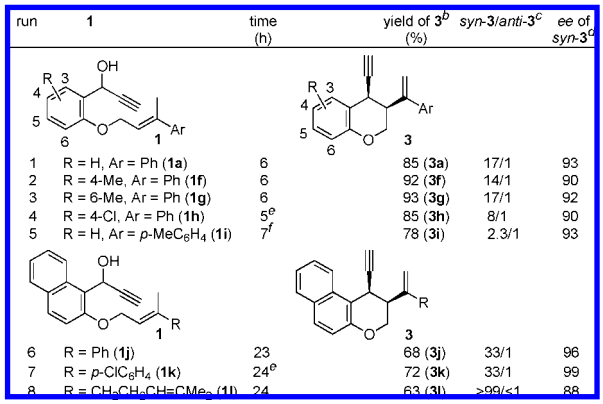
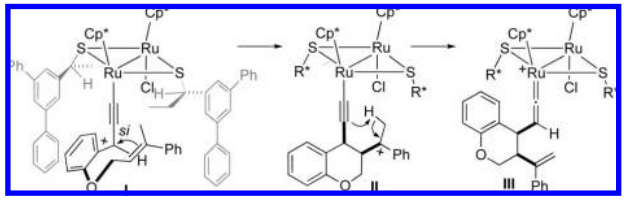
Table 2. Ru-Catalyzed Formation of Chiral Chromanes (**3**)[a]



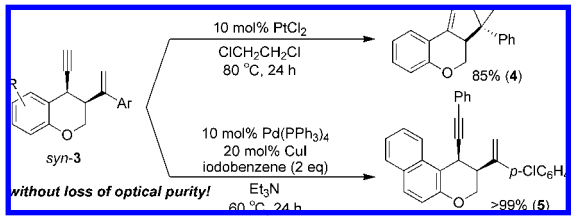
run	1	time (h)	yield of 3[b] (%)	syn-3/anti-3[c]	ee of syn-3[d]
1	R = H, Ar = Ph (**1a**)	6	85 (**3a**)	17/1	93
2	R = 4-Me, Ar = Ph (**1f**)	6	92 (**3f**)	14/1	90
3	R = 6-Me, Ar = Ph (**1g**)	6	93 (**3g**)	17/1	92
4	R = 4-Cl, Ar = Ph (**1h**)	5[e]	85 (**3h**)	8/1	90
5	R = H, Ar = *p*-MeC$_6$H$_4$ (**1i**)	7[f]	78 (**3i**)	2.3/1	93
6	R = Ph (**1j**)	23	68 (**3j**)	33/1	96
7	R = *p*-ClC$_6$H$_4$ (**1k**)	24[e]	72 (**3k**)	33/1	99
8	R = CH$_2$CH$_2$CH=CMe$_2$ (**1l**)	24	63 (**3l**)	>99/<1	88

[a] All reactions of **1** (0.20 mmol) were carried out in the presence of **2a** (0.01 mmol) and NH_4BF_4 (0.02 mmol) at 60 °C in $ClCH_2CH_2Cl$ (5 mL). [b] Isolated yield. [c] Determined by ^1H NMR. [d] Determined by HPLC. [e] **2a** (0.02 mmol) and NH_4BF_4 (0.04 mmol) were used. [f] $ClCH_2CH_2Cl$ (20 mL) was used.

Scheme 3



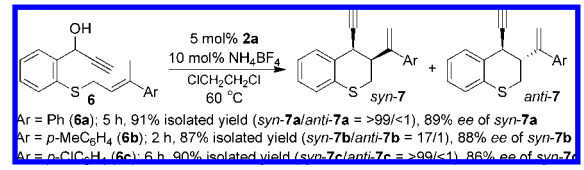
Scheme 4



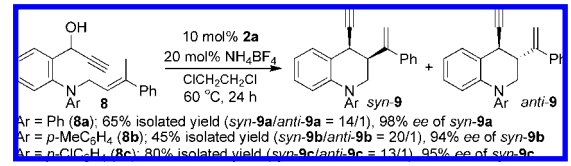
should proceed via a stepwise process (Scheme 3).[9] At present, we consider that the intramolecular attack of an alkene on the cationic γ-carbon in **I** occurs from the *si* face[7,8] to give the corresponding alkynyl complex (**II**), followed by the smooth transfer of one of the terminal protons into the alkynyl moiety to give the corresponding vinylidene complex (**III**). Intramolecular cyclization step seems to be essential for achievement of a high enantioselectivity. In fact, an intermolecular reaction of 1-phenyl-2-propyn-1-ol with α-methylstyrene in the presence of a catalytic amount of **2a** or **2c** at 60 °C proceeded smoothly, but only a moderate enantioselectivity in the produced 2,4-diphenyl-1-hexen-5-yne was observed. As described in our previous reports,[10] we believe that the synergistic effect in the diruthenium complexes is also quite important for promotion of this catalytic reaction.

Separately, we have already confirmed that some chiral chromanes (**3**) can be converted into their derivatives (**4**[11] and **5**) without any loss of optical purity (Scheme 4), indicating that cyclized products

Scheme 5



Scheme 6



obtained by the present method may be employed for producing more useful products.

Finally, this methodology for the preparation of chiral chromanes and benzochromanes can also be extended to the enantioselective formation of other hetereocycles containing a sulfur or nitrogen atom. Thus, reactions of propargylic alcohols bearing a thioether moiety (**6**) in the presence of a catalytic amount of **2a** at 60 °C gave the corresponding thiochromanes (**7**) in excellent yields with a high enantioselectivity (Scheme 5). In addition, reactions of propargylic alcohols bearing an allylic amine moiety (**8**) under the same reaction conditions gave the corresponding 1,2,3,4-tetrahydroquinolines (**9**) in good to high yields with an excellent enantioselectivity (Scheme 6).

In summary, we have succeeded in applying our previously disclosed ruthenium-catalyzed carbon−carbon bond forming reaction[4] to an enantioselective intramolecular cyclization by use of a suitable chiral diruthenium complex as a catalyst for producing a variety of optically active heterocycles such as chromane, thiochromane, and 1,2,3,4-tetrahydroquinoline derivatives.

Supporting Information Available: Experimental procedures and spectroscopic data, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) See Supporting Information for experimental details.
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(11) The molecular structure of **4** was confirmed by X-ray analysis.[6]

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