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Participation of an organosulfur functionality in asymmetric Pauson–Khand reactions using (*S*)-methionine-derived amides as enantiocontrollable substrates

Kunio Hiroi * and Takashi Watanabe

Department of Synthetic Organic Chemistry, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 981-8558, Japan

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Abstract

An asymmetric Pauson–Khand reaction was successfully accomplished using chiral phenylpropiolic carboxamides derived from (*S*)-methionine. Participation of the organosulfur functionality with cobalt catalysts in the asymmetric Pauson–Khand reaction is clearly demonstrated, giving the corresponding Pauson–Khand reaction products with extremely high diastereoselectivity in comparison to other substrates without similar sulfenyl groups. The absolute configuration of the newly created chiral carbon centers was determined by X-ray crystallographic analysis. The mechanism for the asymmetric induction is proposed on the basis of the stereochemistry of the reactions determined by us.

The asymmetric Pauson–Khand reaction has received much attention,[1] since it provides a synthetically valuable way to optically active 2-cyclopentenones. Quite recently, we reported the first successful catalytic asymmetric Pauson–Khand reactions with chiral phosphine ligands.[2]

We have so far studied highly stereoselective reactions with the assistance of organosulfur and transition metal chemistry for the development of new asymmetric synthetic methodologies and explored novel asymmetric synthesis with palladium catalysts using an organosulfur functionality as a stereocontrollable factor.[3] We wish to demonstrate herein the participation of an organosulfur functionality in asymmetric Pauson–Khand reactions,[4] and to reveal the mechanism of the asymmetric induction on the basis of the stereochemistry of the reactions determined by us.

As the chiral alkynyl counterparts in Pauson–Khand reactions, we employed optically active phenylpropiolic carboxamides (*S*)-**1a**–**i** (Scheme 1) and the derivatives (*S*)-**4a**–**c**, prepared starting from optically active α-amino acids, (*S*)-methionine, (*S*)-*S*-cysteine, (*S*)-norvaline, and (*S*)-norleucine.

The reactions of (*S*)-**1a** with norbornene (**2**) were carried out in the presence of $Co_2(CO)_8$ (1.2 equiv.) under various reaction conditions using *N*-methylmorpholine *N*-oxide (NMO) or trimethylamine *N*-oxide

* Corresponding author.

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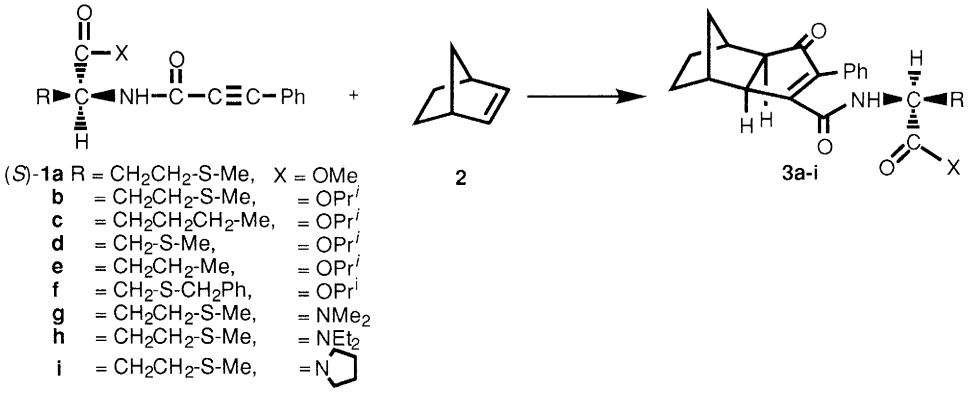


Scheme 1.

(TMAO) (10 equiv.) in some cases as shown in Table 1. The reaction in toluene at 70°C gave (2*R*,6*S*)-**3a** with 12% diastereomeric excess (*de*), whereas the reaction using NMO improved the enantioselectivity of the product in CH_2Cl_2 (−20°C), toluene (0°C), or DME (−20°C) with 41, 34, or 64% *de*, respectively.

Table 1
The cobalt-mediated asymmetric reactions of (*S*)-**1a–i** and (*S*)-**4a–c** with **2**[a)]

Substrate	*N*-Oxide	Solvent	Reaction temp. (°C)	Reaction time (h)	Product yield (%)[b)]		d.e. (%) of Products[c)]
1a	-	toluene	70	6	70	(**3a**)	12
	NMO	CH_2Cl_2	-20	36	85	(**3a**)	41
	NMO	toluene	0	22	55	(**3a**)	34
	NMO	DME	0	24	38	(**3a**)	44
	NMO	DME	-20	48	32	(**3a**)	64
1b	NMO	CH_2Cl_2	0	24	68	(**3b**)	48
	NMO	CH_2Cl_2	-20	50	67	(**3b**)	51
	TMAO	CH_2Cl_2	-20	49	78	(**3b**)	55
1c	NMO	CH_2Cl_2	0	24	88	(**3c**)	6
1d	NMO	CH_2Cl_2	0	24	62	(**3d**)	7
1e	NMO	CH_2Cl_2	0	24	72	(**3e**)	5
1f	NMO	CH_2Cl_2	0	24	91	(**3f**)	6
1g	NMO	CH_2Cl_2	0	36	58	(**3g**)	63
	NMO	CH_2Cl_2	-20	60	64	(**3g**)	77
1h	NMO	CH_2Cl_2	0	38	79	(**3h**)	37
	NMO	CH_2Cl_2	-20	72	79	(**3h**)	79
1i	NMO	CH_2Cl_2	0	35	40 (54)	(**3i**)	52
	NMO	CH_2Cl_2	-20	61	13 (28)	(**3i**)	90
	NMO	DME	0	26	13 (20)	(**3i**)	52
	NMO	DME	-20	50	5 (9)	(**3i**)	84
4a	NMO	CH_2Cl_2	0	24	59	(**5a**)	44
	NMO	CH_2Cl_2	-20	48	67	(**5a**)	48
4b	-	toluene	70	6	58	(**5b**)	18
4c	NMO	CH_2Cl_2	-20	48	87	(**5c**)	55
	NMO	DME	-20	48	53	(**5c**)	49
	TMAO	CH_2Cl_2	-20	48	53	(**5c**)	63

a) The cobalt-mediated reactions of (*S*)-**1a-i** and (*S*)-**4a-c** with **2** (10 equiv.) were carried out in the presence of $Co_2(CO)_8$ (1.2 equiv.) and *N*-methylmorpholine *N*-oxide (NMO) or trimethylamine *N*-oxide (TMAO) (10 equiv.).
b) Yields based on the recovered starting material are listed in parentheses.
c) The diastereomeric excess (d.e.) of the products was determined by HPLC analysis with CHRALCEL OD.

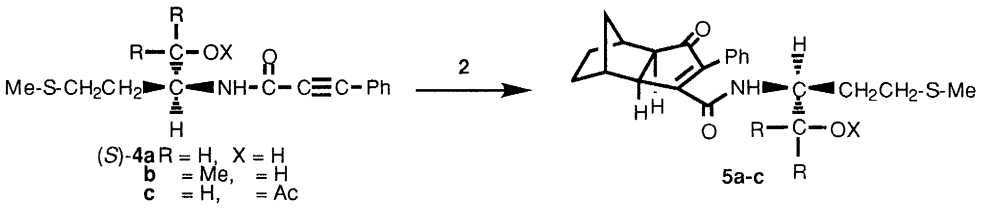
Replacement of the methyl ester in the substrate **1a** with *i*-propyl ester slightly improved the enantio-

control, as shown in Table 1. In order to reveal the direct participation of the sulfenyl groups, we examined the substrate **1c** incorporating a methylene group instead of the sulfenyl sulfur atom. Interestingly, the replacement of the sulfenyl atom in (*S*)-**1b** with a methylene group resulted in a drastic decrease of the enantiocontrol, providing (2*R*,6*S*)-**3c** with 6% *de*.

Shortening of a carbon chain in the methylthioalkyl group of the substrate (*S*)-**1b** provided extremely low enantioselectivity. The reaction of (*S*)-**1d** with **2** gave (2*R*,6*S*)-**3d** with 7% *de*. The reactions of similar substrates (*S*)-**1e** and **1f** with **2** afforded (2*R*,6*S*)-**3e**,**f** with 5 and 6% *de*, respectively. These results indicate that the methylthioethyl substituent would play a seriously important role in achieving the high enantioselectivity, with participation of the sulfenyl group presumably by coordination to the cobalt catalyst which is complexed with the alkyne group in the substrate.

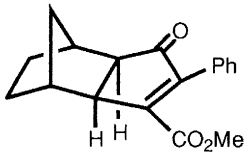
Replacement of the ester group in (*S*)-**1a**,**b** with pyrrolidine amide (*S*)-**1i** markedly improved the enantioselectivity, as expected. The reaction of (*S*)-**1i** with **2** gave (2*R*,6*S*)-**3i** with 90% *de*; however, the yield was very low, presumably owing to the steric effect of the amide group. Other amides, *N*,*N*-dimethyl or -diethylamides (*S*)-**1g**,**h**, provided (2*R*,6*S*)-**3g**,**h** with considerably high *de* (77 or 79%), upon treatment with $Co_2(CO)_8$ and NMO in CH_2Cl_2 at −20°C.

Transformation of the ester group in (*S*)-**1a**,**b** into alcohols (*S*)-**4a**,**b** or its acetate (*S*)-**4c** achieved a slight increase of the enantioselectivity in the cobalt-catalyzed reactions, as listed in Table 1. The reactions of (*S*)-**4a** with **2** were carried out in CH_2Cl_2 at 0 or −20°C in the presence of NMO to give (2*R*,6*S*)-**5a** with 44 or 48% *de*, respectively, whereas the use of the rather bulky dimethyl alcohol (*S*)-**4b** was not effective in the asymmetric synthesis because of the unaccessibility of the reactant in the sterically crowded environment induced by the dimethyl group. The cobalt-mediated reactions of (*S*)-**4c** with **2** using NMO or TMAO gave (2*R*,6*S*)-**5b** with 55 or 63% *de*, respectively (Scheme 2).



Scheme 2.

The structure of the reaction product **3a** derived from (*S*)-**1a** and **2** was determined by the X-ray crystallographic analysis as shown in Fig. 1, and thus the absolute configuration of the newly created chiral carbon centers was determined as (2*R*,6*S*)-configuration.[5] The absolute configuration of the newly created asymmetric carbon centers in other reaction products was determined as the same (2*R*,6*S*)-configuration by the chemical correlation of **3b**–**i** and **5a**,**c** to a methyl ester (via hydrolysis) (2*R*,6*S*)-**6** which was derived from the structurally confirmed (*S*)-**3a** by hydrolysis of the amide group followed by methylation with (trimethylsilyl)diazomethane.



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On the basis of the absolute configuration of the products determined by X-ray crystallographic analysis, a plausible mechanism of the asymmetric synthesis is proposed.

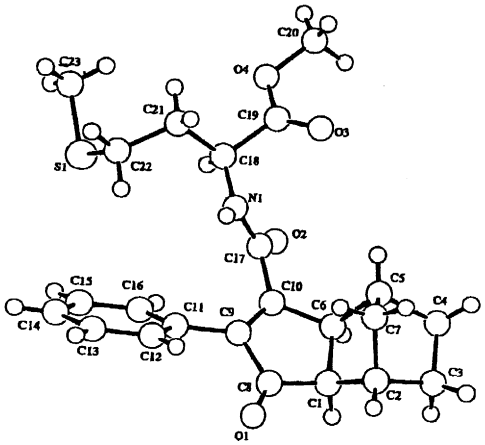
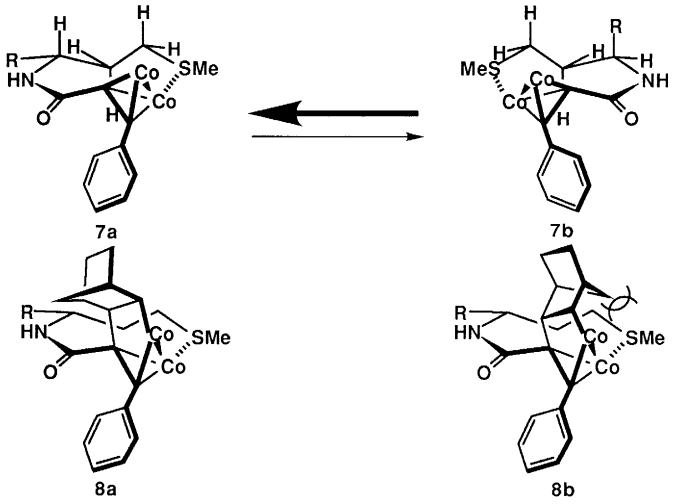


Fig. 1. Molecular structure (ORTEP drawing) of (*S*)-**3a**

As described earlier, it can certainly be assumed that the sulfenyl groups in the substrates participate seriously in the asymmetric induction, presumably by direct coordination of the sulfur atoms to the cobalt catalysts in the alkyne complexes.[6] Accordingly, the cobalt–alkyne complexes would form an eight-membered intermediate by this coordination of the sulfenyl groups. In the conformational equilibrium of the eight-membered intermediate, the thermodynamically more stable chair-like eight-membered intermediate **7a** is preferred to another chair-like intermediate **7b**, since **7b** has 1,3-diaxial-like steric hindrance between the substituent R and the hydrogen atom. The olefin in **2** reacts from the sterically less crowded side of **7a**, namely, from the upper side of **7a** as designated in **8a**. In regard to the selection of the direction of the carbon–carbon double bond side in norbornene, the sterically preferred *exo* side would be attacked as shown in **8a**, and the reaction proceeds through **8a** in preference to **8b**, because of the steric hindrance of the norbornene skeleton as designated in **8b**. Thus, insertion of carbon monoxide occurs via **8a** to afford the products of (2*R*,6*S*)-configuration (Scheme 3).



Scheme 3.

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5. Crystallographic data for **3a**: $C_{23}H_{27}NO_4S$. *Mr*=413.53, monoclinic, space group $P2_1$(#4), *a*=11.894(2) Å, *b*=17.136(2) Å, *c*=20.849(3) Å, β=91.85(1)°, *V*=2130.7(5) Å,^{3} *Z*=4, *D*c=1.289g/cm^3, *F*(000)=880.00, max2θ=136.5°, graphite monochromated CuKα (λ=1.54178 Å), 3964 observations (*I*>0.00 (*I*)), *R*=0.076, *Rw*=0.047.
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