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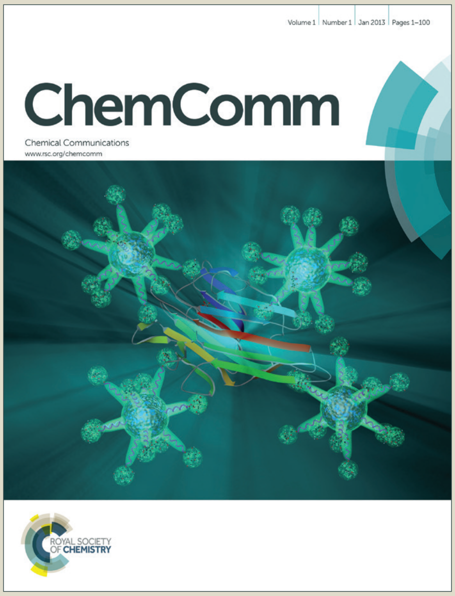

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Enantio- and diastereoselective asymmetric allylic alkylation catalyzed by planar-chiral cyclopentadienyl ruthenium complex

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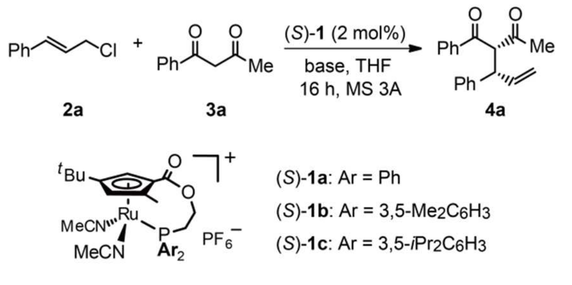
Naoya Kanbayashi*, Kazuki Hosoda, Masanori Kato, Koichiro Takii, Taka-aki Okamura and Kiyotaka Onitsuka*

We report asymmetric allylic alkylation of allylic chloride with *β*-diketones as the prochiral carbon nucleophile using a planar-chiral Cp′Ru catalyst. The reaction proceeds under mild conditions; the resulting chiral products containing vicinal tertiary stereocenters are obtained with high regio-, diastereo-, and enantioselectivities. These chiral products can then be transformed to a chiral diol controling the four stereocentres.

Asymmetric allylic substitution is one of the most promising methods for constructing stereogenic centres in organic synthesis.[1] By the appropriate combination of a transition metal and chiral ligands, reactions can be conducted between monosubstituted allylic substrates and carbon nucleophiles such as symmetrical dialkyl malonates, affording the corresponding product in good yield with high regio- and enantioselectivities.[2] However, the reaction is difficult and challenging with prochiral carbon nucleophiles, because multiple stereogenic centres of such nucleophiles must be controlled. Thus far, several efficient reaction systems catalyzed by Pd[3], Mo[4] and Ir[5]complexes have been reported. In recent years, Trost[4d], Stoltz[5b], and Careirra[5d, 5e] have demonstrated allylic alkylation using linear prochiral nucleophiles, such as *β*-cyanoesters, *β*-ketoesters and aldehydes to form vicinal quaternary and tertiary stereocenters with regio-, diastereo- and enantioselectivities. However, it is difficult to control two vicinal tertiary stereocenters by allylic substitution, because the α-carbon of the nucleophile is sterically less hindered and the resulting products have an α-proton, which can undergo epimerization under basic conditions. Thus, to prevent the epimerization of the resulting products is crucial to achieve diastereoselective allylic alkylation under mild conditions.

The cyclopentadienyl-ruthenium complex is one of the effective catalysts for stereoselective allylic substitutions. [6] [7] In recent years, we have already reported that planar-chiral cyclopentadienyl-ruthenium (Cp′Ru) complexes ((*S*)-**1**)[8] are proficient catalysts for the regio- and enantioselective allylic substitution of monosubstituted allylic halides with nucleophiles containing oxygen[9] and nitrogen[10] atoms. The reaction proceeds via the formation of π-allyl intermediates, which are generated by the oxidative addition of allylic chloride.[9a] From mechanistic studies, the reaction is thought to occur by an inner-sphere mechanism, in which the nucleophile coordinates to ruthenium with high diastereoselectivity at the metal centre prior to attack the π-allyl group. The reaction then proceeds by the inside attack of the coordinated nucleophile at the substituted allylic carbon atom of the π-allyl group and metal centre chirality is maintained, which is the key step to achieving high selectivities. The reaction mechanism prompted us to examine this diastereoselective reaction using achiral nucleophiles. Moreover, in this catalytic system, Cp′Ru catalysts exhibited characteristic reactivity toward less reactive nucleophiles such as metal carboxylates,[9b] water,[9c] and *N*-alkokybenzamide under mild conditions. Herein, we present Cp′Ru-complex-catalyzed asymmetric allylic alkylation of allylic chloride with *β*-diketones as the prochiral carbon nucleophile under mild conditions, which is the novel example of ruthenium-catalyzed allylic substitution with high regio-, diastereo-, and enantioselectivities.

Table 1 Screening of reaction conditions. [a]



(*S*)-**1a**: Ar = Ph

(*S*)-**1b**: Ar = 3,5-$Me_2C_6H_3$

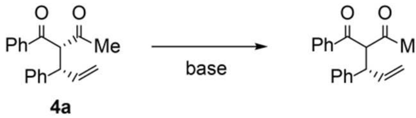
(*S*)-**1c**: Ar = 3,5-*i*$Pr_2C_6H_3$

entry	cat.	temp (ºC)	base	*b*/*l* [b]	yield (%) [b]	dr [b]	ee (%) [c]
1	**1a**	25	K_2CO_3	>20/1	99	2/1	62
2	**1a**	25	Na_2CO_3	10/1	99	2/1	78
3	**1a**	35	Li_2CO_3	>20/1	99	4/1	92
4	**1a**	25	Cs_2CO_3	7/1	99	1/1	7
5	**1a**	25	$KHCO_3$	>20/1	99	3/1	98
6	**1a**	25	$NaHCO_3$	>20/1	99	6/1	97
7	**1a**	25	K_3PO_4	>20/1	99	1/1	18
8	**1a**	25	*i*-Pr_2EtN	10/1	99	2/1	75
9	**1a**	30	$NaHCO_3$	>20/1	99	6/1	93
10	**1a**	20	$NaHCO_3$	>20/1	99	6/1	93
11[d]	**1a**	10	$NaHCO_3$	>20/1	99	6/1	91
12[e]	**1a**	0	$NaHCO_3$	>20/1	99	7/1	92
13	**1b**	25	$NaHCO_3$	>20/1	99	4/1	94
14	**1c**	25	$NaHCO_3$	>20/1	99	3/1	91

[a] Reaction conditions: **2a** (1.0 mmol), **3a** (0.5 mmol), cat (2 mol%), base (1.2 mmol), THF (2.0 mL) for 16 h. [b] Determined by ^{1}H NMR. [c] Determined by HPLC analysis on a chiral stationary phase. Reaction temperature at 35 ºC. [d] Reaction time for 48 days. [e] Reaction time for 72 days.

Initially, the reaction between cinnamyl chloride (**2a**) and prochiral *β*-diketone (**3a**) as the nucleophile was investigated to assess the effect of the base on reactivity and selectivity. On the base of our previous conditions,[9-10] the reaction between **2a** and **3a** was conducted in THF for 24 h at 25 °C in the presence of (*S*)-**1a** (2 mol%) as the catalyst, K_2CO_3 as the base, and molecular sieves 3A (MS 3A).[11] Although the reaction proceeded smoothly to produce the corresponding branched product (**4a**) in good yield, the diastereo- and enantioselectivities were low (99%, dr 2:1, 62% ee, entry 1). The absolute configuration of **4a** was determined to be (*S*,*S*) by X-ray crystallography,[12] which is reasonable for the reaction mechanism in previous study.[9] Our previous studies have shown that the bases as an additive in the asymmetric allylic substitution catalyzed by **1** is crucial for achieving high enantioselectivity of the product.[9] Hence, to improve stereoselectivity, the effect of base was examined; the results are summarized in Table 1. When the base was changed from K_2CO_3 to Na_2CO_3, enantioselectivity increased slightly (78% ee), while regioselectivity was decreased and diastereoselectivity remained unaffected (*b*/*l* = 10/1, dr 2:1, entry 2). In contrast, when the base was changed to Li_2CO_3, both the diastereo- and enantioselectivities increased (dr 4:1, 92% ee, entry 3). Furthermore, when the reaction was conducted using Cs_2CO_3 as the base, product **4a** was obtained in poor selectivity (entry 4). On further screening various bases, metal bicarbonate, which is a weaker base than carbonate, was found to be optimal. Meanwhile, the reaction in the presence of $KHCO_3$ proceeded with quantitative conversion despite it being a weak base, and the enantioselectivity of the product significantly increased (98% ee, entry 5). Moreover, when $NaHCO_3$ was used as the base, **4a** was obtained with higher diastereo- and enantioselectivities (dr 6:1, 97% ee, entry 6). Poor selectivities were obtained when K_3PO_4 and tertiary amine were used (entries 7 and 8, respectively). Meanwhile, higher diastereoselectivity and slightly lower enantioselectivity were observed at lower temperatures (entries 10–12). Previously, we have reported that the aryl group on the phosphine ligand in Cp′Ru complex plays an important role for achieving high enantioselectivity in allylic substitution.[9c] Although the reactions were conducted using (*S*)-**1b** and **1c** as the catalysts (entries 13 and 14, respectively), the diastereo- and enantioselectivities of the resulting products were slightly lower than those observed for the reaction with (*S*)-**1a**. Thus,

Table 2 Epimerization of **4a** [a]



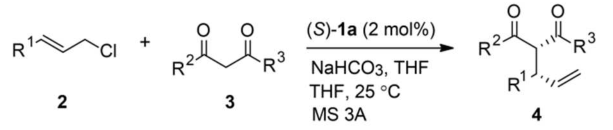
4a

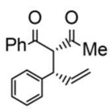
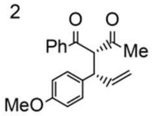
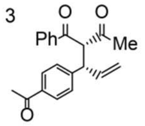
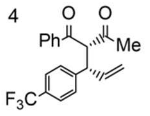
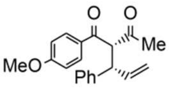
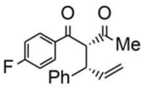
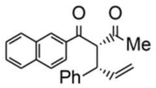
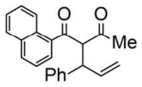
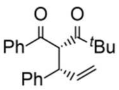
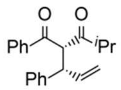
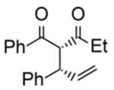
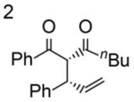
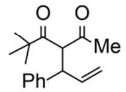
entry	base	reaction time (h)	dr	
			before [b]	after [b]
1	DBU	4	6:1	1:1
2	K_2CO_3	20	6:1	2:1
3	K_2CO_3	72	6:1	1:1
4	$NaHCO_3$	20	20:1	20:1
5	$NaHCO_3$	72	20:1	16:1

[a] Reaction conditions: **4a** (0.30 mmol), at 25 ºC, base (0.90 mmol), THF (2.0 mL). [b] Determined by ^{1}H NMR spectroscopic analysis of crude reaction mixture.

As product **4** has an acidic α-methine proton, epimerization occurs in the presence of a storonger base. The reaction of **4a** (dr 6:1) was conducted in the presence of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) as the base in THF at 25 °C (Table 2, entry 1). After 4 h, diastereoselectivity decreased because of epimerization. When K_2CO_3 was used as the base, epimerization was observed (entries 2 and 3), which is consistent with the results shown in entry 1 of Table 1. On the other hand, epimerization was not observed in the presence of $NaHCO_3$, which is a relatively weak base, and the diastereoselectivity of **4a** was retained after 20 h (entry 4). On the other hand, when the reaction time was extended to 72 h, diastereoselectivity slightly decreased. Thus, these results show that the use of $NaHCO_3$ as a base is essential for realizing high diastereoselectivity.

Table 3 Effect of Substituent on Substrates [a]



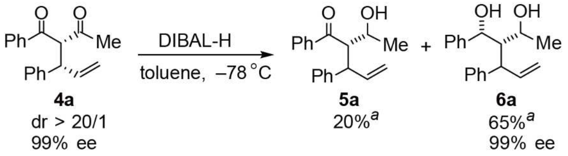
Entry	Product		Yield	ee	dr
1		4a	99% yield	97% ee	dr = 6:1
2		4b	99% yield	- % ee [b]	dr = 5:1
3		4c	99% yield	93% ee	dr = 4:1
4		4d	99% yield	92% ee	dr = 3:1
5		4e	99% yield	92% ee	dr = 6:1
6		4f	88% yield	86% ee	dr = 3:1
7		4g	91% yield	84% ee	dr = 5:1
8		4h	92% yield	90% ee	dr = 5:1
9		4i	79% yield	70% ee	dr = 3:1
10		4j	93% yield	94% ee	dr = 4:1
11		4k	84% yield	92% ee	dr = 7:1
12		4l	79% yield	90% ee	dr = 5:1
13		4m	83% yield	92% ee	dr = 1:1

[a] Reaction conditions: **2a** (1.0 mmol), **3a** (0.5 mmol), cat **1a** (2 mol%) at 25 ºC, $NaHCO_3$ (1.2 mmol), THF (2.0 mL) for 16 h. Yield of isolated product after column chromatography. Diastereomer ratio is determined by ^{1}NMR spectroscopic analysis of crude reaction mixtures. Enantiomer excess is determined by HPLC analysis on chiral stationary phase. [b] Not determined.

The scope of diastereoselective allylic alkylation was examined under optimized conditions; the results are summarized in Table 3. In all reactions, as described below, regioselectivity was high because linear products were not formed. The reaction of **3a** with substituted cinnamyl chlorides possessing electron-rich and electron-deficient aromatic groups produced the corresponding branched products (**4a**-**4d**) in high yield with dr 6:1-3:1 and 92-97% ee (entries 1-4). Moreover, carbonyl groups can be tolerated in this reaction becaouse of the mild reaction conditions (entry 3).

The scope of this reaction was also tested using various achiral *β*-diketones. First, the reaction of **3m** as the nucleophile, which has a ^{t}Bu group instead of a phenyl group, also selectively afforded branched product **4m** with high enantioselectivity, but low diastereoselectivity (92% ee, dr 1:1, entry 13) in spite of that the steric effect ^{t}Bu group is larger than that of phenyl moiety. These results show that the diastereoselectivity is not depended solely on the steric effect of R^2 in the system, and the aryl-substituted group plays an important role in controlling the diastereoselectivity. The reaction of *β*-diketones bearing different substituted-aryl groups (R^2) was examined, and products **4e**–**4h** were obtained with diastereo- and enantioselectivities (entries 5–8, respectively), but when the **3f** having an electron deficient fluoro group was used as nucleophile, the diastereoselectivity was slightly decreased (dr 3:1, entry 6). Therefore, the stereoelectronic effect of aryl group, such as π-interaction, probably exists in the reaction mechanism. Next, alkyl-substituted groups (R^3) were optimized (entries 9–12). When *β*-diketones bearing linear alkyl groups such as ethyl groups were used (entries 10-12), diastereoselectivity was most high (**4k**; dr = 7:1). On the other hand, bulky substituents of R^3, such as ^{t}Bu and ^{i}Pr group, were decreased the diastereoselectivity (entries 9 and 10). The size of R^3 relative to that of R^2 is crucial for diastereoselectivity.

Finally, to demonstrate the utility of **4** as a chiral building block, we examined the transformation of the resulting chiral *β*-diketone **4** to a useful structure. The reduction of **4a** (>99% ee, dr > 20/1)[13] with diisobutylaluminium hydride (DIBAL-H) afforded chiral alcohol **5a** and diol **6a** with diastereoselectivity. After its purification by silica-gel chromatography, **6a** was obtained in 65% yield as a single diastereomer.[14]



[a] Isolated yield

Scheme 1 The diastereoselective reduction of **4a**.

In conclusion, we demonstrated allylic alkylation of allylic chloride with prochiral *β*-diketone using planar-chiral Cp′Ru complex **1** as the catalyst. The reaction affords chiral diketones having vicinal tertiary stereocentres. Because of very mild reaction conditions, the epimerization of **4a** does not occur.[15] The resulting chiral diketone can be converted to chiral diol as single diastereomer, which possess multiple stereocentres, in moderate yield. Hence, the use of this system can be extended to applications in organic synthesis. Further development for diastereo- and enantioselective reactions is currently underway.

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10. (a) N. Kanbayashi, K. Takenaka, T. Okamura and K. Onitsuka, *Angew. Chem. Int. Ed.*, 2013, **52**, 4897-4901; (b) N. Kanbayashi, T.-a. Okamura and K. Onitsuka, *Macromolecules*, 2014, **47**, 4178-4185.
11. NaHCO$_3$ was used as a base in this reaction, water would be formed as a byproduct, and the water should work as a nucleophile in this catalystic system to produce branched allylic alcohole. Therefore, all of the reactions described below have been conducted in the presence of MS 3A as a descant agent.
12. Summary of the crystal data for **4a** is given in the Supporting Information. CCDC 1055406 (**4a**) contain the supplemental crystallographic data dor this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data centre via www. ccdc.cam.ac.uk/data_request/cif.13. Upon recrystalization the products of entry 1 in Table 2, diastereo- and enatiopure of **4a** was obtained in 60 % yield.
14. The realative configulation of 1,3-diol (**6a**) was determined by Rychnovsky's method (S. D. Rychnovsky, D. J. Skalitzky, *Tetrahedron Lett.*, 1990, **31**, 945-948.) and NOESY spectrum of 2,2,4-trimethyl-6-phenyl-5-(1-phenylallyl)-1,3-dioxane (**7**) which is transformed from 1,3-diol. See the ESI.
15. NaHCO$_3$ is retatively week base, which is insufficient for the complete deprotonation of **3**. Thus, the epimerization of **4** due to carbanion of **3** is quite unlikely under the reaction system.