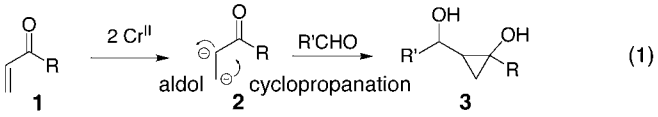
Cross-Coupling Reactions between α,β-Unsaturated Ketones and Aldehydes with $CrCl_2$: Aldol Condensation and Cyclopropanol Formation**

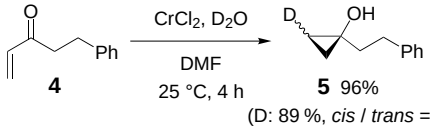
Chika Toratsu, Takafumi Fujii, Takuma Suzuki, and Kazuhiko Takai*

The reduction of carbon–carbon unsaturated bonds by chromium(II) has been observed since the 1920s,[1] and in some cases dianionic species have been postulated.[2] However, most of these reactions were conducted in protic solvents, and protonated anionic species were produced which cannot be employed for carbon–carbon bond formation except in a few cases.[3, 4] We report here that the α,β-unsaturated ketone **1** is reduced with chromium(II) in an aprotic solvent to give the ketone α,β-dianion equivalent **2**, which reacts with an aldehyde at the α position (aldol condensation) followed by intramolecular cyclopropanation to afford *cis*-2-(1-hydroxyalkyl)-substituted cyclopropanol **3** in a stereoselective manner [Eq. (1)].



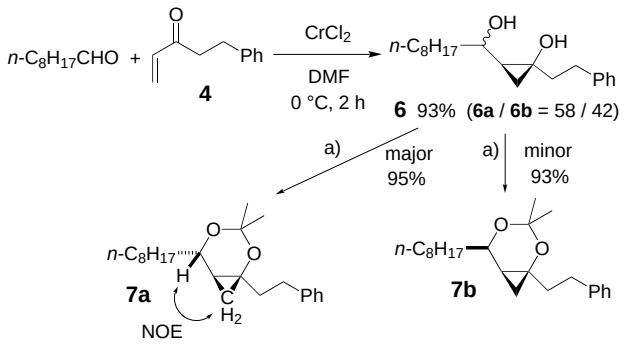
(1)

Treatment of enone **4** [see Eq. (2)] with $CrCl_2$ in DMF under strictly water-free conditions did not give cyclopropanol **5**, but instead resulted in a complex mixture.[5] However, when water was added to the reaction mixture before addition of the enone, the cyclopropanol formation proceeded smoothly.[6] For example, treatment of enone **4** with a mixture of $CrCl_2$ (4 equiv) and D_2O (2 equiv) in DMF at 25 °C for 4 h gave cyclopropanol **5** in 96% yield, and deuterium was incorporated in 89% content [Eq. (2)].



(2)

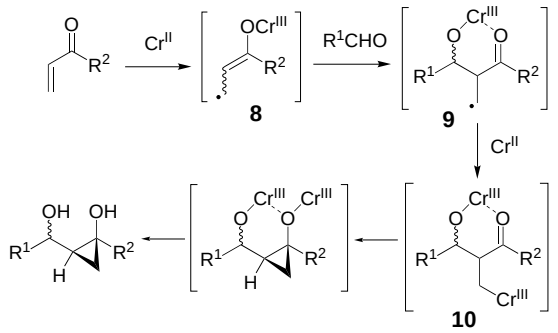
To clarify the reactivity of the nucleophilic position, the reaction was conducted in the presence of an aldehyde under water-free conditions. A solution of enone **4** and nonanal in dry DMF was added at 0 °C to a blue-green solution of $CrCl_2$ in DMF, and the resulting mixture was stirred for 2 h at 0 °C to give diol **6** in 93% yield (Scheme 1). The two isomers **6a** and **6b** (**6a**/**6b** = 58/42)[7] were produced selectively out of four



Scheme 1. Sequential aldol condensation and cyclopropanol formation followed by acetalization. a) $Me_2C(OMe)_2$, cat. PPTS, acetone, 25 °C, 2 h.

possible diastereomers, and the relative configuration of the cyclopropane rings was shown to be *cis* by quantitative transformation to the corresponding acetonides **7a** and **7b** with 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate (PPTS). The NOE experiments of the acetonides showed that the octyl group and the cyclopropane ring of the acetonide **7a**, derived from the major adduct **6a**, had a *trans* configuration of the acetonide ring.

A possible mechanism which explains the configuration of the cyclopropane rings is shown in Scheme 2. One-electron reduction of an enone with chromium(II) gives the enolate



Scheme 2. Mechanism of the coupling reaction

radical **8**,[2] which reacts with an aldehyde to give **9**.[8] Reduction of the radical **9** with chromium(II)[9] followed by intramolecular addition gives a cyclopropanol.[10] Because the reducing power of chromium(II) is moderate, the first one-electron transfer proceeds selectively to the enone without affecting the coexistent aldehyde.[11] Coordination of both the alkoxy and carbonyl groups to chromium(III) in **10** fixes the conformation leading to the *cis* cyclopropane ring. The Lewis acidity of the chromium salt could also facilitate the first electron transfer to the enone as well as the cyclopropanation.

Several products resulting from the coupling reactions between α,β-unsaturated ketones and aldehydes are summarized in Table 1. Diastereomers having a *trans* configuration at

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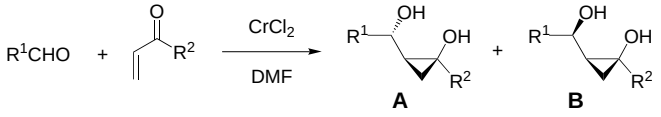
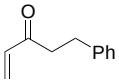
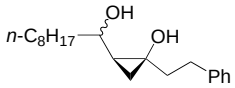
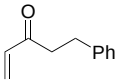
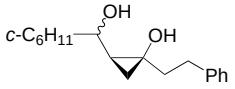
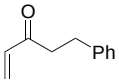
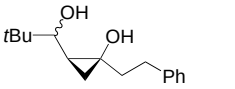
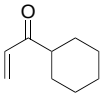
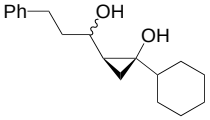
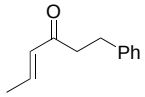
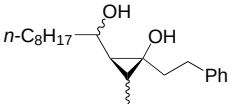
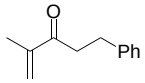
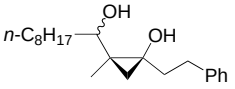
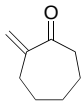
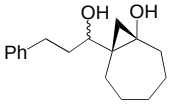
Table 1. Sequential aldol-cyclopropanation of α,β-unsaturated ketones and aldehydes.[a]

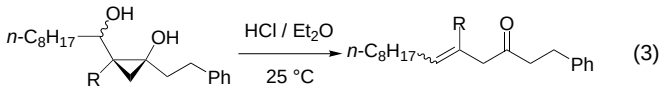


Entry	R^1	Enone	t [h]	Products	Yield [%] [b]	**A**:**B**[c]
1	n-C_8H_{17}		2		93	58:42 (**6a**:**6b**)
2	c-C_6H_{11}		2		89	79:21
3	tBu		2		76	51:49
4	$Ph(CH_2)_2$		2		62	74:26
5	n-C_8H_{17}		2		28	–[d]
6	n-C_8H_{17}		18		78	91:9 (**11a**:**11b**)
7	$Ph(CH_2)_2$		24		54	85:15

[a] The reaction was conducted on a 1.0-mmol scale. Chromium(II) chloride (8.0 mol) and enone (2.0 mol) were used per mole of aldehyde. [b] Yields of isolated products. [c] Isomer ratios were determined by isolation, GLPC, and/or NMR spectroscopy. [d] Mixture of diastereomers. The configuration of the methyl group on the cyclopropane was not determined.

the cyclopropane ring were not obtained in all cases. Substituents at the olefin positions of the enones retarded the coupling reactions, especially in the case of a β-substituted enone (Table 1, entries 5 and 6). An enone fixed to s-*cis* could also be used for the coupling reaction (entry 7).

The produced diols **6** and **11** could be transformed to the β,γ-unsaturated ketones **12**[12] and **13**[13] by treatment with hydrochloric acid in diethyl ether in 93% and 96% yields, respectively [Eq. (3)].[13] The ketones underwent an exchange



6: R = H
11: R = Me

12: 93% (*E* / *Z* = 89 / 11)
13: 96%[13]

(3)

between the α and β carbon atoms from the starting enones, and displayed alkylidenation at the α-carbon atom.

Experimental Section

Representative procedure for the reaction in Table 1, entry 1: To a mixture of $CrCl_2$ (0.98 g, 8.0 mmol)[14] in dry, oxygen-free DMF (10 mL)[15] was added a solution of nonanal (0.14 g, 1.0 mmol) and 5-phenyl-1-penten-3-one (**4**, 0.32 g, 2.0 mmol) in DMF (10 mL) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was poured into water (20 mL). The mixture was extracted with diethyl ether (4×15 mL), and the organic extracts were dried over anhydrous magnesium sulfate and concentrated. Purification by column chromatography on silica gel (hexane/ethyl acetate, 50/1) gave 2-(1-hydroxynonyl)-1-(2-phenylethyl)-cyclopropanol in 93% yield (**6**, 0.28 g; **6a**/**6b** = 58/42).

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[4] Intramolecular carbon–carbon bond formation between α,β-acetylenic ketones and carbonyl groups with chromium(II) was reported: A. B. Smith III, *Strategies and Tactics in Organic Synthesis* (Ed.: T. Lindberg), Academic Press, Orlando, **1984**, p. 252; see also A. B. Smith III, P. A. Levenberg, J. Z. Suits, *Synthesis* **1986**, 184–189.

[5] 2-(1-Oxo-3-phenylpropyl)-1-(2-phenylethyl)cyclopentanol was obtained as a major product (44% yield); see also ref. [3c].

[6] In 1993 Stevenson et al. first observed formation of a cyclopropanol by treatment of α,β-unsaturated aldehydes with $CrCl_2$ and a catalytic amount of $NiCl_2$: D. Montgomery, K. Reynolds, P. Stevenson, *J. Chem. Soc. Chem. Commun.* **1993**, 363–364. Our observations[5] suggest that the presence of water is necessary to promote the cyclopropanol formation. Also, in our experiments the presence of a catalytic amount of the nickel salt did not affect the transformation.

[7] When the reaction was conducted at 25 °C, the diastereomeric ratio **6a**/**6b** changed from 58/42 to 80/20 with a decrease in the total yield to 57%. This is because the minor product **6b** is more unstable than **6a** under the slightly acidic reaction conditions.

  0044-8249/00/11215-2838 $ 17.50+.50/0

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[10] For cyclopropanation of enones mediated by zinc and BF_3, see I. Elphimoff-Felkin, P. Sadra, *Tetrahedron* **1975**, *31*, 2781 – 2784.
[11] The following functional substrates were recovered under the standard reaction conditions (Table 1, entry 1) due to the mild nucleophilicity of the organochromium reagent: 1-dodecene (97 %), 1-dodecyne (93 %), 1-chlorododecane (91 %), ethyl octanoate (93 %), nonanenitrile (93 %), 3-phenylpropyl acrylate (95 %), nonanal ethylene acetal (94 %), 4-phenyl-2-butanone (96 %).
[12] Both diastereomers of **6** gave an *E* isomer of **12** as a major product. This is probably due to the stability of a carbocation adjacent to the cyclopropane ring; see H. Maeta, T. Nagasawa, Y. Handa, T. Takei, Y. Osamura, K. Suzuki, *Tetrahedron Lett.* **1995**, *36*, 899 – 902.
[13] The β,γ-unsaturated ketone **13** was obtained as a mixture of geometrical isomers.
[14] Chromium(II) chloride (99.9 % purity, anhydrous powder, <100 ppm H_2O) was purchased from Aldrich Chemical Co.
[15] Dehydrated DMF was purchased from Wako Pure Chemical Industries Ltd., and stored with 4-Å molecular sieves.

Highly 1,2-*trans* Stereoselective Allylations of 1,2-*O*-Isopropylidene-Protected Glycofuranosides**

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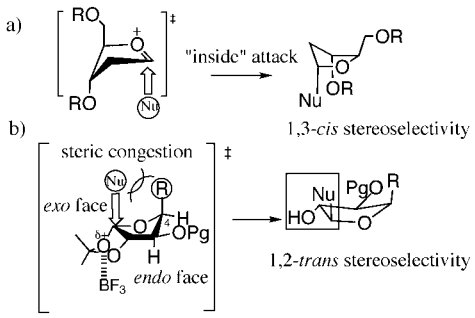
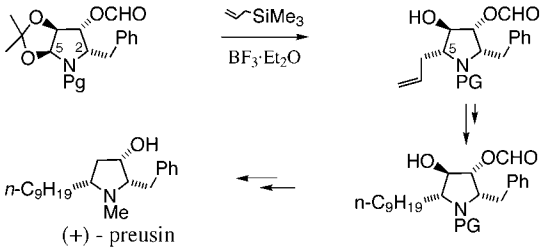
Dedicated to Professor Antonio González on the occasion of his 83rd birthday

Lewis acid mediated cleavage of chiral cyclic acetals is a useful synthetic tool for the asymmetric synthesis of C–C bonds.[1] Specifically, one of the most widely used methods for the formation of C-glycosides involves a glycosidic acetal, a Lewis acid, and a carbon nucleophile.[2] The reaction proceeds via a cyclic oxocarbenium ion, which undergoes nucleophilic attack in a stereoelectronically controlled manner to provide the product with high stereoselectivity.[3–5] Conformational effects have been invoked to explain the stereoselective reactions of substituted five-membered-ring oxocarbenium ions (Scheme 1 a).[4]



Scheme 1. a) The postulated stereoelectronic model for reactions of substituted five-membered-ring oxocarbenium ions. Nucleophilic attack occurs by a stereoelectronically controlled "inside attack" on the lower energy conformer of the cation to provide the product in its lower energy form. b) Schematic representation of the *exo* facial template effect exercised by the 1,2-*O*-isopropylidene protecting group. The nucleophilic attack is directed by the acetal onto the *exo* face of the molecule to give the 1,2-*trans* product.

Because of the biological and chemical importance of C-glycofuranosides,[2, 6] we undertook a study of the Lewis acid promoted cleavage of 1,2-*O*-isopropylidene-protected glycofuranosides by allyltrimethylsilane as a feasible and stereoselective route to these structures.[7] This procedure was introduced by us in the formal synthesis of the antibiotic (+)-preusin to install the C5 nonyl chain with the required *R* configuration (Scheme 2).[8] We hypothesized that the high



Scheme 2. The formal stereoselective synthesis of (+)-preusin. The alkyl chain at C5 is introduced with the required *R* configuration by diastereoselective allylation of the bicyclic 1,2-*O*-isopropylidene-protected dihydroxypyrrolidine intermediate. PG = protecting group.

diastereoselectivity obtained in this experiment was due to the bicyclic nature of these acetals, which confers an intrinsic and general *exo*-facial bias to the incoming nucleophile, regardless of the other substituents on the heterocyclic ring (Scheme 1 b). If this were the case, then this template effect of the bicyclic acetal should be general for any 1,2-*O*-isopropylidene-protected glycofuranoside, and thus provide invariable 1,2-*trans* stereoselectivity for nucleophilic substitution at the anomeric center. Here we present experimental evidence to confirm our initial hypothesis and establish the generality of this remarkable *exo*-facial template effect exercised by the 1,2-*O*-isopropylidene protecting group.

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