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Radical [3+2]-cycloaddition reaction with alkenes using dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate as a new homoallyl radical precursor

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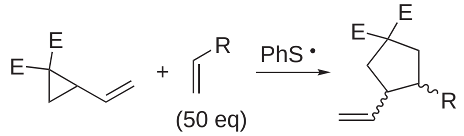
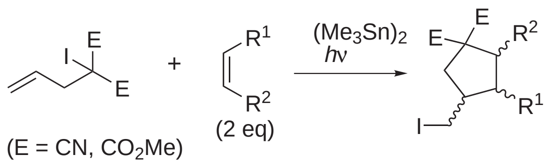
Abstract—Radical iodine atom transfer [3+2]-cycloaddition with various alkenes using dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate as a new precursor of homoallyl radical species smoothly proceeds to give functionalized cyclopentane derivatives in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

[3+2]-Cycloaddition reaction of a homoallyl radical with an alkene is one of the powerful means for one-step synthesis of a cyclopentanoide skeleton.[1] Radical [3+2]-cycloaddition reaction with simple alkenes (without electron withdrawing groups) has been achieved by the use of electron-deficient homoally radicals generated from vinylcyclopropane and allylated α-iodoactive methine derivatives (Eq. (1) and (2)).[1g–j] However, Feldman and Oshima's method using vinylcyclopropane derivatives as the homoallyl radical precursor required a large excess of simple alkenes (50 equiv.) and could not be applied to the reaction with less reactive 1,2-disubstituted alkenes (Eq. (1)).[1e,j] Although Curran et al. have succeeded in reactions with various 1-alkenes, 1,1- and 1,2-disubstituted alkenes by the use of allyl-α-iodomalononitrile,[1i,j] it was not applicable to the reaction with electron-rich alkenes because of the nature as an electrophilic iodine source of unstable ally-α-iodoactive methines (Eq. (2)).[2] In this paper, we report radical iodine atom transfer [3+2]-cycloaddition with various alkenes using dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **1** as a new homoallyl radical precursor (Eq. (3)).



(1)



(2)

We expected that dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **1** may efficiently produce an allylmalonate radical **1A** via regioselective cleavage of the C–C(CO_2Me)$_2$ bond of a cyclopropylmethyl radical, and the resulting **1A** would possibly give iodoalkylated cyclopentane derivatives through radical iodine atom transfer reaction with alkenes (Eq. (3)).[3] In addition, the reagent **1**, which does not have an alkenyl group and does not work as an electrophilic iodine source, may be an efficient homoallyl radical precursor. That is, the use of radical precursor **1** not having an alkenyl group such as that in vinylcyclopropane (Eq. (1))[1g] and allyl-α-iodoactive methines (Eq. (2))[1h–j] may bring about an increase in the chemical yield, because the attack of the resulting homoallyl radical to the precursor should be ignored. Furthermore, since this stable (iodomethyl)cyclopropane **1** does not have the nature as an electrophilic iodine source such as unstable ally-α-iodoactive methines (Eq. (2)), the reaction with electron-rich alkene may be also possible.[2] (Iodomethyl)cyclopropane **1** can be easily prepared through iodocarbocyclization reaction of allylmalonate which was previously found by our group.[4]

Radical iodine atom transfer [3+2]-cycloadditions of **1** with various alkenes such as electron-rich alkene, 1-alkene and 1,1-, 1,2-disubstituted alkene were examined

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Keywords: radicals and radical reactions; cycloadditions; cyclopropanes; cyclopentanes.

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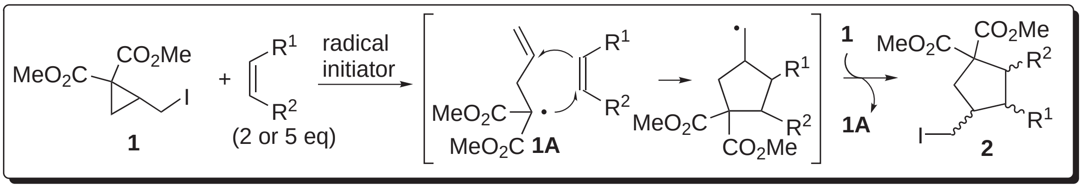
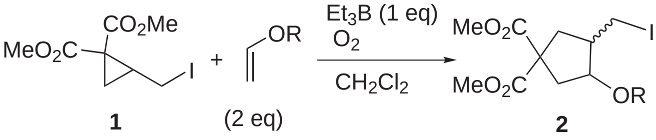


(3)

(Eq. (4) and Table 1). The reaction of **1** with electron-rich alkene (2 equiv.) such as alkyl vinyl ether and silyl enol ether smoothly proceeded in the presence of Et_3B (1 equiv., O_2 atmosphere) to give functionalized cyclopentane derivatives **2a** and **2b** in good yields (66, 79%), respectively, while the diastereoselectivities of these reactions were low (Eq. (4)).[5]

In contrast to the reaction with enol ether derivatives, reaction of **1** with 1-hexene gave the product **2c** in poor yield (22%) under the same conditions. On the other hand, the addition of $Yb(OTf)_3$ was found to lead to the improvement of the chemical yield.[6,7] That is, the reaction of **1** with 1-hexene (2 equiv.) in the presence of Et_3B (1 equiv.) and $Yb(OTf)_3$ (1 equiv.) under an O_2 atmosphere gave **2c** in good yield (82%) with high diastereoselectivity (*cis*/*trans* = 11.2) (Table 1, Entry 1).[8] $Yb(OTf)_3$ may promote both the rate of addition of the

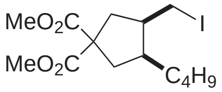
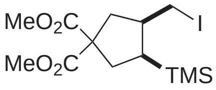
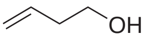
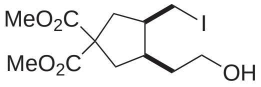
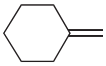
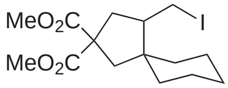
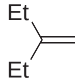
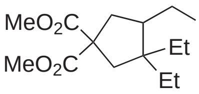
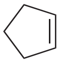
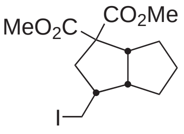
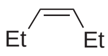
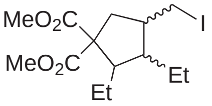


R		Yield (%)	*cis/trans*
n-Bu	**2a**	66	1.2
TMS	**2b**	79	1/1.8

(4)

Table 1. Radical [3+2]-cycloaddition with (iodomethyl)cyclopropane **1**

$$\mathbf{1} + \underset{(2\ \text{eq})}{\text{Alkene}} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{Et}_3\text{B (1 eq), Yb(OTf)}_3\text{ (1eq), O}_2} \underset{\mathbf{2}}{\text{Products}}$$

Entry	Alkene	Products		Yield (%)[a]	*cis/trans*
1			**2c**	82	11.2 [b]
2			**2d**	67	6.0 [b]
3			**2e**	68	10.8 [b]
4			**2f**	88	—
5			**2g**	73	—
6 [c]			**2h**	70	> 50
7 [c]			**2i**	65	2.2 [d,e]

[a] Isolated yield.

[b] The ratio was determined by ^{13}C-NMR.

[c] 5 eq of alkene was used.

[d] Two stereoisomers were mainly obtained, while the stereochemistries were not determined.

[e] The ratio was determined by ^1H-NMR.

malonate radical and the iodine abstraction through the formation of bidentate complex with the malonate.[7b,c,9] The reaction with other 1-alkenes such as vinylsilane and homoallyl alcohol also proceeded with *cis*-selectivity (**2d**: *cis*/*trans* = 6, **2e**: *cis*/*trans* = 10.8) to give product **2d** and **2e** in good yields (67 and 68%, Entries 2,3). In the reactions with 1-hexene and vinylsilane, considerable increase in both the chemical yields and diastereoselectivities was observed in comparison with those attained by Curran's method (**2c**: 53%, *cis*/*trans* = 4, **2d**: 46%, *cis*/*trans* = 2) which gives the same products **2c** and **2d** on using allyliodomalonate.[1h] Similar to that with 1-alkenes, in the cycloaddtion reaction with 1,1-disubstituted alkenes, products **2f** and **2g** were obtained in good yields (88 and 73%), respectively (Entries 4,5).

The present reaction is applicable not only to 1-alkenes and 1,1-disubstituted alkenes but also to less reactive 1,2-disubstituted alkenes; that is, the reaction with cyclopentene and 3-hexene also gave the products **2h**[5] and **i** in good yields (70 and 65%), respectively (Entries 6,7). These results should be noteworthy, because it has been reported that the reaction with 1,2-disubstituted alkene hardly proceeds under Curran's conditions using allyliodomalonate.[1h] Thus, we found radical iodine atom transfer [3+2] cycloaddition of homoallyl radical species which can be applied to a wide range of 1-alkene, 1,1-, 1,2-disubstituted alkenes and electron-rich alkenes.

In conclusion, we have succeeded in the development of radical iodine atom transfer [3+2] cycloaddition with various alkenes using dimethyl 2-(iodomethyl)-cyclopropane-1,1-dicarboxylate as a new homoallyl radical precursor. The present reaction should provide an efficient and practical synthetic method of functionalized cyclopentane skeletons.

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8. General procedure of radical [3+2] cycloaddition reaction of dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **1** with alkenes. *Under an argon atmosphere*, to a solution of dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate **1** (149 mg, 0.5 mmol), 1-hexene (0.13 mL, 1 mmol) and $Yb(OTf)_3$ (310 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) was added Et_3B (0.5 mL, 1 M hexane solution). After being stirred for 5 h at 0°C *under an O_2 atmosphere*, the mixture was poured into aqueous NH_4Cl solution and extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by silica-gel column chromatography (hexane/AcOEt = 20) gave an inseparable mixture of *cis*-**2c** and *trans*-**2c** (157 mg, 82%, *cis*/*trans* = 11.2).
9. In the reaction with alkyl vinyl ether and silyl enol ether, addition of $Yb(OTf)_3$ resulted in the formation of a complex mixture.