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Communication

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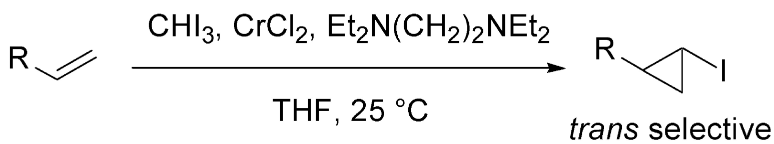

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Stereoselective Iodocyclopropanation of Terminal Alkenes with Iodoform, Chromium(II) Chloride, and *N*,*N*,*N*′,*N*′-Tetraethylethylenediamine

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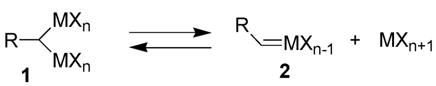
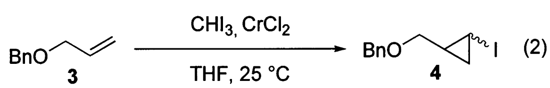
Geminal dimetallic organic compounds **1** are employed as reactive intermediates for organic synthesis.[1,2] The Tebbe reagent, a typical example of **1**, shows nucleophilic reactivity toward carbonyl compounds to afford their methylenation products.[1b] The dimetallic species **1** of early transition metals are postulated in equilibrium with the metal-alkylidene complex **2** and MX_{n+1} (eq 1),[3] and the equilibrium shift is caused by the addition of an appropriate amine.[4] In this Communication, we disclose that the reactivity of a 1,1-dichromium compound derived from iodoform and chromium(II) chloride changes markedly by addition of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) or TEEDA (*N*,*N*,*N*′,*N*′-tetraethylethylenediamine), and that *trans*-iodocyclopropanes[5,6] are produced stereoselectively from terminal alkenes by treatment with the base-added reagent system.



(1)

Treatment of allyl benzyl ether (**3**) with a mixture of iodoform (2 equiv) and chromium(II) chloride (4 equiv) in THF at 25 °C for 24 h afforded (2-iodocyclopropyl)methyl benzyl ether (**4**) in 32% yield along with the recovery of **3** in 64% yield (eq 2). The trans:cis ratio of the produced cyclopropanes was 63:37. Addition of several amines was examined, and it was found that both TMEDA and TEEDA accelerate the iodocyclopropanation. For example, when chromium(II) chloride (4 equiv) was pretreated with TMEDA (4 equiv) in THF before addition of **3** and iodoform, the reaction was complete at 25 °C in 3 h, and **4** was obtained in 87% yield (trans:cis = 85:15).[7] The yield increased to 97% and the trans:cis ratio improved to 93:7 by using TEEDA (4 equiv).



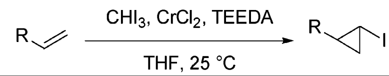
(2)

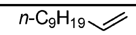
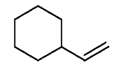
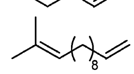
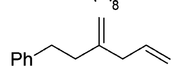
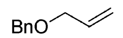
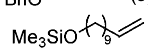
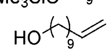
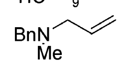
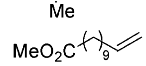
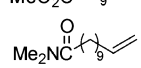
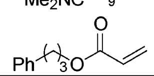
additive:			
none	24 h	32%	(*trans* : *cis* = 63 : 37)
TMEDA	3 h	87%	(*trans* : *cis* = 85 : 15)
TEEDA	4 h	97%	(*trans* : *cis* = 93 : 7)

The results of the iodocyclopropanation of alkenes with iodoform, chromium(II) chloride, and TEEDA are shown in Table 1. It is worth noting that the iodocyclopropanation proceeded smoothly without the presence of a hydroxy or an alkoxy group near the double bond (Table 1, entries 1−4), which is necessary for the cyclopropanation of iodoalkenes mediated with zinc carbenoids.[5a] On the other hand, a steric hindrance around the double bond affected the yield considerably. For example, terminal alkenes afforded the corresponding iodocyclopropanes in 89−96% yields; however, an (*E*)-disubstituted alkene [(*E*)-2-dodecene], a 1,1-disubstituted alkene (2-methyl-1-undecene), and a trisubstituted alkene (2-methyl-2-dodecene) were recovered unchanged after 24 h of stirring at 25 °C in 99%, 95%, and 97% yields, respectively. The selectivity of the iodocyclopropanation is shown with a substrate having both a terminal and a trisubstituted (or 1,1-disubstituted) double bond; **5** and **6** were produced in selective manners, respectively (entries 3 and 4). This reactivity contrasts with that of the Simmons−Smith zinc carbenoid, which reacts faster with more substituted electron-rich alkenes.[8] The iodocyclopropanation reaction proceeded without affecting the following functional groups: benzyl and silyl ethers, tertiary amine, ester, and amide (entries 5, 6, 8−10). It is worth noting that the reaction proceeded without protecting the hydroxyl group, although 3 equiv of the reagent was required to obtain a high yield (entry 7). Electron-rich dodecyl vinyl ether was recovered in 85% yield after being stirred for 24 h; however, electron-deficient α,*β*-unsaturated ester **7** reacted with the reagent to give **8** in 37% yield (entry 11).

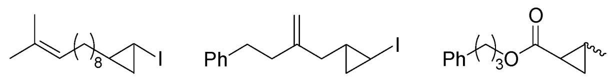
The increased reactivity toward olefinic double bonds by addition of TMEDA or TEEDA to the iodoform-chromium(II) chloride reagent is further demonstrated using terminal alkenes having

Table 1. Iodocyclopropanation of Alkenes[a]



entry	Alkene	Time (h)	Yield (%)	*trans* : *cis*[b]
1		4	93	95 : 5
2		16	89	97 : 3
3		4	90 (**5**)	96 : 4
4		8	96 (**6**)	96 : 4
5	 (**3**)	4	97	93 : 7
6		8	97	97 : 3
7		8	87[c]	95 : 5
8		8	79	91 : 9
9		8	91	96 : 4
10		8	80	98 : 2
11	 (**7**)	24	37 (**8**)	78 : 22

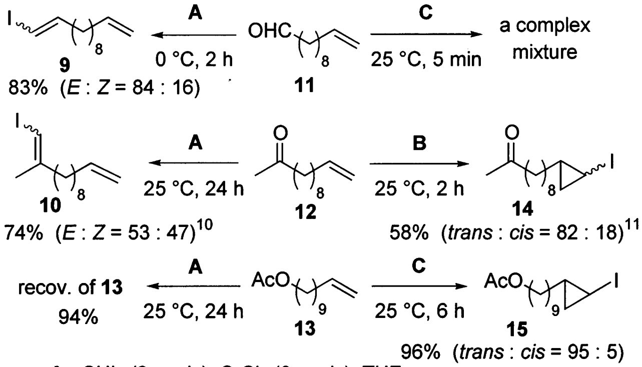
[a] The reactions were conducted on a 1.0 mmol scale. Iodoform (1.5 mol), $CrCl_2$ (4 mol), and TEEDA (4 mol) were used per mol of an alkene. [b] Isomeric ratios were determined by isolation and ^1H NMR spectroscopy. [c] Iodoform (3 mol), $CrCl_2$ (8 mol), and TEEDA (8 mol) were used per mol of 10-undecen-1-ol.



5 **6** **8**

10.1021/ja0373061 CCC: $25.00

Scheme 1. Comparison of the Reactivity in the Presence and Absence of Diamines

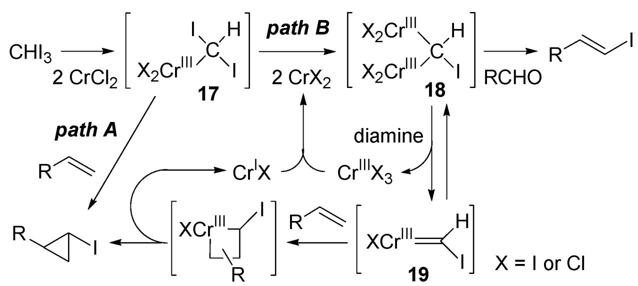


A: CHI_3 (2 equiv), $CrCl_2$ (8 equiv), THF

B: CHI_3 (2 equiv), $CrCl_2$ (4 equiv), TMEDA (4 equiv), THF

C: CHI_3 (2 equiv), $CrCl_2$ (4 equiv), TEEDA (4 equiv), THF

Scheme 2. A Plausible Mechanism



carbonyl groups (Scheme 1). The reagent derived from iodoform and chromium(II) chloride in the absence of diamines reacted only with aldehyde and ketone carbonyl groups, and selective iodoolefination occurred to give iodoalkenes **9** and **10** in 83% and 74% yields, respectively. An ester carbonyl group was inert to the reagent, and **13** was recovered in 94% yield. In contrast, when the diamines were added to the reaction mixture and the amount of chromium(II) chloride reduced to one-half of the iodoolefination reagent, the product distributions changed markedly. Although the aldehyde **11** gave a complex mixture, the terminal alkenes **12** and **13** were selectively converted to the corresponding iodocyclopropanes **14** and **15** in 58% and 96% yields, respectively. The dramatic effect on the reactivity of the reagents derived from iodoform and chromium(II) chloride, caused by the addition of the diamines, suggests that different reactive species are generated in the reaction mixture.[9]

Cyclopropanation of alkenes can be accomplished by both metal-carbenoid species and metal-carbene complexes.[12] Thus, there are two possible reaction pathways for the production of iodocyclopropanes (Scheme 2). The active species of path A is the chromium-carbenoid **17**, and that of path B is the chromium-carbene species **19**.[13] When a diamine is added to the preformed geminal dichromium species **18**, the reactivity of the reagent changes and iodocyclopropanation occurs selectively.[14] Therefore, we are tempted to assume that the chromium-carbene species **19**[15] could be involved in the cyclopropanation.

The family of *trans*-iodocyclopropanes[5,6] are good precursors for constructing cyclopropyl-cyclopropyl and -vinyl carbon skeletons of such natural products[16] as FR-900848 and U-106305 using Suzuki−Miyaura-type cross-coupling reactions.[17] Although the iodocyclopropanation of alkenes is an attractive direct approach to *trans*-iodocyclopropanes due to the accessibility of the starting materials,[6] this approach has not been popular. This is because there have been no appropriate reagents for simple terminal alkenes which satisfy both yield and stereoselective requirements. The proposed method will provide an alternative route to *trans*-iodocyclopropanes.

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Supporting Information Available: General experimental procedure and characterization data for all compounds in Table 1 and compounds **14** and **15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(1) (a) Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241−3267. Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1039−1042. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270−3272. (c) Charette, A. B.; Gagnon, A.; Fournier, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 386−387.

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(3) Beckhaus, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 686−713.

(4) For example, the Tebbe reagent reacts with olefins via a titanocene-methylene complex after treatment with DMAP. Lee, J. B.; Gajda, G. J.; Schaefer, W. P.; Howard, T. R.; Ikariya, T.; Straus, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 7358−7361.

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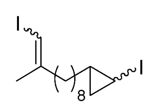
(6) Yang, N. C.; Marolewski, T. A. *J. Am. Chem. Soc.* **1968**, *90*, 5644−5646. Nishimura, J.; Furukawa, J. *Chem. Commun.* **1971**, 1375−1376. Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1500−1503. Marolewski, T. A.; Yang, N. C. *Org. Synth.* **1988**, *Coll. Vol. 6*, 974−975. Dehmlow, E. V.; Soufi, J.; Stammler, H.-G.; Neumann, B. *Chem. Ber.* **1993**, *126*, 499−502.

(7) Effects of additives on the yields and stereoselectivities of **4** are as follows: Et_3N, 25% (trans:cis = 70:30); $Me_2NCH_2NMe_2$, 0%; $Me_2N(CH_2)_3NMe_2$, 69% (83:17); *i*-PrMeN$(CH_2)_2$N(*i*-Pr)Me, 19% (71:29); DL-$Me_2NCHPhCHPhNMe_2$, 61% (82:18), 2,2′-bipyridyl, 13% (64:36).

(8) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1−415.

(9) The amount of $CrCl_2$ is not important for the chemoselectivity. For example, treatment of **12** with iodoform (2 equiv) and $CrCl_2$ (4 equiv) resulted in iodoolefination, but the yield of **10** decreased to 54% (*E*:*Z* = 54:46), and **12** was recovered in 43% yield; **14** was not detected.

(10) When 2-fold amounts of the reagent **A** were used, **16** was obtained in 13% yield (a diastereomeric mixture) along with **10** in 75% yield (*E*:*Z* = 54:46).



16

(11) The reactant **12** was recovered in 27% yield. The iodoolefins **10** and **16** were obtained as byproducts in 3% and 6% yields, respectively.

(12) Dorwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, 1999; pp 105−119.

(13) For the formation of cyclopropanes by reductive elimination of metallocyclobutanes, see: (a) Ti: Horikawa, Y.; Nomura, T.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Org. Chem.* **1997**, *62*, 3678−3682. (b) Re: Yang, G. K.; Bergman, R. G. *Organometallics* **1985**, *4*, 129−138.

(14) The geminal dichromium reagent was generated by stirring iodoform (1.5 equiv) and $CrCl_2$ (4 equiv) in THF at 25 °C for 30 min. Treatment of 3-phenylpropanal with the reagent gave 1-iodo-4-phenyl-1-butene in 70% yield (*E*:*Z* = 82:18) after stirring at 25 °C for 30 min.[2] In contrast, when TMEDA (4 equiv) was added to the geminal dichromium reagent generated at 25 °C for 1 h, and the mixture was stirred for a further 15 min, treatment of **12** with the new base-added reagent at 25 °C for 2 h gave **14** in 38% yield (trans:cis = 80:20) along with **10** and **16** in 1% and 3% yields, respectively. The reactant **12** was recovered in 37% yield.

(15) A chromium-alkylidene complex having a TMEDA ligand was isolated, see: Hao, S.; Song, J.-I.; Berno, P.; Gambarotta, S. *Organometallics* **1994**, *13*, 1326−1335.

(16) For a review, see: Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589−8627.

(17) (a) Charette, A. B.; Giroux, A. *J. Org. Chem.* **1996**, *61*, 8718−8719. (b) Charette, A. B.; De Freitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809−2812.

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