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"Tailor-Made" Carbonyl Ylides: [3 + 2] Cycloaddition of the Parent and Optionally Substituted Nonstabilized Carbonyl Ylides

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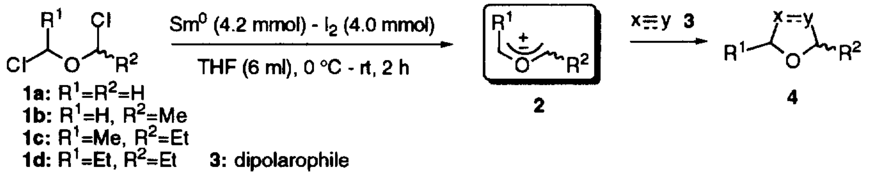
Abstract: *"Tailor-made"* carbonyl ylides bearing only alkyl substituents or no substituents were efficiently generated from α-chloroalkyl α'-chloroalkyl ethers in the presence of samarium reagents. Using these novel and synthetically practical carbonyl ylides, optionally substituted and stereochemically defined tetrahydrofurans, dihydrofurans and dioxolane were synthesized in a single step.

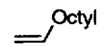
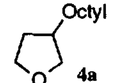
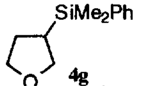
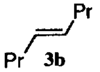
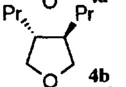
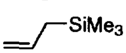
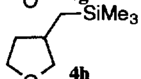
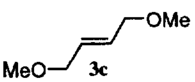
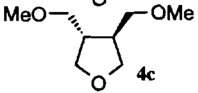
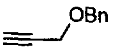
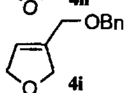
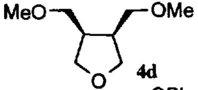
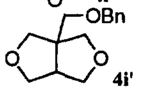
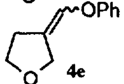
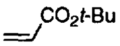
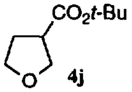
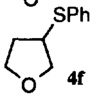
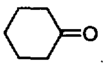
By virtue of their stereospecific [3 + 2] cycloaddition, carbonyl ylides are potentially efficient chemical species for the synthesis of tetrahydrofurans and dihydrofurans which are important components of biologically active natural products. However, hitherto known carbonyl ylides have been restricted to those bearing electron-withdrawing and conjugating functionalities such as cyano and alkoxycarbonyl groups which stabilize dipolar centers of the ylides electronically and, therefore, only a particular kind of carbonyl ylides is available.[1] The fact that there is no generality in organic synthesis using carbonyl ylides stems from lack of expedient methods to generate versatile carbonyl ylides.[2] In order to overcome these limitations, stepwise transformations using the synthetic equivalents of nonstabilized carbonyl ylides were previously reported.[3] These reactions proceeded regiospecifically, but not stereospecifically as expected to reactions mediated by real carbonyl ylides. We recently developed convenient methods for the generation of the monoaryl- and symmetrically α,α'-dialkyl-substituted carbonyl ylides.[4] Even if these methods would partially solve the above-mentioned problems, the realized species are still limited only to the "mono-substituted" and "symmetrically substituted" carbonyl ylides. In such a context, it is highly desired to generate optionally substituted nonstabilized carbonyl ylides at will. We report herein a new generation of the parent carbonyl ylide and optionally substituted *nonstabilized* carbonyl ylides in a *tailor-made* manner and their conventional intermolecular [3 + 2] cycloaddition reactions. (eq. 1)



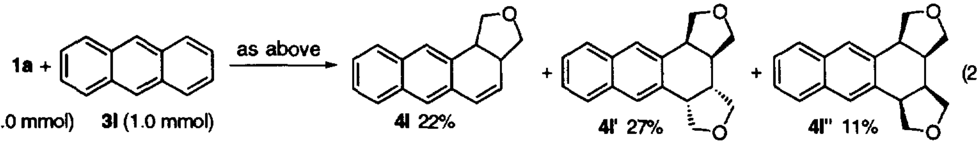
(1)

Of all carbonyl ylides, the parent one **2a** will exhibit the most fundamental and characteristic features in reactivities, not affected sterically and electronically, while only theoretical calculations for it[5] and experimental evidence for its generation are so far reported.[6] We found the parent carbonyl ylide **2a** was generated from easily available bis(chloromethyl) ether **1a**[7] in a SmI_2-Sm^0 system, and as the first case, smoothly reacted toward a wide variety of unsaturations to give the corresponding [3 + 2] cycloadducts in high yields.[8] Representative results are listed in Table 1. The [3 + 2] cycloaddition of **2a** proceeded stereospecifically with retention of the stereochemistry around carbon-carbon double bonds of the dipolarophiles and, therefore, configurations of 3,4-positions of the tetrahydrofurans (*e.g.* **4b**, **4c**, and **4d**) were completely controlled. To the allylsilane **3h**, a typical electron-rich alkene, **2a** reacted to produce the tetrahydrofuran derivative **4h** in high yield. With the propargyl ether **3i**, the dihydrofuran **4i** was obtained in 92% yield, while the double cycloadduct **4i'** of **2a** was also accessible (76% yield) only by using an excess amount of **1a**. Using bis(iodomethyl) ether as a precursor, even an electron-deficient alkene, *t*-butyl acrylate (**3j**), could be directly subjected to the reaction and also with cyclohexanone (**3k**), the corresponding dioxolane **4k** was obtained.[9,10] Interestingly, to aromatic hydrocarbons the parent carbonyl ylide **2a** added to produce the nonaromatic fused compounds **4l**-**4l''**, revealing the high reactivity of **2a**.[11] (eq. 2)

Table 1. [3 + 2] Cycloaddition of the Parent Carbonyl Ylide **2a** with Dipolarophiles[a]

Dipolarophile 3	Cycloadduct 4	%Yield[b]	Dipolarophile 3	Cycloadduct 4	%Yield[b]
 **3a**	 **4a**	94	 **3g**	 **4g**	97
 **3b**	 **4b**	58	 **3h**	 **4h**	86
 **3c**	 **4c**	94	 **3i**	 **4i**	92[d]
 **3d**	 **4d**	92	**3i**	 **4i'**	76[e]
 **3e**	 **4e**	78 (55/45)[c]	 **3j**	 **4j**	62[f]
 **3f**	 **4f**	94	 **3k**	 **4k**	64[f]

[a] See ref. 8. [b] Isolated yield of **4** based on **3**. [c] *E/Z* ratio. [d] A reaction was carried out using **1a** (1.0 mmol), **3i** (2.0 mmol) and Sm metal (2.1 mmol) - I_2 (2.0 mmol) in THF (3.0 ml), and the yield was based on **1a**. [e] A reaction was carried out using **1a** (4.0 mmol), **3i** (1.0 mmol) and Sm metal (8.2 mmol) - I_2 (8.0 mmol) in THF (12.0 ml). [f] Bis(iodomethyl) ether was used as a precursor of **2a**.

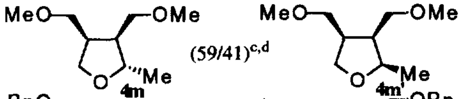
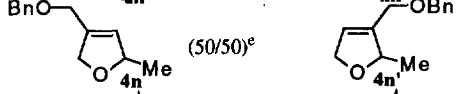
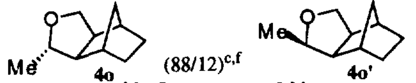
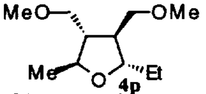
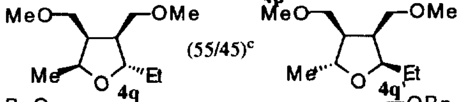
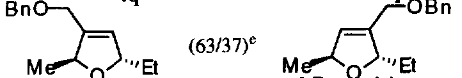
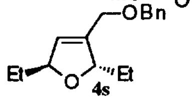


(2.0 mmol) **3l** (1.0 mmol) **4l** 22% **4l'** 27% **4l''** 11% (2)

This protocol can be applicable to a "tailor-made" method for the formation of **2** since the generation is not influenced by any structural factors. When unsymmetrical carbonyl ylides, *e.g.*, the methyl-substituted **2b** and the methyl-ethyl substituted **2c**, are desired, we can surely generate them only by preparing the α-chloroethyl α'-chloromethyl ether **1b** and the α-chloroethyl α'-chloropropyl ether **1c**, respectively, as a source of carbonyl ylides in advance.[12] Using this method, the symmetrical carbonyl ylide **2d** is also accessible. These carbonyl ylides react intermolecularly with alkenes and alkynes as shown in Table 2.

Some characteristic reactivities of the carbonyl ylides which deserve comments emerged. As for stereochemistries of the substituents on the produced tetrahydrofurans, those at 3,4-positions are conserved in the case of stereo-defined alkenes, and those at 2,5-positions are stereoselectively controlled to *trans*; presumably, the latter should depend on the conformation of the ylides **2**. It is worthy to note that in the reaction of **2b** with norbornene (**3m**), a mixture of two diastereomers **4o** and **4o'**, both resulting from the attack to an *exo*-face of norbornene, is obtained and this diastereoselectivity may be induced by the conformational ratio of a substituent on the ylide, or more possibly, by the ratio of two diastereomeric transition states in the cycloaddition. In any case, the more sterically crowded the transition state becomes, the higher the stereoselectivities at 2,3- and/or 4,5-positions are. A reaction using the symmetrical carbonyl ylide **2d** gave essentially similar results as those in the previous report.[4c]

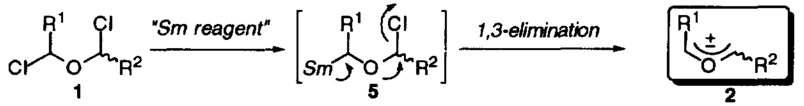
Table 2. [3 + 2] Cycloaddition of Carbonyl Ylide **2** with Dipolarophiles[a]

Carbonyl Ylide **2**	Dipolarophile **3**	Cycloadduct **4**	%Yield[b]
2b	**3d**	 **4m** (59/41)[c,d] **4m'**	86
2b	**3i**	 **4n** (50/50)[e] **4n'**	99
2b	 **3m**	 **4o** (88/12)[c,f] **4o'**	99
2c	**3c**	 **4p**	87
2c	**3d**	 **4q** (55/45)[c] **4q'**	96
2c	**3i**	 **4r** (63/37)[e] **4r'**	90
2d	**3i**	 **4s**	94

[a]See, ref 8. [b]Isolated yield of **4** based on **3**. [c]The ratio of diastereomers. [d]The structure of a major isomer was determined as **4m**. [e]The ratio of regioisomers. [f]The structure of a major isomer was determined as **4o**.

A plausible mechanism for the generation of the carbonyl ylides presented here is shown in Scheme 1. Samarium reduces a chloromethyl ether **1** to give a (chloromethoxy)methylsamarium **5**, from which the 1,3-elimination of samarium and a chlorine atom takes place to generate a carbonyl ylide **2**.[13] Interestingly, in our operation, metals other than samarium as a reductant never worked well. This suggests the importance of the selective reduction of one chlorine-carbon bond in **1** and the successive elimination of another chlorine atom.[14]

Scheme 1.



A new tailor-made access to the carbonyl ylides using the 1,3-elimination reaction made it possible to generate the desired nonstabilized ylides, including the parent one which was essential in organic synthesis. Using these synthetically practical carbonyl ylides, optionally substituted and stereochemically defined tetrahydrofurans, dihydrofurans and dioxolane were synthesized in a single step. Applications to related active species are now under investigation.

Acknowledgments: This work is partly supported by Grants-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science, Sports and Culture, Japan.

References and Notes

1. For reviews, see a) Huisgen, R. *Angew. Chem. Int . Ed. Engl.* **1963**, *2*, 565-598. b) Huisgen, R. *Angew. Chem. Int . Ed. Engl.* **1977**, *16*, 572-585. c) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; pp 1-176. For a term *nonstabilized*, see d) Vedejs, E. In *Advances in Cycloaddition*, Curran, D. P., Ed.; JAI Press Inc.: Greenwich, Connecticut, 1988; Vol. 1, pp. 33-51.
2. To our knowledge, the generation methods of the carbonyl ylides were classified into four types. Original works on their [3 + 2] cycloaddition are referred to. Thermolysis of oxiranes; a) Linn, W. J.; Benson, R. E. *J. Am. Chem. Soc.* **1965**, *87*, 3657-3665. Thermolysis of oxadiazolines; b) Rajagopalan, P.; Advani, B. G. *Tetrahedron Lett.* **1967**, 2689-2695. Photolysis of oxiranes; c) Arnold, D. R.; Karnischky, L. A. *J. Am. Chem. Soc.* **1970**, *92*, 1404-1406. Reaction of carbenes with carbonyl compounds; d) Kharasch, M. S.; Rudy, T.; Nudenberg, W.; Büchi, G. *J. Org. Chem.* **1953**, *18*, 1030-1044. e) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952. See also ref. 1a.
3. Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438-7439. It should be noted that the real carbonyl ylides react stereospecifically with alkenes because of their concerted process, while regiochemistries are not so high due to their dependence on the MO coefficients at the reaction sites. On the other hand, the synthetic equivalents of the nonstabilized carbonyl ylides reacted regiospecifically. The importance of and difficulty in the generation of the nonstabilized carbonyl ylides were mentioned by the authors.
4. a) Hojo, M.; Ohkuma, M.; Ishibashi, N.; Hosomi, A. *Tetrahedron Lett.* **1993**, *34*, 5943-5946. b) Hojo, M.; Ishibashi, N.; Hosomi, A. *Synlett*, **1996** (3), 234-236. c) Hojo, M.; Aihara, H.; Hosomi, A. *J. Am. Chem. Soc.* **1996**, *118*, 3533-3534.
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6. Prakash, G. K. S.; Ellis, R. W.; Felberg, J. D.; Olah, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 1341-1342.
7. Buc, S. R. *Org. Syntheses* **1963**, *Coll. Vol. 4*, 101-103.
8. To a well-dried flask containing samarium metal (4.2 mmol), iodine (4.0 mmol) and THF (6.0 ml) were introduced at room temperature under argon, and the mixture was refluxed for 5 h. A dipolarophile **3** (1.0 mmol) and a bis(chloromethyl) ether **1** (2.0 mmol) were added to the mixture at 0 °C and a cooling bath was removed. After stirring at room temperature for 3 h, saturated $NaHCO_3$ was added to the mixture. The conventional workup gave a crude product **4** which was purified by column chromatography on alumina. By the control experiments, the conditions of high concentration used here compared to an ordinary SmI_2 system[9] seem to be suitable for the intermolecular cycloadditions, not for the generation of the ylides. For the generation of SmI_2, see Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501-502.
9. For the SmI_2 reagent and its use for the reduction of α,β-unsaturated esters and ketones, Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693-2698.
10. Bis(iodomethyl) ether (2 mmol) was prepared *in situ* quantitatively with stirring **1a** (2 mmol) and NaI (4 mmol) in THF (2 ml) at room temperature under monitoring its generation by ^1H NMR and the resultant suspension was used without isolation.
11. The structure of 2:1 adducts **4l'** and **4l''** was tentatively assigned. See also ref. 2a.
12. The bis(chloromethyl) ethers **1b**, **1c**, and **1d** were quantitatively prepared by passing chlorine gas under irradiation of light (tungsten lamp) at -20 - -35 °C through chloromethyl ethyl ether, α-chloropropyl ethyl ether, and α-chloropropyl propyl ether, respectively. Hall, G. E.; Ubertini, F. M. *J. Org. Chem.* **1950**, *15*, 715-719.
13. For the reduction of chloromethyl ethers by SmI_2, see Imamoto, T.; Takeyama, T.; Yokoyama, M. *Tetrahedron Lett.* **1984**, *25*, 3225-3226.
14. For the reaction of **1a** with the dipolarophiles, we examined lithium naphthalenide, $CrCl_2$, and metals such as Li, Na, Mg, Ba, Zn in place of Sm, some of which were activated by washing their surface in an ordinary manner or prepared by the reduction of MX_2 with lithium naphthalenide (the Rieke method).

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