

Aldol-type carbon bond formation of ethereal oxonium ylide†

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The Rh(2)-catalyzed reaction of 2-(3-diazo-1,1-dimethyl-2-oxopropyl)-2-methyldioxolane (**1b**) with arylaldehyde in the presence of $(\text{Me}_3\text{SiCl}$ and $\text{Ti}(\text{i-PrO})_4$ gave 2-aryl-(hydroxy)methyl-8,8-dimethyl-7-methylene-3,6-dioxocane-1-one (**6**) and 2-aryl(hydroxy)methyl-4-(2-chloroethoxy)-4,5,5-trimethyl-3-oxacyclopentanone (**7**); these are the first examples of C–C bond formation of ethereal oxonium ylide *via* enol silyl ether intermediates.

In general, when the ambiphilic character of onium ylides is properly controlled by imparting a relatively long lifetime, consecutive C–C bond formation on the carbanion can be realized as already exemplified widely by phosphonium and sulfonium ylides.^{1,2}

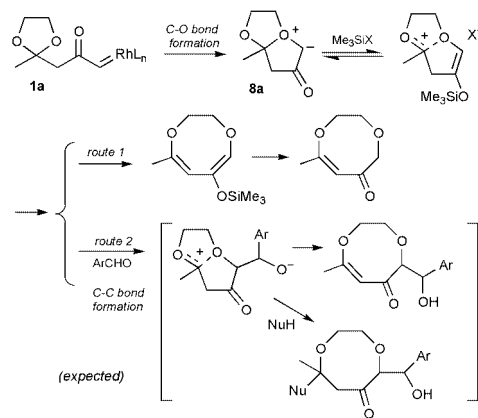
However, similar bond formations have not been reported for ethereal oxonium ylides. This is probably because their extremely short lifetime³ kinetically retards electrophilic attack by ordinary carbon electrophiles. Despite this defect, the [1,*n*]-ambiphilicity of intramolecularly formed bicyclic O-ylide, *e.g.* **8**, will enable the ylide to react with carbon electrophiles under appropriate conditions such as, for example, transforming the ylide to a more stable intermediate which retains the nucleophilic character of the ylide and also the use of a Lewis acid.

As the study model of this reaction, we chose the transition metal-catalyzed reaction of diazo ketones bearing a cyclic acetal ring to be carried out in the presence of a silyl reagent.⁴ This is because we recently found evidence that bicyclic oxonium ylide, generated from a diazoketone-substituted cyclic acetal, was transiently transformed by the action of chlorotrimethylsilane (Me_3SiCl) to the corresponding enol silyl ether as evidenced by the chlorosilane-catalyzed ring-expansion reaction (Scheme 1, *route 1*).⁵ On this basis, we expected that the intermediate enol ether would react with a carbon electrophile, particularly in the presence of an appropriate acid catalyst, to give a C–C bonded adduct (*route 2*). Considering chlorosilane as the acid-catalyst,⁶ we designed a one-pot reaction of

diazocarbonyl-substituted cyclic acetals with aldehydes in hope of realizing the aldol-type C–C bond formation in conjunction with a ring-enlargement reaction. In this paper we would like to report the first example of the C–C bond formation of ethereal oxonium ylide.

As the model compounds to be studied, dioxolane-substituted diazoketones **1a** and **1b** were prepared.^{4b} First of all, as a standard reaction, Rh(2)-catalyzed reaction of **1a** was performed in the presence of benzaldehyde (3 eq.) but in the absence of chlorosilane reagents. Products obtained were the [1,2]-rearrangement product **2a** and ring-expansion product **3** (Table 1, entry 1), but none of the expected aldol-type products, *e.g.* **6** and **7**. Introducing an electron-withdrawing group to the *para*-position of arylaldehyde was also unsuccessful (entry 2). Thus, the direct reaction of oxonium ylide with aldehyde is much slower than the [1,2]-rearrangement giving **2a** and β -elimination giving **3**. To suppress the rearrangement, Me_3SiCl was added to trap the ylide intermediate and, in fact, remarkably promoted the ring-expansion to give **3** (entry 3).⁸ This indicates that Me_3SiCl promotes the β -elimination (ring-expansion) of ylide **8a** whereas it suppresses the [1,2]-rearrangement,⁹ when the ylide has enolizable hydrogens at the 4-position of 1-oxonium-6-oxabicyclo[3.3.0]octan-3-one (**8a**).

Based on this finding a similar reaction with **1b**, which bears two methyl substituents on the side chain, was examined in expectation of suppressing the enone formation. When benzaldehyde or anisaldehyde was used as the electrophile, the expected C–C bond formation between the ylide and aldehyde did not take place but, instead, ring-expansion product **4** and ring-switching product **5** were obtained (entries 4 and 5). However, with *p*-nitrobenzaldehyde, the expected C–C-bonded products **6d** and **7d** were obtained (entry 6) (Scheme 2). Both were unequivocally formed by the aldol-type reaction between the aldehyde and oxonium ylide **8b** or its enol silyl ethers **10b** and **11b** (Scheme 3). The reaction was highly stereoselective because **6d** and **7d** were formed as a single diastereoisomer.¹⁰ At low temperature (entry 7), although product yields were not improved, ring-expansion product **6d** was suppressed to some



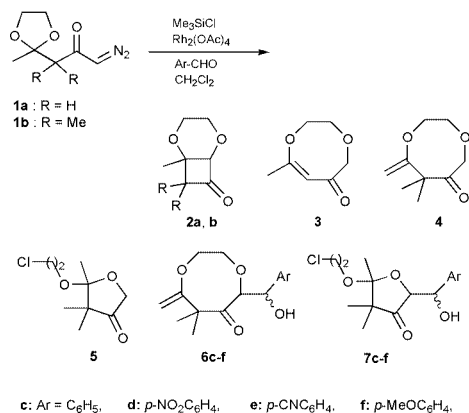
Scheme 1

† Electronic supplementary information (ESI) available: experimental details, ¹H NMR spectra and ¹³C NMR spectral data of compounds **1b**, **2b**, **4–7**. See <http://www.rsc.org/suppdata/cc/b1/b102248m/>

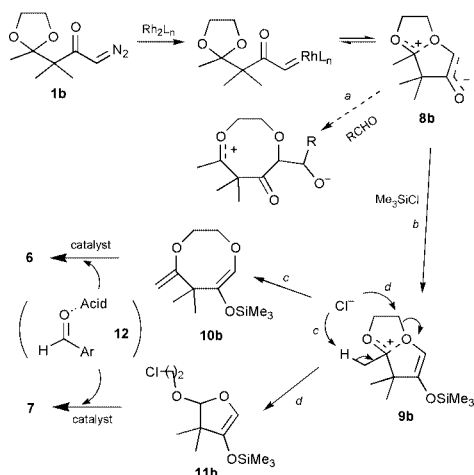
Table 1 Rh(2)-catalyzed reaction of **1** with aldehyde and Me_3SiCl

Entry	Substrate	ArCHO	Lewis acid (mol%)	Products (%)	
1 ^a	1a	C_6H_5	—	2a (15)	3 (7)
2 ^a	1a	<i>p</i> -NO ₂ C ₆ H ₄	—	2a (49)	3 (35)
3	1a	<i>p</i> -NO ₂ C ₆ H ₄	—	—	3 (91)
4	1b	C_6H_5	—	4 (18)	5 (14)
5	1b	<i>p</i> -MeOC ₆ H ₄	—	4 (20)	5 (14)
6	1b	<i>p</i> -NO ₂ C ₆ H ₄	—	6 (54)	7 (7)
7 ^b	1b	<i>p</i> -NO ₂ C ₆ H ₄	—	4 (4)	5 (6)
8	1b	<i>p</i> -CNC ₆ H ₄	—	6 (27)	7 (8)
				4 (4)	5 (6)
				6 (38)	7 (3)
9	1b	<i>p</i> -MeOC ₆ H ₄	Ti(<i>i</i> PrO) ₄ (5)	6 (25)	7 (56)
10	1b	<i>p</i> -MeOC ₆ H ₄	Al(<i>t</i> -BuO) ₃ (5)	4 (—)	5 (4)
				6 (11)	7 (17)
11	1b	C_6H_5	Ti(<i>i</i> PrO) ₄ (5)	6 (27)	7 (32)

^a Me_3SiCl was not used. In other runs, amount of Me_3SiCl used was 3 mol eq. *vs.* 1. ^b At -40°C .



Scheme 2



Scheme 3

extent, indicating that the ring-expansion from the bicyclo[3.3.0] system to an eight-membered ring requires a higher activation energy than the S_N2 attack by Cl^- ion (Scheme 3). Similarly, with *p*-cyanobenzaldehyde C–C-bonded products **6e** and **7e** were again obtained (entry 8).

Not only benzaldehydes bearing withdrawing groups but also unsubstituted benzaldehyde and even anisaldehyde afforded similar C–C bonded products provided that an appropriate Lewis acid was used in addition to $Rh_2(OAc)_4$ and Me_3SiCl (entries 9–11). Among several Lewis acids examined, $Ti(i-OPr)_4$ was the most appropriate for this reaction. Stereoselectivity of the C–C bond formation in the presence of Lewis acid, however, was not so high as was observed with electron-deficient aldehydes without Lewis acid (*vide supra*). Thus, two isomers were formed for **6f** in which the isomer ratio was *anti/syn* = 2.5, whereas for **7f** it was 2.0.

Kanemasa and coworkers recently reported that, in the presence of trimethylsilyl triflate or $ZnCl_2 \cdot Me_3SiCl$, ethyl diazoacetate reacts with aldehyde to give a β -keto ester.¹¹ In the Rh-catalyzed reaction of **1b**, however, a similar diketone was not obtained indicating that **1b** cannot react directly with aldehyde but only *via* oxonium ylide **8b** (Scheme 3).

In Scheme 3, route *a* shows direct nucleophilic attack of ylide **8b** on aldehyde, but that this did not occur is evidenced by the

negative results obtained in the absence of Me_3SiCl (Table 1, entries 1 and 2). Route *b* shows an indirect route to the C–C bond formation from **8b** *via* enol silyl ethers **10b** and **11b**. First, oxonium ion intermediate **9b** may be formed from **8b**. Subsequently, conjugate base Cl^- attacks **9b** on either the bridgehead methyl group for abstracting proton (route *c*) or the methylene group of the acetal ring in an S_N2 manner (route *d*), cleaving C–O bonds, to give **10b** or **11b**, respectively. Hydrogen chloride, generated from the proton abstraction process, acts as an acid-catalyst to activate aldehydes and enol silyl ethers as well to undergo the aldol-type C–C bond-forming reaction.¹² This was verified by the finding that addition of Et_3N to the reaction with nitrobenzaldehyde suppressed the formation of **6d** and **7d**. Another possible route to **6** or **7** by the reaction of **4** or **5** with aldehyde was ruled out by the negative result of independent treatment of **4** or **5** with nitrobenzaldehyde in the presence of Me_3SiCl .

In conclusion, the formation of **6** and **7** can be attributed to the aldol-type reaction between aldehyde and enol silyl ethers **10b** and **11b**, both derived from ylide **8b**, in that not only Lewis acids but also Me_3SiCl act as the catalyst. To expand the scope of C–C-bond formation of ethereal oxonium ylides, further study will be needed.

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- Chlorosilanes did not decompose diazo ketones **1** under these reaction conditions. They are weaker acids than those reported in: A. B. Smith III and R. K. Dieter, *Tetrahedron*, 1981, **37**, 2407.
- A catalytic amount of Me_3SiCl was also effectively used.
- 1,2-Rearrangement product **2** might isomerize to ring-expanded product **3** by the catalytic effect of Me_3SiCl . However, this possibility was ruled out by the independent treatment of **2** with Me_3SiCl in the presence of Rh-catalyst.
- The 1H NMR coupling constants for the newly composed CH–CH moiety are $J = 8.8$ and 7.0 Hz for **6d** and **7d**, and also 8.5 and 7.0 Hz for **6e** and **7e**, respectively.
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