Reactivity of *N*-alkanoyloxy-2,2,6,6-tetramethylpiperidines (*O*-acylTEMPOs) towards hydride-transferring or metallic alkylating reagents; unprecedented stability and application to chemoselective transformations†

**Tsutomu Inokuchi,**[*a] **Hiroyuki Kawafuchi**[b] **and Junzo Nokami**[c]

Owing to the unprecedented stability of *O*-acylTEMPOs towards hydride-transferring and metallic alkylating reagents such as LiAlH$_4$ and RMgX, chemoselective transformation of diacid mixed alkyl/TEMP-1-yl esters, where *O*-acylTEMPOs remained intact, is achieved with these reagents, giving the corresponding carbinols, respectively.

Although a variety of procedures have been developed for the preparation of *N*-alkanoyloxy-2,2,6,6-tetramethylpiperidines **1** (*O*-acylTEMPOs) by nucleophilic acyl substitution of acyl halides and acid anhydrides with TEMPO$^-$M$^+$ (the TEMPO anion),[1] trapping of acyl radicals with TEMPO$^{\cdot}$,[2] and addition reaction of TEMPO$^{\cdot}$ to ketenes,[3] little is known about their properties and reactivity towards nucleophiles in spite of their carboxylic acid derivative-like structure. Only the thermal stability of *O*-triphenylacetyl TEMPO[4] and alkaline hydrolysis of a formyl derivative[1] were, to the best of our knowledge, reported. In our preceding paper,[5] we reported the reaction of **1** with DIBAL-H (2–3 equiv.), giving the corresponding aldehydes, the high selectivity of which was rationalized by stabilization of the hydride adduct by chelation with the 2,2,6,6-tetramethylpiperidinyl function in close resemblance to the case of the Weinreb amide.[6]

O-acylTEMPO, **1**   Weinreb amide
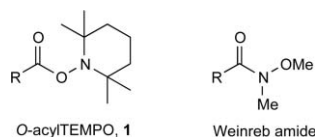
Incidentally, we encountered unprecedented stability of **1** towards LiAlH$_4$ (LAH), a highly powerful reagent towards ordinary carboxylic acid derivatives, including Weinreb amides. In this communication, we unveil the reactivity of **1** towards hydride-transferring or metallic alkylating reagents and examine chemoselective transformations,[7] where an *O*-acylTEMPO group is utilized as an inert function to LAH.[8]

We first examined the LAH reduction (2 equiv.) of aromatic **1a** (R = 4-MeOC$_6$H$_4$), allylic **1b** (R = C$_6$H$_5$CH=CH), and aliphatic **1c** (R = *c*-C$_6$H$_{11}$) *O*-acylTEMPOs under varying reaction temperatures. Although the DIBAL-H reduction (3 equiv.) of **1a–c** smoothly proceeded even at –78 to –50 °C, giving the corresponding aldehydes **2a–c** in 83–92% yields (Scheme 1), the reduction of these *O*-acylTEMPOs **1a–c** with the more powerful LAH at the same temperature resulted in a complete recovery of the starting materials.

Accordingly, the reduction of **1a** with LAH was examined by increasing the temperature from −78 °C to room temperature and it turned out that compound **1a** was quite inert at less than −25 °C. The reductions slowly proceeded at 0 °C, and substantial conversion was only achieved by raising to room temperature (*ca.* 20–30 °C) to give the corresponding carbinol **3a** in 95% yield, which was complementary to the aldehyde synthesis by DIBAL-H reduction. A 1:1 LAH–*N*-methylpyrrolidine complex[9] was also effective at room temperature for the reduction of **1a**, giving **3a** (80% yield). Similarly, the *O*-acylTEMPOs **1b** and **1c** were reduced with LAH at about 0 °C, giving **2b** and **2c** in 40 and 69% yields, respectively.

Other reducing reagents such as NaBH$_4$, LiBH$_4$, NaAlH$_2$(OCH$_2$CH$_2$OMe)$_2$ were of no use for the reduction of **1a** at room temperature, and the starting **1a** was unchanged. Furthermore, the reaction of **1a** with PhMgBr at room temperature resulted in recovery of the starting **1a**.

We postulated that the low reactivity of **1** to an ate complex like LAH at low temperature is ascribable to the donating nature of the nitrogen atom of the tetramethylpiperidinyl moiety which is linked with carboxyl oxygen.[10] It is conceived that the ate complex comprised of two different kinds of Lewis acid metals would form specific coordination with the molecule bearing two Lewis base sites.[11] This is the case for the reaction of **1** with LAH. Thus, as shown in Scheme 2, the aluminium of LAH may be fixed with the nitrogen and the Li cation would be coordinated by the nearby carbonyl oxygen to form a highly rigid chelated architecture such as structure **A**.[12] The fixed structure **A** is considered to be unable to deliver a hydride to the carbonyl carbon if kept at low temperature. On the other hand, the reaction of **1** with DIBAL-H would first lead to nitrogen-coordinated structure **B**,[13] which
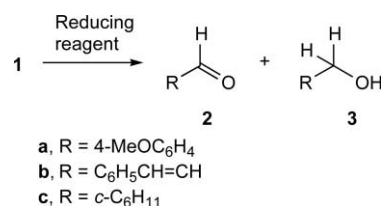
a, R = 4-MeOC$_6$H$_4$
b, R = C$_6$H$_5$CH=CH
**c**, R = *c*-C$_6$H$_{11}$
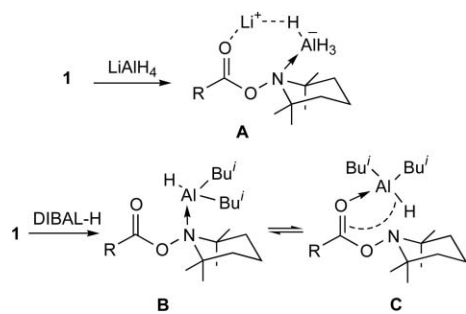
Scheme 1

Scheme 2

will be in equilibrium with carbonyl oxygen-coordinated structure **C**, in which the two electron-donated aluminium reagents would transfer a hydride to the carbonyl carbon even at low temperature, leading to aldehyde.

We applied this stability of *O*-acylTEMPOs towards LAH or RMgX to the chemoselective transformation of the ester function in the presence of *O*-acylTEMPOs. As shown in Table 1, entry 1, the treatment of ethyl/2,2,6,6-tetramethylpiperidine-1-yl adipate **4**, derived from adipic acid half-ester by chlorination of the carboxylic acid followed by nucleophilic acyl substitution with the TEMPO anion, with LAH afforded the corresponding carbinol **7a** (98% yield), the *O*-acylTEMPO moiety being unaffected. Furthermore, compound **4** was selectively alkylated at the alkyl ester site, giving the corresponding tertiary carbinols **7** (**b**, R = Ph, 83%; **c**, R = Me 54% (61% conversion); **d**, R = allyl 68%; **e**, PhCC, 45% (54% conversion)) on treatment with the respective alkylmetallic reagents such as PhMgBr, MeLi, allylMgBr and acetylenic PhCCMgBr (entries 2–5).‡ A similar trend in reactivity towards LAH and RMgX was found with derivatives of the glutarate (**5**) (entries 6 and 7) and the succinate (**6**) (entry 8). The carbinol **7b** obtained as above was easily converted into the corresponding carboxylic acid upon treatment with NaOH in MeOH–H₂O.

Having succeeded in the selective reduction and alkylation of linear alkanedioic acids mixed esters **4–6**, we next examined a more congested nonlinear 1,2-diacid mixed ester in order to ascertain the
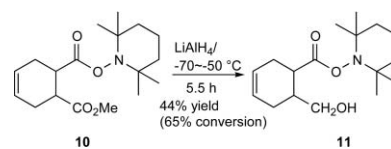
Scheme 3

applicability of the present reaction. The reduction of **10**, prepared from 4-cyclohexene-1,2-dicarboxylic anhydride by consecutive treatment with the TEMPO anion and MeI in THF–DMF, with LAH at −70 to −50 °C for 5.5 h afforded the corresponding carbinol **11** in 44% yield (65% conversion, Scheme 3). The run at higher temperature than this led to reduction of two carbonyl functions of **10**, giving the corresponding diol. It is likely that reduction of the mixed ester is affected with the TEMPO substitution in the vicinity, but details are not clear at present.

In summary, the *O*-acylTEMPOs **1** were quite stable to hydride-transferring or metallic alkylating reagents, in contrast to Weinreb amide, and can be employed as an inert ester towards these reagents in the chemoselective transformation of diacid mixed alkyl/TEMP-1-yl esters to the corresponding carbinols. After the nucleophilic additions, the *O*-acylTEMPOs were converted to the corresponding carboxylic acids by hydrolysis.

Tsutomu Inokuchi,[*a] **Hiroyuki Kawafuchi**[b] **and Junzo Nokami**[c]
[a]*Department of Bioscience and Biotechnology, Faculty of Engineering, Okayama University, Tsushima-naka, Okayama, 700-8530, Japan. E-mail: inokuchi@cc.okayama-u.ac.jp; Fax: (+81) 86 251 8021; Tel: (+81) 86 251 8210*
[b]*Department of Chemical and Biochemical Engineerings, Toyama National College of Technology, Hongo-machi, Toyama, 939-8630, Japan. E-mail: kawafuti@toyama-nct.ac.jp*
[c]*Department of Applied Chemistry, Faculty of Engineering, Okayama*

Table 1 Chemoselective reductions and alkylations[a]

4, n = 3, Y = Et **7**, n = 3
5, n = 2, Y = Me **8**, n = 2
6, n = 1, Y = Me **9**, n = 1

Entry	Substrate	Reagent (equiv.)/conditions	Product	R	Yield[b] (%)
1	**4**	LiAlH₄ (2)/−30 to −35 °C, 1 h	**7a**	H	98 (100)
2	**4**	PhMgBr (3)/0 °C to RT, 2 h	**7b**	Ph	83 (100)
3	**4**	MeLi (2)/−30 to −40 °C, 2 h	**7c**	Me	54 (61)
4	**4**	allylMgBr (3)/RT, 2 h	**7d**	allyl	68 (100)[c]
5	**4**	PhCCMgBr (3)/70 °C, 3.5 h	**7e**	PhCC	45 (54)
6	**5**	LiAlH₄ (2)/−50 to −20 °C, 1 h	**8a**	H	75 (100)
7	**5**	PhMgBr (3)/0 °C to RT, 1 h	**8b**	Ph	62 (86)
8	**6**	MeMgBr (4.5)/0 °C, 4 h	**9a**	Me	58 (100)

[a] The reactions were carried out by using **4–6** (0.32 mmol) in THF (2 cm³) under N₂. [b] Yields are based on isolated products and the value in the parentheses is the conversion (%) of **4–6**. [c] Diol due to double bisallylation was found in 27% yield.

University of Science, Ridai-cho, Okayama, 700-0005, Japan.
E-mail: nogami@dac.ous.ac.jp

Notes and references

‡ *Experimental*: **LiAlH₄ reduction of 1a**. To a solution of **1a** (100 mg, 0.34 mmol) in THF (2 cm³) was added LiAlH₄ (80%, 39 mg, 0.82 mmol) at room temperature under N₂ and the mixture was stirred for 1 h, quenched with cold sat. NH₄Cl, and worked up in the usual manner to give 45 mg (95%) of **3a** after column chromatography (SiO₂, hexane–AcOEt 10:1 and 5:1). **Grignard reaction of 4**. To a solution of **4** (100 mg, 0.32 mmol) in THF (2 cm³) was added dropwise PhMgBr (1.0 M in THF, 0.96 cm³, 0.96 mmol) at 0 °C under N₂ and the mixture was stirred at room temperature for 2 h, quenched with cold sat. NH₄Cl. Usual workup and purification by column chromatography (SiO₂, hexane–AcOEt 10:1 and 5:1) gave 112 mg (83%) of **7b** (R = Ph).[14]

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14 **3a**: IR (Neat) 3367, 3003, 2935, 2837, 1612, 1585, 1514, 1464, 1302, 1248, 1174, 1111, 1034, 818, 754, 708 cm⁻¹; ¹H NMR (400 MHz): δ 2.27, (br s, 1H, OH), 3.78 (s, 3H), 4.56 (s, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (100 MHz): δ 55.2, 64.8, 113.7 (2C), 128.4 (2C), 132.9, 158.8. **7b**: mp 111–112 °C; IR (KBr) 3462, 3057, 2939, 2870, 1753, 1599, 1493, 1448, 1363, 1263, 1132, 1063, 972, 937, 872, 752, 700 cm⁻¹; ¹H NMR (400 MHz): δ 0.94, 1.06 (s, 12H), 1.20–1.70 (m, 10H), 2.10, (br s, 1H), 2.22–2.28 (m, 4H), 7.13–7.17 (m, 2H), 7.22–7.25 (m, 4H), 7.31–7.36 (m, 4H); ¹³C NMR (100 MHz): δ 17.1, 20.6 (2C), 23.8, 25.7, 32.0 (2C), 33.1, 39.0 (2C), 41.7, 59.9 (2C), 78.1, 125.8 (4C), 126.6 (2C), 128.0 (4C), 146.7 (2C), 172.8. HRMS (EI) calc. for C₂₇H₃₇NO₃: *m/z* 423.2773; found: 423.2766.