

CHEMOSELECTIVE METHYLENATION WITH A METHYLENEDIANION SYNTHON

Takashi Okazoe, Jun-ichi Hibino, Kazuhiko Takai,* and Hitosi Nozaki¹
 Department of Industrial Chemistry, Faculty of Engineering,
 Kyoto University, Yoshida, Kyoto 606, Japan

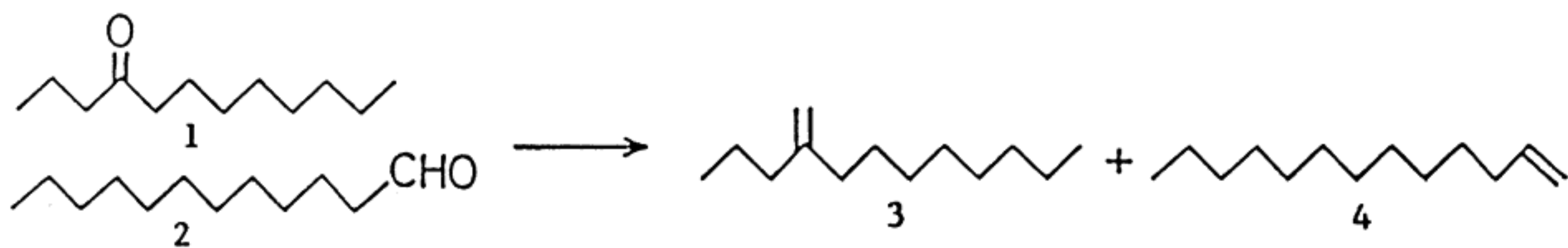
Summary: The combination of $\text{CH}_2\text{I}_2\text{-Zn-Ti}(\text{O}^i\text{Pr})_4$ or $\text{CH}_2\text{I}_2\text{-Zn-Me}_3\text{Al}$ is effective for the selective methylenation of aldehydes. Selective methylenation of a ketone group is performed by pretreatment of a substrate with $\text{Ti}(\text{NEt}_2)_4$.

Chemoselectivity (referring to functional group differentiation)² presents a major challenge in organic synthesis. Organochromium³ and -titanium⁴ compounds have been found to be useful in the chemoselective carbonyl additions. We report here aldehyde⁻⁵ and ketone-selective methylenation methods using gem-dimetallated carbodianion reagent^{6,7} derived from zinc reduction of diiodomethane in the presence of Lewis acid.

Yields of the products obtained by methylenation of dodecanal and 4-dodecanone with several reagents are summarized in Table 1. The aldehyde:ketone selectivity of the Wittig reagent⁸ was not high in our hands (run 1). The methylenedianion synthon produced from CH_2Br_2 , Zn, and TiCl_4 ⁶ affords a considerable amount of the pinacol-type diol and the yield of 1-tridecene was 10% (run 2). The $\text{CH}_2\text{I}_2\text{-Zn-TiCl}_4$ system⁹ was too reactive to give selectivity (run 3). In contrast, the combination of $\text{CH}_2\text{I}_2\text{-Zn-Ti}(\text{O}^i\text{Pr})_4$ (method A) or $\text{CH}_2\text{I}_2\text{-Zn-Me}_3\text{Al}$ ⁶ was found to be highly effective for the aldehyde-selective methylenation (runs 4 and 5).^{10,11}

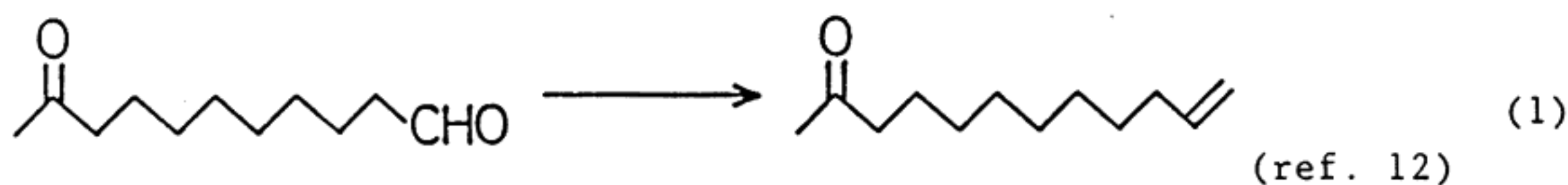
Treatment of 10-oxoundecanal with the $\text{Ti}(\text{O}^i\text{Pr})_4$ or Me_3Al system afforded exclusively 11-dodecen-2-one¹² arising from selective methylenation of the aldehyde moiety (Eq. 1). An aromatic keto aldehyde, 4-acetylbenzaldehyde, was also converted to the corresponding keto olefin in good yields with these two methods (Eq. 2).

On the other hand, selective methylenation of a ketone group was performed using the Reetz's method.¹³ The aldehyde group was protected in situ with $\text{Ti}(\text{NEt}_2)_4$ in dichloromethane. Treatment of a mixture of 4-dodecanone and the protected dodecanal with $\text{CH}_2\text{I}_2\text{-Zn-TiCl}_4$ system⁹ at 25°C

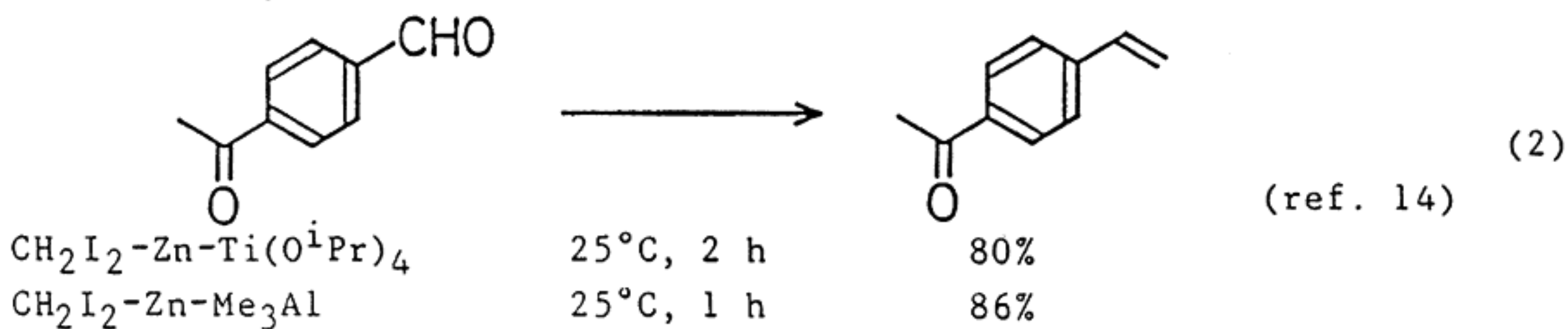
Table 1. Methylenation of a mixture of dodecanal and 4-dodecanone.^a

Run	Reagents (equiv)	Temp (°C)	Time (h)	Yields ^b (%)			
				3 (recov. 1)		4 (recov. 2)	
1	Ph ₃ P=CH ₂ (1.0)	0	0.5	12	(88)	64	(19)
2	CH ₂ Br ₂ -Zn-TiCl ₄ ^c (1.5, 4.5, 1.1)	25	2	17	(71)	10	(2) ^d
3	CH ₂ I ₂ -Zn-TiCl ₄ (5.0, 9.0, 1.0)	25	0.5	53	(25)	78	(0)
4	CH ₂ I ₂ -Zn-Ti(O ⁱ Pr) ₄ (5.0, 9.0, 1.0)	25	5	0	(97)	86	(6)
5	CH ₂ I ₂ -Zn-Me ₃ Al (3.0, 9.0, 0.6)	25	2	0	(100)	89	(6)
6	Ti(NEt ₂) ₄ , CH ₂ I ₂ -Zn-TiCl ₄ (1.1) (5.0, 9.0, 1.0)	25	0.5	95	(0)	0	(95)

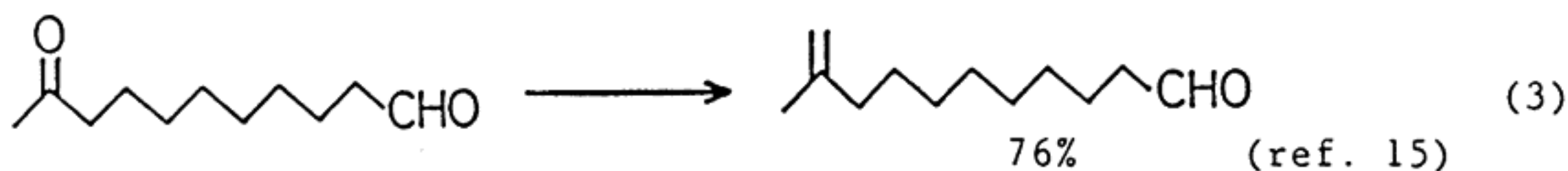
a) A mixture of dodecanal (1.0 mmol) and 4-dodecanone (1.0 mmol) was treated with a reagent in THF. b) GLPC yield (Silicone OV-17, 105°C). c) ref. 6. d) Pinacol-type dimer of dodecanal was produced as a main product (42%).



CH₂I₂-Zn-Ti(OⁱPr)₄ 25°C, 3 h 83%
 CH₂I₂-Zn-Me₃Al 25°C, 4 h 96%



CH₂I₂-Zn-Ti(OⁱPr)₄ 25°C, 2 h 80%
 CH₂I₂-Zn-Me₃Al 25°C, 1 h 86%



1. Ti(NEt₂)₄/CH₂Cl₂ 2. CH₂I₂-Zn-TiCl₄/THF, 25°C, 0.5 h 3. H₃O⁺

for 30 min gave 95% of 2-propyl-1-decene and the unchanged dodecanal (95%) after workup (Method B, run 6). Ketone-selective methylenation of 10-oxoundecanal with Method B is shown in Eq 3.

Aldehyde-selective methylenation (method A): To a stirring suspension of zinc (0.60 g, 9.0 mmol) in THF (10 ml) is added CH_2I_2 (0.40 ml, 5.0 mmol) at 25°C under an argon atmosphere. After 30 min, a THF solution of $\text{Ti}(\text{O}^i\text{Pr})_4$ (1.0 M, 1.0 mL) is added and the resulting mixture is stirred at 25°C for 30 min. A solution of 10-oxoundecanal (0.18 g, 1.0 mmol) in THF (8 mL) is then added. After being stirred for 3 h, the mixture is diluted with hexane (15 mL), poured into 1 N HCl (30 mL), and extracted with hexane (3 x 20 mL). The organic extracts are washed with brine (20 mL), dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (hexane-ethyl acetate, 5:1) gives 0.15 g of 11-decen-2-one¹² (83%).

Ketone-selective methylenation (method B): A solution of 10-oxoundecanal (0.18 g, 1.0 mmol) in THF (8 mL) is treated at 25°C with a CH_2Cl_2 solution of $\text{Ti}(\text{NEt}_2)_4$ (1.0 M, 1.1 mL) for 30 min under an argon atmosphere.¹³ The resulting orange solution is added to a stirring suspension of the reagent⁹ prepared from CH_2I_2 (0.40 mL, 5.0 mmol), zinc (0.60 g, 9.0 mmol), and TiCl_4 (1.0 M of a CH_2Cl_2 solution, 1.0 mL) in THF (10 mL). After being stirred at 25°C for 30 min, the mixture is diluted with hexane (15 mL), poured into 1 N HCl (30 mL), and extracted with hexane (3 x 20 mL). The separated organic layer is washed with brine (20 mL), dried over Na_2SO_4 , and concentrated. Purification of the crude product by chromatography on an alumina column (hexane-ethyl acetate, 5:1) provides 0.14 g of 10-methyl-10-undecenal¹⁵ (76%).

References and Notes

- 1) Present address: Okayama University of Science, Ridai-cho, Okayama 700, Japan.
- 2) B. M. Trost, Chem. Br., 1984, 315.
- 3) (a) T. Hiyama, Y. Okude, K. Kimura, and H. Nozaki, Bull. Chem. Soc. Jpn., 55, 561 (1982). (b) K. Takai, K. Kimura, T. Kuroda, T. Hiyama, and H. Nozaki, Tetrahedron Lett., 24, 5281 (1983).
- 4) (a) M. T. Reetz, Top. Curr. Chem., 106, 1 (1982). (b) D. Seebach, "Modern Synthetic Methods," vol. 3, ed by R. Scheffold, Salle+Sauerlaender, Aarau and John Wiley and Sons, New York, 1983, p. 217.

- 5) Peterson-type carbonyl methylenation using Ti(II) or Cr(III) as the counter ion was reported to have aldehyde-selectivity. See, T. Kauffmann, R. Koenig, C. Pahde, A. Tannert, Tetrahedron Lett., **22**, 5031 (1981).
- 6) K. Takai, Y. Hotta, K. Oshima, and H. Nozaki, Bull. Chem. Soc. Jpn., **53**, 1698 (1980); idem, Tetrahedron Lett., 1978, 2417.
- 7) (a) F. Bertini, P. Graselli, G. Zucchini, and G. Cainelli, Tetrahedron, **26**, 1281 (1970); G. Cainelli, F. Bertini, P. Grasselli, and G. Zucchini, Tetrahedron Lett., 1967, 5153. (b) G. Zweifel and H. Arzoumanian, ibid., 1966, 2535. (c) F. N. Tebbe, G. W. Parshall, G. S. Reddy, J. Am. Chem. Soc., **100**, 3611 (1978); S. H. Pine, R. Zahler, D. A. Evans, and R. H. Grubbs, ibid., **102**, 3270 (1980). (d) F. W. Hartner, Jr., J. Schwartz, and S. M. Clift, ibid., **105**, 640 (1983).
- 8) A. Maercker, Org. React., **14**, 270 (1965)
- 9) J. Hibino, T. Okazoe, K. Takai, and H. Nozaki, see the previous paper.
- 10) The reagent derived from an excess amount of Zn and CH₂I₂ was reported to show a similar aldehyde selectivity.¹¹ However, addition of the Lewis acid such as Me₃Al or Ti(OⁱPr)₄ gave better yields and reproducibility. For instance, treatment of cinnamaldehyde with the CH₂I₂-Zn-Ti(OⁱPr)₄ reagent in THF at 25°C for 45 min gave 1-phenyl-1,3-butadiene in 74% yield, while the reported yield of the same reaction without Ti(OⁱPr)₄ is 29%.¹¹
- 11) H. Hashimoto, M. Hida, S. Miyano, J. Organomet. Chem., **10**, 518 (1967).
- 12) Bp 95°C (bath temp, 4 Torr); IR (neat): 3076, 2926, 2852, 1717, 1640, 1358, 993, 909 cm⁻¹; NMR (CCl₄): δ1.15-1.68 (m, 12H), 2.00 (s, 3H), 1.76-2.17 (m, 2H), 2.31 (t, J=7 Hz, 2H), 4.88 (d, J=11 Hz, 1H), 4.93 (d, J=18 Hz, 1H), 5.75 (ddt, J=11,18,7 Hz, 1H).
- 13) M. T. Reetz, B. Wenderoth, and R. Peter, J. Chem. Soc., Chem. Commun., **1983**, 406 and references cited therein.
- 14) Bp 99°C (bath temp, 7 Torr); IR (neat): 1679, 1604, 1402, 1357, 1267, 844 cm⁻¹; NMR (CCl₄): δ2.50 (s, 3H), 5.34 (d, J=11 Hz, 1H), 5.82 (d, J=18 Hz, 1H), 6.75 (dd, J=10,18 Hz, 1H), 7.33-8.00 (m, 4H).
- 15) Bp 85°C (bath temp, 2 Torr); IR (neat): 3072, 2928, 2854, 2712, 1727, 1648, 1458, 885 cm⁻¹; NMR (CCl₄): δ1.16-1.75 (m, 12H), 1.67 (s, 3H), 1.81-2.07 (m, 2H), 2.33 (dt, J=1,7 Hz, 2H), 4.63 (s, 2H), 9.75 (t, J=1 Hz, 1H).