JOC Note

Transition-Metal-Catalyzed Chemoselective Methylenation of Dicarbonyl Substrates

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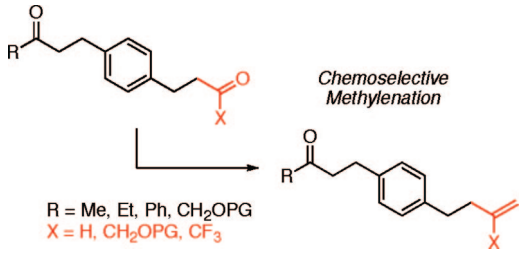
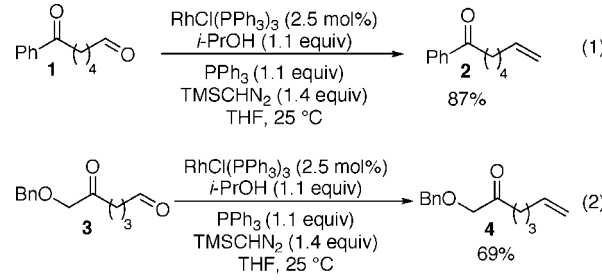


Rhodium- and copper-catalyzed methylenation reactions with trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol were used to react chemoselectively with aldehydes, alkoxymethylketones, and trifluoromethylketones in substrates also containing a less reactive carbonyl group. Terminal alkenes were obtained in high yields, and no protecting group was necessary in the methylenation process.

Nucleophilic additions to carbonyl compounds typically follow the reactivity order of aldehydes > ketones > esters ≫amides ≫ carboxylic acids.[1] Such an order can be perturbed by coordination of the carbonyl group with a Lewis acid.[2] A number of scattered examples of chemoselective olefination reactions with carbonyl compounds have been previously published,[3] whereas only a few systematic studies were reported. Among them, the chemoselectivity of the methylenation reaction using the Oshima−Lombardo reagent has been extensively studied.[4] Indeed ketoaldehyde substrates produced both monoalkenes resulting from the methylenation of either the aldehyde or the ketone moiety. Despite significant advantages, several drawbacks remain associated with such a reaction, including the use of stoichiometric amount of expensive and/or toxic metals. We have recently disclosed a novel transition-metal-catalyzed methylenation reaction of carbonyl compounds using trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol.[5,6] Mechanistic studies revealed that methylenetriphenylphosphorane was the active species; [7] this completely salt-free ylide reacted with high chemoselectivity.[5e] However, no systematic investigation has been published so far for the chemoselectivity of the methylenation reaction using a phosphorus ylide reagent. In this paper, we describe the use of bis-hydrocinnamate derivatives as a conserved backbone to thoroughly study the reactivity of ketones and aldehydes under various methylenation reaction conditions using methylenetriphenylphosphorane.

We have previously reported that the rhodium-catalyzed methylenation with trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol of ketoaldehyde substrates **1** and **3** produced exclusively the corresponding monoalkene (**2** and **4**, respectively) resulting from the aldehyde methylenation (eqs 1 and 2).[5e] Conversely, when methylenetriphenylphosphorane was generated from methyltriphenylphosphonium bromide and sodium hexamethyldisilazide, 15−30% of the corresponding diene was observed leading to lower yields for the desired product.



To further investigate the chemoselectivity of the methylenation reaction, we have prepared a series of bis-hydrocinnamate derivatives containing various carbonyl groups. Such substrates (**7**−**13**) display a conserved backbone, and thus each

(1) Saito, S.; Yamamoto, H. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 33−67.

(2) (a) Asao, N.; Asano, T.; Yamamoto, Y. *Angew Chem., Int. Ed.* **2001**, *40*, 3206–3208, and references therein. (b) Yamamoto, H.; Maruoka, K.; Araki, Y. *Tetrahedron Lett.* **1988**, *29*, 3101–3104.

(3) Selected examples: (a) Olpp, T.; Bruckner, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 4023–4027. (b) Trost, B. M.; Dirat, O.; Gunzner, J. L. *Angew. Chem., Int. Ed.* **2002**, *41*, 841–843. (c) Mergott, D. J.; Frank, S. A.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3157–3160. (d) Kahnberg, P.; Lee, C. W.; Grubbs, R. H.; Sterner, O. *Tetrahedron* **2002**, *58*, 5203–5208. (e) Oesterreich, K.; Klein, I.; Spitzner, D. *Synlett* **2002**, 1712–1714. (f) Faure, S.; Piva, O. *Tetrahedron Lett.* **2001**, *42*, 255–259. (g) Kim, D.; Lee, J.; Chang, J.; Kim, S. *Tetrahedron* **2001**, *57*, 1247–1252. (h) Colombo, M. I.; Zinczuk, J.; Mischne, M. P.; Ruveda, E. A. *Tetrahedron: Asymmetry* **2001**, *12*, 1251–1253. (i) Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. *Bioorg. Med. Chem.* **1999**, *7*, 665–697. (j) Hsu, P.-Y.; Lee, Y.-C.; Liao, C.-C. *Tetrahedron Lett.* **1998**, *39*, 659–662. (k) Paquette, L. A.; Heidelbaugh, T. M. *Synthesis* **1998**, 495–508. (l) Evans, D. A.; Trotter, B. W.; Cote, B.; Coleman, P. J.; Dias, L. C.; Tyler, A. N. *Angew. Chem., Int. Ed.* **1997**, *36*, 2744–2747. (m) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977.

(4) (a) Matsubara, S.; Oshima, K.; Utimoto, K. *J. Organomet. Chem.* **2001**, *617*, 39–46. (b) Matsubara, S.; Mizuno, T.; Otake, Y.; Kobata, M.; Utimoto, K.; Takai, K. *Synlett* **1998**, 1369–1371. (c) Okazoe, T.; Hibino, J.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5581–5584.

(5) (a) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2887–2890. (b) Grasa, G. A.; Moore, Z.; Martin, K. L.; Stevens, E. D.; Nolan, S. P.; Paquet, V.; Lebel, H. *J. Organomet. Chem.* **2002**, *658*, 126–131. (c) Lebel, H.; Paquet, V. *Org. Lett.* **2002**, *4*, 1671–1674. (d) Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.* **2004**, *6*, 3047–3050. (e) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320–328. (f) Paquet, V.; Lebel, H. *Synthesis* **2005**, 1901–1905. (g) Lebel, H.; Davi, M.; Diez-Gonzalez, S.; Nolan, S. P. *J. Org. Chem.* **2007**, *72*, 144–149.

(6) For recent examples of application in total synthesis, see: (a) Kwon, M. S.; Woo, S. K.; Na, S. W.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 1733–1735. (b) Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1272–1275. (c) Lebel, H.; Parmentier, M. *Org. Lett.* **2007**, *9*, 3563–3566.

(7) Lebel, H.; Paquet, V. *Organometallics* **2004**, *23*, 1187–1190.

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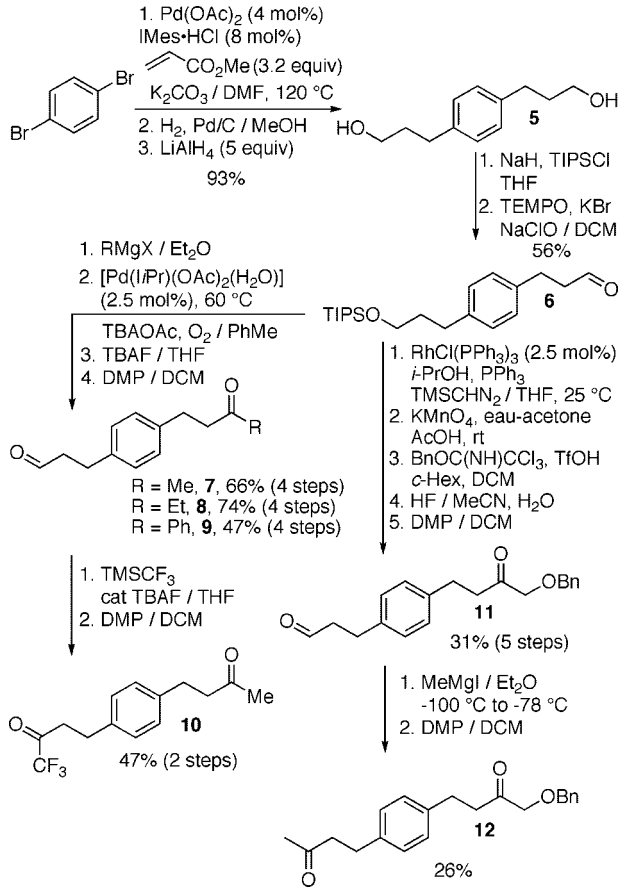
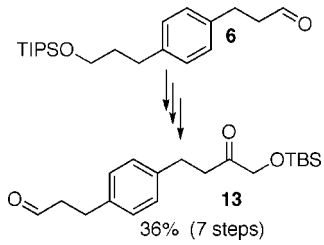
SCHEME 1. Preparation of Dicarbonyl Substrates



SCHEME 2. Preparation of Ketoaldehyde 13



carbonyl group has a similar steric environment. These substrates are prepared by desymmetrization of diol **5**, which is obtained in three steps from 1,4-dibromobenzene via a double Heck reaction, followed by a reduction (Scheme 1).

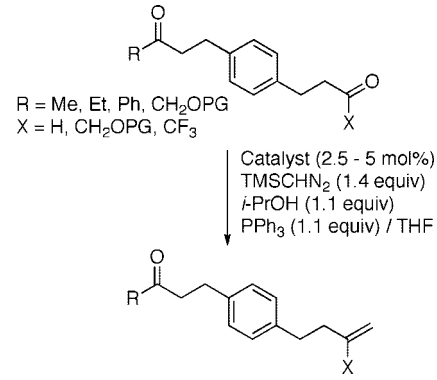
The functionalization of aldehyde **6** by Grignard addition, followed by oxidation, deprotection and oxidation produced ketoaldehydes substrates **7**−**9** in 47−74% overall yields.

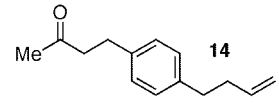
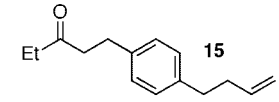
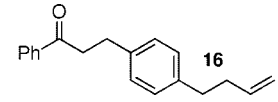
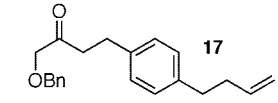
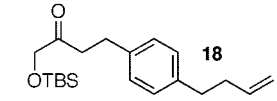
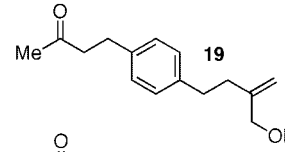
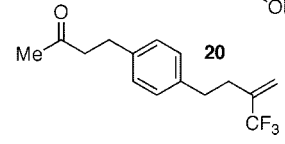
Trifluoromethylketone **10** was further elaborated from ketoaldehyde **7**. In addition, aldehyde **6** was derived to lead to ketoaldehyde **11** and diketone **12**. Similar chemical steps were used to prepare ketoaldehyde **13** from aldehyde **6** (Scheme 2), by exchange of protecting groups (see Supporting Information for details).

With these substrates in hand, both the copper- and the rhodium-catalyzed methylenation reactions were tested and compared to the reaction with methylenetriphenylphosphorane generated by deprotonation of methyltriphenylphosphonium bromide (Table 1).

In all cases, a high chemoselectivity was observed for the transition-metal-catalyzed methylenation reactions, as no diene

TABLE 1. Chemoselective Methylenation of Dicarbonyl Substrates



entry	product	yield (%)[a] CuCl[b]	$RhCl(PPh_3)_3$[c]	Ph_3PCH_3Br[d]
1	 **14**	75	85	77[e]
2	 **15**	80	80	62
3	 **16**	78	83	59[f]
4	 **17**	72	74	56[f]
5	 **18**	58	78	35[f]
6	 **19**	68	83	56
7	 **20**	84	79	93

[a] Isolated yields. [b] CuCl (5 mol%), 0.1 M in THF at 60 °C. [c] $RhCl(PPh_3)_3$ (2.5 mol%), 0.1 M in THF at 23 °C. [d] Ph_3PCH_3Br (1.1 equiv), NaHMDS (1.1 equiv), 0.1 M in THF at 23 °C. [e] Eight percent isolated yields of the diene. [f] Approximately 30% isolated yields of the diene.

was formed under these reaction conditions, using either copper chloride or Wilkinson's catalyst. The more expensive rhodium catalyst gave yields slightly higher than those using copper chloride, and the reaction was run at room temperature. A good chemoselectivity was also observed for the reaction of ketoaldehydes **7** and **8** with methylenetriphenylphosphorane generated by deprotonation of methyltriphenylphosphonium bromide to produce monoalkene **14** and **15** in 77% and 62% yields, respectively (entries 1 and 2). However, in the case of substrates containing an activated ketone, such as an aromatic ketone or an alkoxymethylketone, such reaction conditions led to a substantial amount of the corresponding diene. Conversely, only

the monoalkene product was isolated when the methylenetriphenylphosphorane was generated from trimethylsilyldiazomethane and triphenylphosphine. Methylenation reactions catalyzed by copper chloride produced monoalkene **16**−**18** in 58−72% yields, whereas 74−83% isolated yields were obtained with Wilkinson's catalyst (entries 3−5). In the case of diketone substrates containing an activated ketone, such as an alkoxymethylketone or a trifluoromethylketone, all reaction conditions provided exclusively the monoalkene product (entries 6 and 7).

The difference in the chemoselectivity of methylenetriphenylphosphorane generated from the transition metal decomposition of trimethylsilyldiazomethane versus the deprotonation of methyltriphenylphosphonium bromide is quite intriguing. In both cases the same ylide reagent has been identified as the reactive species, suggesting that the difference in reactivity is due to byproduct formed during the generation of the ylide. The only byproduct obtained when the methylenetriphenylphosphorane is generated from trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol is the highly volatile and inert 2-propyloxytrimethylsilane. In contrast, the deprotonation of methyltriphenylphosphonium bromide provides a bromide salt as byproduct, which can play a role as a Lewis acid catalyst. It has been previously shown that lithium salts can have a pronounced effect on *E*:*Z* ratio in Wittig olefination, whereas sodium and potassium salts had little effect.[8] However, in the cases of chemoselective methylenation reactions, it appears that not only are soluble lithium salts able to activate the more basic carbonyl moiety (presumably by Lewis acid type activation), but sodium and potassium salts can also alter chemoselectivities.[9] This is in contrast to the chemoselectivity afforded by completely salt-free methods of producing methylenetriphenylphosphorane.

In conclusion, this systematic study illustrates the power of copper- and rhodium-catalyzed methylenation with trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol in chemoselective reactions with dicarbonyl substrates. Although methylenetriphenylphosphorane is the active reagent in this process (as in the Wittig reaction through deprotonation of methyltriphenylphosphonium bromide), the absence of salts profoundly affected the chemical behavior of this reagent and thus led to highly chemoselective reactions with a variety of dicarbonyl substrates.

Experimental Section

Catalytic Methylenation using Wilkinson's Catalyst. To a solution of chlorotris(triphenylphosphine)rhodium (23 mg, 0.025 mmol) and triphenylphosphine (288 mg, 1.10 mmol) in THF (10 mL) was added 2-propanol (75.0 μL, 1.00 mmol) followed by the aldehyde (1.00 mmol). To the resulting red mixture was then added a solution of trimethylsilyldiazomethane in THF (0.82 mL, 1.40 mmol). Gas evolution was observed, and the resulting dark orange mixture was stirred at room temperature. After 2 h, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel.

Catalytic Methylenation using CuCl as Catalyst. To a solution of CuCl (5 mg, 0.05 mmol) and triphenylphosphine (288 mg, 1.10 mmol) in THF (10 mL (0.1 M)) at 25 °C, was added 2-propanol (84 μL, 1.1 mmol) followed by the aldehyde (1.00 mmol) and the trimethylsilyldiazomethane ether solution (0.82 mL, 1.40 mmol). The resulting mixture was then heated at 60 °C and stirred until the reaction showed completion by TLC analysis. Aqueous 3% H_2O_2 (10 mL) was added, and the organic layer was washed with ether (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude alkene was purified by flash chromatography on silica gel.

1-(Benzyloxy)-4-(4-(but-3-enyl)phenyl)butan-2-one (17). The title compound was prepared from 3-(4-(4-(benzyloxy)-3-oxobutyl)phenyl)propanal (**11**) (120 mg, 0.39 mmol) according to the general procedure using CuCl as catalyst (reaction time 16 h). The desired alkene **17** (86 mg, 72%) was obtained as a colorless oil after flash chromatography (2% EtOAc/hexanes). R_f 0.35 (10% EtOAc/hexanes). IR (neat) 2925, 2856, 1723, 1437, 1102, 913 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.30 (m, 5H), 7.09 (s, 4H), 5.85 (ddt, J = 17, 10, 7 Hz, 1H), 5.03 (d, J = 17 Hz, 1H), 4.97 (d, J = 10 Hz, 1H), 4.55 (s, 2H), 4.02 (s, 2H), 2.90−2.86 (m, 2H), 2.80−2.76 (m, 2H), 2.69−2.65 (m, 2H), 2.37−2.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 139.6, 138.1, 138.0, 137.0, 128.5, 128.4, 128.2, 127.9, 127.8, 114.8, 75.1, 73.3, 40.6, 35.4, 34.8, 28.8. HRMS (CI) calcd for $C_{21}H_{24}NaO_2$ $[M + Na]^+$ 331.1668, found 331.1679.

4-(4-(But-3-enyl)phenyl)-1-(*tert*-butyldimethylsilyloxy)-butan-2-one (18). The title compound was prepared from 3-(4-(4-(*tert*-butyldimethylsilyl)-3-oxobutyl)phenyl)propanal (**13**) (103 mg, 0.21 mmol) according to the general procedure using Wilkinson's catalyst (reaction time 2 h). The desired alkene **18** (80 mg, 78%) was obtained as a colorless oil after flash chromatography (2% EtOAc/hexanes). R_f 0.40 (10% EtOAc/hexanes). IR (neat) 2929, 2856, 1718, 1252, 1154, 1101, 845, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 4H), 5.86 (ddt, J = 17, 10, 7 Hz, 1H), 5.04 (d, J = 17 Hz, 1H), 4.98 (d, J = 10 Hz, 1H), 4.14 (s, 2H), 2.92−2.78 (m, 4H), 2.70−2.65 (m, 2H), 2.39−2.32 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 139.5, 138.3, 138.1, 128.4, 128.2, 114.8, 69.4, 39.8, 35.5, 34.9, 28.8, 25.7, 18.2, −5.5. HRMS (CI) calcd for $C_{19}H_{31}O_3Si$ $[M + H]^+$ 357.1856, found 357.1854.

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Supporting Information Available: Experimental procedures and characterization data and spectra (^{1}H and ^{13}C NMR) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Reitz, A. B.; Nortey, S. O.; Jordan, A. D., Jr.; Mutter, M. S.; Maryanoff, B. E. *J. Org. Chem.* **1986**, *51*, 3302–3308.

(9) See Table S1 in Supporting Information for the methylenation reaction of ketoaldehyde **11** using various bases to generate the phosphorous ylide from methyltriphenylphosphonium bromide.