One-Pot Synthesis of Unsymmetrical Ketones by the Reaction of Decacarbonyldimanganese with Two Kinds of Alkyllithiums

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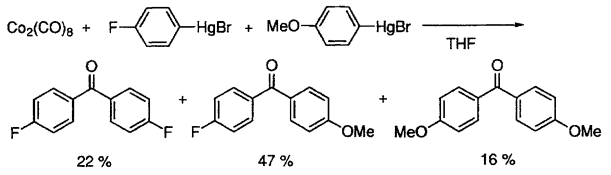
Decacarbonyldimanganese ($Mn_2(CO)_{10}$) is utilized as a phosgene equivalent for the one-pot preparation of unsymmetrical ketones. By a successive treatment of $Mn_2(CO)_{10}$ with two kinds of alkyllithiums, unsymmetrical ketones are obtained in high selectivity. Unsymmetrical α-diketones are generated when the above reaction is carried out in the presence of trimethyl phosphite and is quenched with *N*-bromosuccinimide.

The utility of metal carbonyl compounds as ketone precursors has been well-recognized. In particular, the use of metal carbonyl compounds as acyl anion or formyl dianion equivalents is well established, including the Collman reagent.[1] Although some metal carbonyl compounds are also known to act as phosgene equivalents, they are scarcely utilized for ketone synthesis, because only symmetrical ketones can be prepared effectively. For example, when octacarbonyldicobalt ($Co_2(CO)_8$) reacts with two kinds of arylmercury compounds, all three possible ketones are obtained in a statistical distribution (Eq. 1).[2]

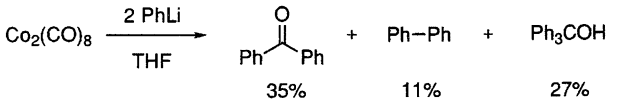


(1)

In this paper we describe the selective preparation of unsymmetrical ketones and α-diketones by the reaction of decacarbonyldimanganese ($Mn_2(CO)_{10}$) with two kinds of alkyllithiums.

Results and Discussion

It has still been challenging to prepare unsymmetrical ketones from two different nucleophiles with phosgene or their analogues. The use of a metal carbonyl compound as a phosgene equivalent is very fascinating to develop such a one-pot preparation of unsymmetrical ketones, because the intermediate acylmetal complex (or Fischer-type carbene complex) is expected to show a different reactivity compared to the starting metal carbonyl compound. Although $Co_2(CO)_8$ is known to act as a phosgene equivalent, three possible ketones were produced even in a reaction with organomercury compounds, as shown in Eq. 1.[2] We attempted the reaction of $Co_2(CO)_8$ with two molar amounts of phenyllithium; unexpectedly, the desired benzophenone was obtained in only 35% yield, and considerable amounts of biphenyl and triphenylmethanol were also formed (Eq. 2).



(2)

To find a suitable metal carbonyl compound as a phosgene equivalent, some representative metal carbonyl compounds were treated with two molar amounts of phenyllithium. As shown in Table 1, when $Mn_2(CO)_{10}$ was treated with two molar amounts of phenyllithium, benzophenone was obtained in 70% yield, and the side-products, such as biphenyl and triphenylmethanol, were detected in less than 1% yield. Furthermore, the addition of hexamethylphosphoric triamide (HMPA) enhanced the yield of benzophenone to 84%.

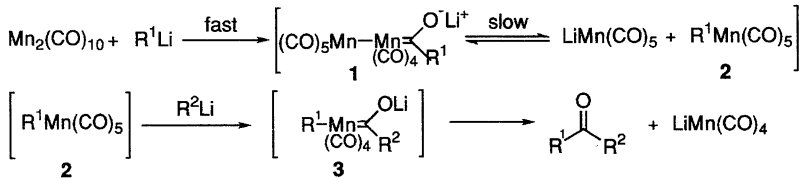
Next, a one-pot preparation of unsymmetrical ketones was attempted by the reaction of $Mn_2(CO)_{10}$ with two kinds of alkyllithiums. $Mn_2(CO)_{10}$ in THF was treated with an equimolar amount of phenyllithium at -78 °C. After stirring for 5 min, equimolar amount of butyllithium and HMPA were added successively. The reaction was quenched with pH 7 buffer to afford valerophenone in 73% yield; symmetrical ketones, benzophenone and dibutyl ketone, were detected in less than 1% yield by a gas-chromatographic analysis. Other examples of unsymmetrical ketone syntheses were examined, and the results are listed in Table 2. Except for the reaction with *t*-BuLi (Entry 3), unsymmetrical ketones were obtained in moderate yield. In addition, as shown in Entries 1 and 4, it is noteworthy that the preparation of valerophenone was not disturbed by the reverse addition of the corresponding lithium reagents.

This reaction is considered to proceed as shown in Scheme 1. It is known that alkyllithium (R^1Li) reacts with $Mn_2(CO)_{10}$ to afford an anionic Fischer-type dimanganese carbene complex **1**.[3] As reported by Casey and Anderson, a mixture of $NaMn(CO)_5$ and $MeMn(CO)_5$ exists in equilibrium with the sodium salt of **1**; the addition of trimethyl-

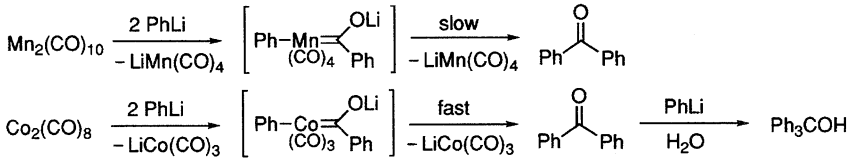
Table 1. Reaction of Metal Carbonyl with 2 Molar Amounts of PhLi

Metal Carbonyl $\xrightarrow[\text{THF, } -78\ ^\circ\text{C}]{\text{2.0 PhLi, additive}}$ Product(s)

Metal carbonyl	Additive	Product(s) (Yield/%)					
$Co_2(CO)_8$	None		(35)	Ph–Ph	(11)	Ph_3COH	(27)
$Fe_2(CO)_9$	None		(21)	Ph–Ph	(15)	Ph_3COH	(10)
$Mn(CO)_5Br$	None		(40)	Ph–Ph	(<1)		
$Mn_2(CO)_{10}$	None		(70)	Ph–Ph	(<1)		
$Mn_2(CO)_{10}$	HMPA		(84)	Ph–Ph	(<1)		



Scheme 1.



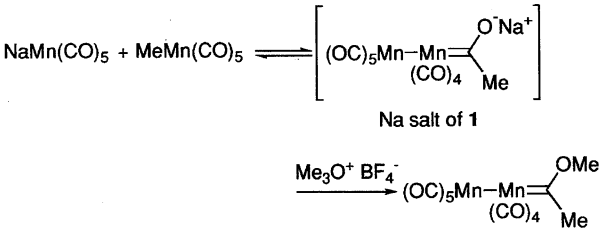
Scheme 2.

Table 2. One-Pot Preparation of Unsymmetrical Ketones

$Mn_2(CO)_{10}$ $\xrightarrow[\text{THF, } -78\ ^\circ\text{C}]{\text{1) } R^1\text{Li 2) } R^2\text{Li 3) HMPA}}$ R^1(C=O)R^2

Entry	R^1	R^2	Yield/%
1	Ph	*n*-Bu	73
2	Ph	*s*-Bu	76
3	Ph	*t*-Bu	13
4	*n*-Bu	Ph	62
5	*n*-Bu	Me	44

oxonium fluoroborate resulted in the formation of a Fischer-type dimanganese carbene complex (Eq. 3).[4] Accordingly, an equilibrium also exists between the lithium salt of the Fischer-type dimanganese carbene complex **1** and the mixture of $LiMn(CO)_5$ and $R^1Mn(CO)_5$ (**2**).

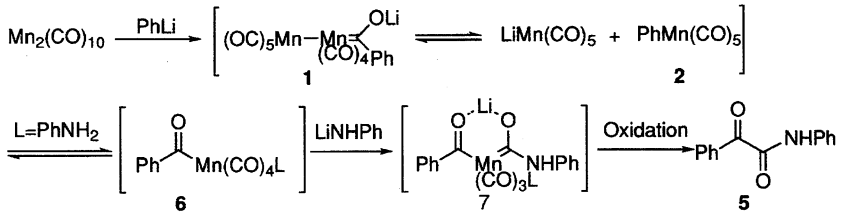


Na salt of **1**

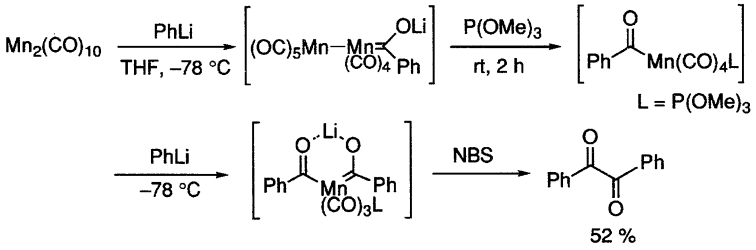
(3)

The resulting alkylmanganese complex **2** reacts with another alkyllithium (R^2Li), giving an anionic Fischer-type monomanganese carbene complex **3**, which is known to fragment into $LiMn(CO)_4$ and a ketone (Scheme 1).[5] Selective unsymmetrical ketone formation might depend on the character of these manganese complexes, described as follows. The reaction of R^1Li with $Mn_2(CO)_{10}$ proceeds quantitatively and much faster than does the fragmentation reaction of the dimanganese carbene complex **1**. R^1Li is, thus, completely consumed before the formation of $R^1Mn(CO)_5$, **2**. This prevents symmetrical ketone formation.

Furthermore, the absence of triphenylmethanol and biphenyl formation in the reaction of $Mn_2(CO)_{10}$ and phenyllithium explains the stability of monomanganese carbene complex **3**. Triphenylmethanol is presumably produced by the reaction of benzophenone with PhLi. In a reaction using $Mn_2(CO)_{10}$, the decomposition of monomanganese carbene complex **3** to benzophenone proceeds more slowly than does the reaction of the carbene complex formation between PhLi and $PhMn(CO)_5$. The added PhLi is thus consumed before the formation of benzophenone. In the reaction using other metal carbonyls, such as $Co_2(CO)_8$, the rate of decomposition of the corresponding carbene complex is relatively fast, so that the resulting ketone further reacts with PhLi, producing triphenylmethanol (Scheme 2).

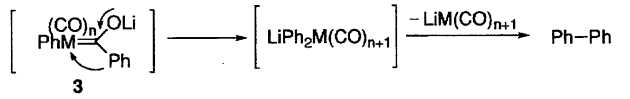


Scheme 3.



Scheme 4.

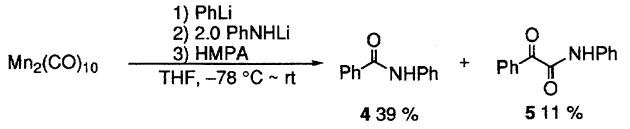
The formation of biphenyl is due to the migration of the phenyl group from **3** to the metal center, as shown in Eq. 4. In the case of the carbene complexes of Co or Fe, phenyl migration proceeds rather easily because only three carbonyl groups coordinate to the metal center, leaving one coordination site vacant. On the other hand, in the Mn carbene complex **3**, the coordination sites are saturated by four carbonyl groups to avoid phenyl migration.



(4)

As described above, $Mn_2(CO)_{10}$ is employed as a phosgene equivalent for the preparation of unsymmetrical ketones. Next, we attempted to apply the above reaction to amide synthesis by adding a lithium amide in place of the second alkyllithium in the above ketone synthesis.

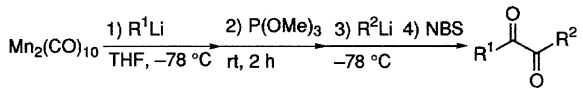
In the reaction of $Mn_2(CO)_{10}$ with PhLi and LiNHPh it was found that the desired benzanilide was not produced under the above-mentioned conditions, owing to the low reactivity of LiNHPh. Two molar amounts of LiNHPh were necessary to accomplish the reaction along with increasing the temperature from −78 °C to room temperature. Benzanilide **4** was obtained in 39% yield, accompanied by an α-oxoacetamide **5** in 11% yield (Eq. 5).



(5)

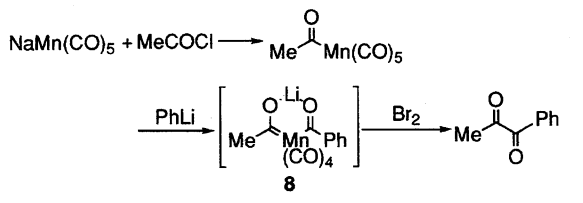
The formation of α-oxoacetamide **5** is explained as follows (Scheme 3). In this reaction, a small amount of aniline is generated because the product, benzanilide, can act as a proton source. When this aniline acts as a ligand, CO insertion reaction of the phenylmanganese complex **3** might be accelerated to give a benzoylmanganese complex **6**,[6] which suffers from a nucleophilic attack of LiNHPh to give a chelate complex **7**. Finally, **7** is converted to the corresponding α-oxoacetamide **5** by spontaneous decomposition or by air oxidation.

Table 3. One-Pot Preparation of Unsymmetrical α-Diketones



R^1	R^2	Yield/%
Ph	Ph	52
Ph	*n*-Bu	41
Ph	*s*-Bu	20
Ph	*t*-Bu	8
n-Bu	*s*-Bu	17

This prompted us to develop an unsymmetrical α-diketone synthesis with $Mn_2(CO)_{10}$. Since aniline seemed not to be an appropriate ligand for promoting CO insertion, a more efficient ligand was sought, using such as CO or organophosphorous compounds. The reaction conditions were optimized by monitoring benzil formation by the reaction of $Mn_2(CO)_{10}$ with PhLi. The CO insertion reaction was firstly examined, showing that $P(OMe)_3$ was a slightly better ligand than CO in accelerating this step. Furthermore, Casey and Bunnnell reported that a chelate complex **8** can be converted to α-diketone by oxidation with Br_2 (Eq. 6).[5a] This indicated that some oxidation process would be required for the formation of benzil.



(6)

Many kinds of oxidants were employed for the oxidation of the chelate complex. Benzil was scarcely obtained by

using metallic oxidants, such as Ce^{4+} or Mn^{3+}. Although Br_2 or I_2 was better, the yield was still unsatisfactory. Finally, *N*-bromosuccinimide (NBS) was found to be a suitable oxidant. That is, as shown in Scheme 4, $Mn_2(CO)_{10}$ was treated with an equimolar amount of PhLi; then, $P(OMe)_3$ was added at room temperature to facilitate CO insertion, and the second PhLi was added at −78 °C. Finally, NBS was added to quench the reaction oxidatively, giving benzil in 52% yield.

The preparation of several kinds of unsymmetrical α-diketones was examined under the above reaction conditions. The results are listed in Table 3. It was found that $Mn_2(CO)_{10}$ can act as an oxalyl chloride equivalent for unsymmetrical α-diketone synthesis as well as a phosgene equivalent. In all cases, the production of symmetrical α-diketone and monoketones were less than 1%, and unsymmetrical α-diketones were obtained selectively.

As described above, commercially available $Mn_2(CO)_{10}$ has a suitable reactivity for the one-pot preparation of unsymmetrical ketones and α-diketones. This reaction can be performed by a simple procedure, because it is not necessary to isolate any intermediate organometallic compounds, which are often unstable.

Experimental

General. The ^{1}H NMR (500 MHz) spectra in $CDCl_3$ were recorded on Bruker AM500 and JEOL α-500 spectrometers using chloroform as an internal standard (δ=7.24). ^{13}C NMR (125 MHz) spectra were measured with a Bruker AM500 spectrometer using $CDCl_3$ as an internal standard (δ=77.0). IR spectra were recorded on a Horiba FT-300S spectrometer. Preparative thin-layer chromatography (TLC) was carried out on silica gel (Wakogel B-5F). Tetrahydrofuran (THF) was freshly distilled from sodium diphenylketyl. Hexamethylphosphoric triamide (HMPA) was distilled under reduced pressure and stored over MS 4A. Trimethyl phosphite and aniline were distilled from CaH_2. Alkyllithiums were purchased from Kanto Chemical Co., Inc. and titrated by a literature procedure.[7] *N*-Bromosuccinimide (NBS) was recrystallized from water and dried under vacuum. Decacarbonyldimanganese was purchased from Strem Chemicals Inc. and purified by sublimation (50 °C, 1.5 mmHg, 1 mmHg=133.322 Pa). All reactions were carried out under an argon atmosphere.

General Procedure for Ketone Synthesis: To a THF (10 ml) solution of decacarbonyldimanganese (390 mg, 1 mmol) was added dropwise the first alkyllithium compound (1 mmol) at −78 °C. After 5 min, the second alkyllithium compound (1 mmol), and then hexamethylphosphoric triamide (1 ml), were added to the reaction mixture. After the resulting solution was stirred at −78 °C for 2 h, water was added. The mixture was extracted with ether (30 ml×3), and the combined extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure; the residue was purified by TLC (hexane–ethyl acetate, 10 : 1) to afford the product.

Procedure for Benzanilide Synthesis: To a THF (10 ml) solution of decacarbonyldimanganese (390 mg, 1 mmol) was added dropwise a hexane–diethyl ether solution (0.97 M, M=mol dm^{-3}) of phenyllithium (1.02 ml, 0.99 mmol) at −78 °C. After 5 min, a THF (1 ml) solution of lithium anilide (prepared from aniline (185 mg, 1.99 mmol) and phenyllithium (0.97 M, 2.05 ml, 1.99 mmol) at −78 °C), and then hexamethylphosphoric triamide (1 ml), were added to the reaction mixture. After the resulting solution was stirred at room temperature for 12 h, water was added. The mixture was extracted with ether (30 ml×3) and the combined extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by TLC (hexane–ethyl acetate, 5 : 1) to afford the products benzanilide (76 mg, 39%) and α-oxophenylacetanilide (25 mg, 11%).

General Procedure for α-Diketone Synthesis: To a THF (10 ml) solution of decacarbonyldimanganese (390 mg, 1 mmol) was added dropwise the first alkyllitium (1 mmol) at −78 °C. After 5 min, a THF solution (6 ml) of trimethyl phosphite (180 mg, 1.46 mmol) was added, and then stirred at room temperature for 2 h. A second alkyllithium (1 mmol) was then added to the reaction mixture at −78 °C. After the resulting solution was stirred at −78 °C for 1 h, a THF (20 ml) solution of *N*-bromosuccinimide (682 mg, 3.84 mmol) was added. The mixture was extracted with dichloromethane (30 ml×3) and the combined extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure; the residue was purified by TLC (benzene or hexane–ethyl acetate, 10 : 1) to afford the product.

Spectral Data. All of the products are known compounds, and their spectral data are in good agreement with those of the literature or authentic samples.

Benzophenone:[8] ^{1}H NMR δ=7.47 (2H, t, J=7.4 Hz), 7.53 (1H, t, J=7.4 Hz), 7.79 (2H, d, J=7.4 Hz); ^{13}C NMR δ=128.3, 130.0, 132.1, 137.7, 196.7.

Valerophenone:[9] ^{1}H NMR δ=0.93 (3H, t, J=7.4 Hz), 1.38 (2H, m), 1.70 (2H, m), 2.94 (2H, t, J=7.5 Hz), 7.43 (2H, t, J=7.3 Hz), 7.52 (1H, t, J=7.3 Hz), 7.93 (2H, d, J=7.3 Hz); ^{13}C NMR δ=13.9, 22.5, 26.5, 38.3, 128.0, 128.5, 132.8, 137.1, 200.5.

2-Methylbutyrophenone:[9] ^{1}H NMR δ=0.89 (3H, t, J=7.4 Hz), 1.17 (3H, d, J=6.8 Hz), 1.47 (1H, m), 1.81 (1H, m), 3.38 (1H, m), 7.43 (2H, t, J=7.5 Hz), 7.52 (1H, t, J=7.5 Hz), 7.93 (2H, d, J=7.5 Hz); ^{13}C NMR δ=11.7, 16.7, 26.7, 42.1, 128.2, 128.6, 132.8, 136.8, 204.5.

2,2-Dimethylpropiophenone:[9] ^{1}H NMR δ=1.34 (9H, s), 7.38 (2H, t, J=7.4 Hz), 7.43 (1H, t, J=7.4 Hz), 7.68 (2H, d, J=7.4 Hz); ^{13}C NMR δ=28.0, 44.2, 127.9, 128.0, 130.8, 138.6, 209.2.

2-Hexanone:[9] ^{1}H NMR δ=0.85 (3H, t, J=7.5 Hz), 1.26 (2H, m), 1.51 (2H, m), 2.09 (3H, s), 2.38 (2H, t, J=7.4 Hz); ^{13}C NMR δ=13.8, 22.2, 25.9, 29.8, 43.4, 209.3.

Benzanilide:[10] ^{1}H NMR δ=7.14 (1H, t, J=7.4 Hz), 7.36 (2H, dd, J=7.4 and 7.7 Hz), 7.47 (2H, dd, J=7.2 and 7.4 Hz), 7.54 (1H, t, J=7.4 Hz), 7.63 (2H, d, J=7.7 Hz), 7.81 (1H, br), 7.85 (2H, d, J=7.2 Hz); ^{13}C NMR δ=120.2, 124.6, 127.0, 128.8, 129.1, 131.9, 135.0, 137.9, 165.7.

α-Oxophenylacetanilide:[11] ^{1}H NMR δ=7.19 (1H, t, J=7.4 Hz), 7.39 (2H, dd, J=7.4 and 8.4 Hz), 7.50 (2H, dd, J=7.5 and 8.3 Hz), 7.65 (1H, t, J=7.5 Hz), 7.69 (2H, d, J=8.4 Hz), 8.40 (2H, d, J=8.3 Hz), 8.92 (1H, br); ^{13}C NMR δ=119.9, 125.3, 128.6, 129.2, 131.5, 133.1, 134.6, 136.6, 158.8, 187.4.

Benzil:[12] ^{1}H NMR δ=7.50 (2H, t, J=7.8 Hz), 7.64 (1H, t, J=7.8 Hz), 7.96 (2H, d, J=7.8 Hz); ^{13}C NMR δ=129.0, 129.9, 133.0, 134.9, 194.4.

1-Phenyl-1,2-hexanedione:[13] ^{1}H NMR δ=0.92 (3H, t, J=7.4 Hz), 1.41 (2H, m), 1.68 (2H, m), 2.85 (2H, t, J=7.3 Hz), 7.49 (2H, t, J=7.3 Hz), 7.63 (1H, t, J=7.3 Hz) 7.99 (2H, d, J=7.3 Hz).

3-Methyl-1-phenyl-1,2-pentanedione:[13] ^{1}H NMR δ=0.94 (3H, t, J=7.5 Hz), 1.16 (3H, d, J=7.0 Hz), 1.45 (1H, m), 1.80 (1H, m), 3.19 (1H, m), 7.48 (2H, t, J=7.4 Hz), 7.62 (1H, t, J=7.4 Hz), 7.92 (2H, d, J=7.4 Hz); ^{13}C NMR δ=11.5, 14.2, 24.6, 43.1, 128.8, 130.0, 132.5, 134.5, 193.8, 200.3.

3,3-Dimethyl-1-phenyl-1,2-butanedione:[13] ^{1}H NMR δ=1.29

(9H, s), 7.48 (2H, t, J=7.8 Hz), 7.62 (1H, t, J=7.8 Hz), 7.81 (2H, d, J=7.8 Hz); ^{13}C NMR δ=26.3, 42.7, 128.9, 129.5, 132.9, 134.5, 195.4, 210.9.

3-Methyl-4,5-nonanedione:[14] ^{1}H NMR δ=0.86 (3H, t, J=7.4 Hz), 0.90 (3H, t, J=7.5 Hz), 1.03 (3H, d, J=7.0 Hz), 1.2—1.7 (6H, m), 2.71 (2H, m), 3.22 (1H, m).

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