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for the Preparation
of Organic Compounds

# Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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*September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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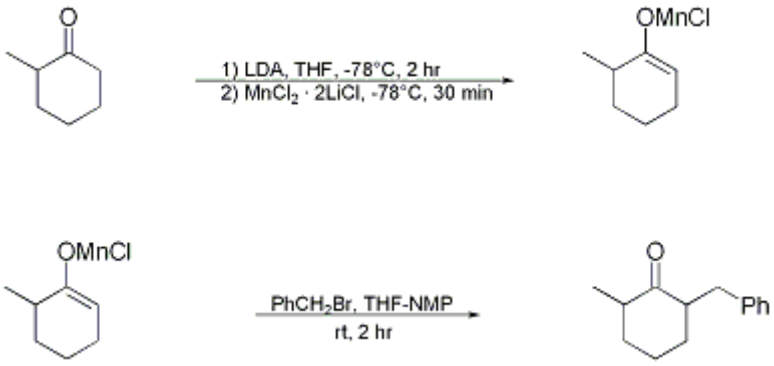
# REGIOSELECTIVE MONOALKYLATION OF KETONES VIA THEIR MANGANESE ENOLATES: 2-BENZYL-6-METHYLCYCLOHEXANONE FROM 2-METHYLCYCLOHEXANONE

**[ Cyclohexanone, 2-methyl-6-(phenylmethyl)- ]**




Submitted by Gérard Cahiez[1] , François Chau, and Bernard Blanchot.
Checked by Jari Yli-Kauhaluoma and Rick L. Danheiser.

## 1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, 100-mL pressure-equalizing dropping funnel, and a Claisen head fitted with a low-temperature thermometer and a nitrogen inlet (Note 1). The flask is charged with 80 mL of tetrahydrofuran (THF) (Note 2) and 5.55 g (55 mmol) of diisopropylamine (Note 3). The resulting solution is cooled to −15°C, and 34.4 mL (55 mmol) of a 1.6 M solution of butyllithium in hexane (Note 4) is added dropwise over a 10-min period. The reaction mixture is stirred at −15°C for 30 min and then cooled to −78°C in a dry ice-acetone bath. A solution of 5.6 g (50 mmol) of 2-methylcyclohexanone (Note 5) in 20 mL of THF is added over 5 min, and the reaction mixture is stirred for 2 hr at −78°C. A solution of 55 mmol of $MnCl_2$·2LiCl (dilithium tetrachloromanganate) in 80 mL of THF (Note 6) is added dropwise over a 15-min period, and after 30 min the resulting clear brown solution is allowed to warm to room temperature.

To this solution of the manganese enolate are added successively (each over 5 min) 80 mL of 1-methyl-2-pyrrolidinone (NMP) (Note 7) and 12.2 g (71.3 mmol) of benzyl bromide (Note 8). The resulting mixture is stirred for 2 hr and hydrolyzed by the dropwise addition of 100 mL of a 1 M aqueous hydrochloric acid solution (HCl) over 15 min. Petroleum ether (35-60°C, 100 mL) is added, and the aqueous layer is separated and extracted three times with 50-mL portions of diethyl ether . The combined organic layers are washed with 100 mL of an aqueous saturated sodium carbonate solution, dried over anhydrous magnesium sulfate , filtered, and concentrated under reduced pressure with a rotary evaporator to afford 13.7-22.3 g of a brown oil (Note 9). Short path distillation under reduced pressure affords 8.8-8.9 g (87-88%) of 2-benzyl-6-methylcyclohexanone as a pale yellow oil, bp 95-100°C (0.3 mm) (Note 10).

## 2. Notes

1. The apparatus is flame-dried under a stream of dry nitrogen or argon. A slight positive pressure of nitrogen or argon is maintained with an oil bubbler throughout the reaction.
2. THF was freshly distilled from sodium benzophenone ketyl under a nitrogen atmosphere.
3. Diisopropylamine (99%, Aldrich Chemical Company, Inc.) was distilled from calcium hydride prior to use.
4. Butyllithium (1.6 M solution in hexane) was purchased from Acros Organics and titrated immediately

before use according to the procedure of Watson and Eastham.[2]
5. 2-Methylcyclohexanone (99%) was purchased from Aldrich Chemical Company, Inc. , and distilled prior to use.
6. A solution of 55 mmol of the ate complex $MnCl_2 \cdot 2LiCl$ is prepared by stirring a suspension of 6.93 g of anhydrous manganese chloride ($MnCl_2$) (Note 11) and 4.65 g of anhydrous lithium chloride (LiCl) (Note 12) in 80 mL of THF at room temperature until an amber solution is obtained. It should be noted that the rate of dissolution (formation of the ate-complex $Li_2MnCl_4$ ) is very dependent on both the grain size of the two salts ($MnCl_2$ and LiCl) and their purity. When unpulverized Aldrich Chemical Company, Inc., or Acros Organics material is used it is necessary to stir for 4 to 24 hr to obtain complete dissolution; on the other hand, with finely pulverized anhydrous $MnCl_2$ obtained by drying analytical grade manganese chloride tetrahydrate (e.g., manganese chloride tetrahydrate purum p.a. Fluka, Inc.), it is possible to obtain complete dissolution after only 5 to 10 min. The formation of the ate-complex in this case is exothermic.
7. The submitters purchased 1-methyl-2-pyrrolidinone (NMP, 99%) from Aldrich Chemical Company, Inc. and distilled it prior to use. The checkers used 99.5% NMP (Aldrich Chemical Company, Inc.) without further purification.
8. Benzyl bromide (99%) was purchased by the submitters from Aldrich Chemical Company, Inc. , and distilled prior to use ( *caution: lachrymator!*).The checkers purified benzyl bromide by filtration through activated neutral alumina (EM Science, ca. 2 g of alumina/12 g of benzyl bromide).
9. The weight of crude product varies depending on how much of the NMP is removed during the work up. The residual NMP is easily separated from 2-benzyl-6-methylcyclohexanone during the subsequent purification by distillation. Alternatively, residual NMP can be removed during the workup by extracting the combined organic phases with four 50-mL portions of 1 M HCl prior to the aqueous $Na_2CO_3$ wash.
10. The checkers determined this material to consist of a mixture of 2-benzyl-6-methylcyclohexanone (94-97%) and 2-benzyl-2-methylcyclohexanone (3-6%). In 10 runs, the submitters found the yield to range from 85 to 90% and the regioselectivity (ratio of 2-benzyl-6-methylcyclohexanone to 2-benzyl-2-methylcyclohexanone) to range from 93:7 to 97:3. The regioisomeric ratio was determined by $^1$H NMR according to House[3] and by GC (capillary column SGE CYDEX B 25 m × 0.22 mm i.d., 0.25 μm film thickness, 165°C), retention time of 2-benzyl-6-methylcyclohexanone: 14.53 min, retention time of 2-benzyl-2-methylcyclohexanone: 14.99 min. The spectral properties of the product were as follows: $^1$H NMR ($C_6D_6$, 500 MHz) δ: 0.92-1.16 (m, 3 H), 1.03 (d, 3 H, J = 6.4), 1.30-1.34 (m, 1 H), 1.59-1.63 (m, 1 H), 1.72-1.77 (m, 1 H), 1.83-1.90 (1 H, app. sept, J = 6.2), 2.17-2.21 (m, 1 H), 2.42 (dd, 1 H, J = 8.3, 13.7), 3.37 (dd, 1 H, J = 5.1, 13.9), 7.07-7.19 (m, 5 H) ; $^{13}$C NMR ($CDCl_3$, 125 MHz) δ: 14.5, 25.4, 34.6, 35.4, 37.3, 45.6, 52.5, 125.7, 128.1 (2C), 129.0 (2C), 140.6, 213.5 ; IR (thin film) cm$^{-1}$: 3082(m), 3058 (m), 3023(m), 1710(s), 1604(m), 1495(m), 1451(m), 1375(m), 920(w), 745(m), 705(m) . Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.04; H,8.90.
11. Manganese(II) chloride tetrahydrate, purum p.a. (Fluka, Inc.) was finely ground using a mortar and pestle and then dried by heating at 180-200°C at 0.01-0.1 mm in a vacuum oven for 10 hr prior to use. The checkers dried 13.8 g of manganese(II) chloride tetrahydrate by heating in a 100-mL flask with magnetic stirring at 205°C/0.1 mm for 15 hr. The submitters found that it was sometimes necessary to grind the dried material again under a dry atmosphere before use. The anhydrous salt is very hygroscopic and must be protected against moisture (a well-closed bottle is adequate); it can, however, be handled *very quickly* in air without special precautions.
12. Anhydrous lithium chloride (99%), purchased from Aldrich Chemical Company, Inc. , was finely pulverized with a mortar and pestle and then dried by heating at 200°C under reduced pressure (0.1-0.01 mm) for 8 hr before use. The salt is hygroscopic and must be handled *very quickly*.

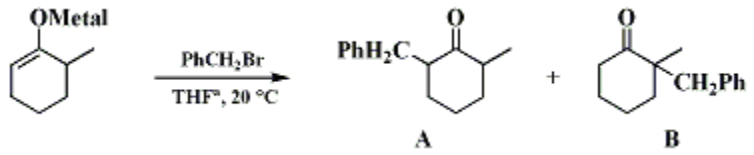
## Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

## 3. Discussion

The procedure described here illustrates a general and very convenient method[4 5 6 7 8] to carry out the regioselective monoalkylation of ketones via their Mn-enolates. A comparison with the classical

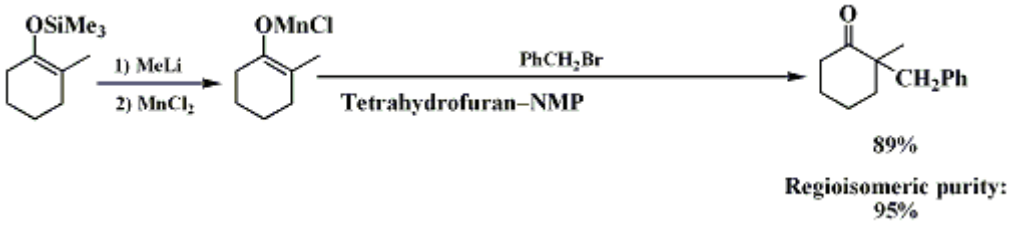
procedure previously reported by House in *Organic Syntheses* to prepare the 2-benzyl-6-methylcyclohexanone via the corresponding Li-enolates[3] clearly shows that the Mn-enolate gives a higher yield of desired product since the regioselectivity is better and the formation of polyalkylated products is not observed.




| Reaction Conditions | Yield (%) | Regioselectivity A/B | Polyalkylated Product (%) |
|---|---|---|---|
| Li-Enolate[a] | 42–45 | 76/24 | 18–19 |
| Mn-Enolate | 85 | 95/5 | < 1 |

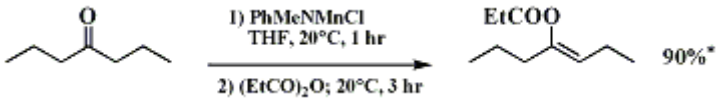
[a]The reaction described by House[3] was performed in dimethoxyethane . The same results have been obtained by using THF.

The other regioisomer, the 2-benzyl-2-methylcyclohexanone, can also be selectively obtained in good yield from the more substituted Mn-enolate.[7] In fact, these results prove that the deprotonation equilibrium that is responsible for the formation of side-products from Li-enolates does not exist under the reaction conditions in the case of Mn-enolates.



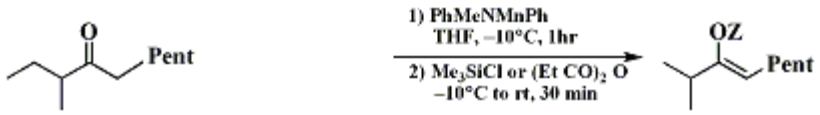

As a rule, this procedure also compares favorably with the other methods previously reported to achieve regioselective monoalkylation of ketones.[9] It gives similar or higher yields and selectivities, and it is clearly easier to carry out since no toxic, expensive or hazardous material such as $Et_3Al$ (Al-enoates), KH then $Et_3B$ (B-enolates), $Bu_3SnCl$ (Sn-enolates) or $Et_2Zn$ (Zn-enolates) is required. Moreover, a large excess of alkylating reagents (Al- and Sn-enolates) is not required.

As shown, Mn-enolates are easily and quantitatively obtained from Li-enolates by transmetalation.[5,7,8] They can also be prepared by deprotonation of ketones with Mn-amides.[4,6]




Note that only Mn-amides prepared from aromatic amines, ArRNH or $Ar_2NH$, give quantitative yields of enolization products. A procedure using only a catalytic amount of aromatic amine has also been described.[10]

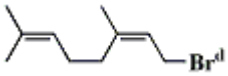
The deprotonation reactions occur regio- and stereoselectively to give the less- substituted Z enolates that can be readily silylated or acylated to afford mainly the less-substituted Z silyl enol ethers or Z enol esters in high yields.[4,11]




**Z = $Me_3Si$: 90% (ZE = 97:3; regioselectivity ≥ 99%)**
**Z = EtCO: 95% (ZE = 93:7; regioselectivity ≥ 99%)**

The regioselective monoalkylation of ketones described above has wide applicability. The monoalkylated products are regioselectively obtained in high yields by reacting Mn-enolates prepared in THF from a wide range of ketones with various reactive organic halides in the presence of a polar cosolvent such as DMSO , NMP, sulfolane , DMF , MeCN [4,5,6,7] (Tables I and II) as well as DMPU.[8] With less reactive alkylating reagents (e.g., BuBr) the reaction rate is slower, and the reaction generally leads to lower yields (Table I). Note that alkyl sulfonates do not undergo reaction. (Table I).

TABLE I
MONOALKYLATION OF Mn-ENOLATES OBTAINED BY DEPROTONATION OF KETONES WITH Mn-AMIDES

| Ketone | Solvent (Alkylation Step)[a] | Reaction Conditions | Alkylating Agent[b] | Yield[c] (%) |
|---|---|---|---|---|
| BuCOBu | THF/DMSO | 20°C, 2 hr | MeI | 93 |
| PrCOPr | THF | 20°C, 3 hr | $PhCH_2Br$ | 43 |
| PrCOPr | THF/NMP | 20°C, 2 hr | $PhCH_2Br$ | 86 |
| PrCOPr | THF/DMSO | 20°C, 2 hr | $PhCH_2Br$ | 91 |
| PrCOPr | THF/NMP | 20°C, 2 hr | $CH_2=CHCH_2Br$ | 81 |
| PrCOPr | THF/DMSO | 20°C, 2 hr | $PhCH=CHCH_2Br$ | 86 |
| PrCOPr | THF/DMSO | 20°C, 2 hr |  | 87 |
| PrCOPr | THF/NMP | −30°C, 2 hr | $BrCH_2COOEt$ | 88 |
| PrCOPr | THF/DMSO | 50°C, 2 hr | BuI | 67 |
| PrCOPr | THF/DMSO | 50°C, 24 hr | BuBr | 48 |
| PrCOPr | THF/DMSO | 50°C, 24 hr | $BuOSO_2Ph$ | 0 |

[a]Deprotonation step: PhMeNMnZ (Z = Cl, Ph), 0°C, 1 hr. [b]1.25 equiv. [c]Yield of isolated product. [d]Only the $S_N2$ product is obtained. The geometry of the allylic double bond is retained (Z > 99%).

TABLE II
REGIOSELECTIVE MONOALKYLATION OF Mn-ENOLATES OBTAINED BY DEPROTONATION OF UNSYMMETRICAL KETONES WITH Mn-AMIDES

| Ketone | Alkylating Agent[a] | Monoalkylated Ketone(%)[b] | Regioselectivity[c] |
|---|---|---|---|
| iso-PrCOHex | $CH_2=CHCH_2Br$ | 80 | > 99:1 |
| iso-PrCOHex | $PhCH_2Br$ | 85 | > 97:3 |
| $PhCH_2(Et)CHCOPr$ | $CH_2=CHCH_2Br$ | 89 | >99:1 |
| 2-Me cyclohexanone | $PhCH_2Br$ | 90 | 93:7 |

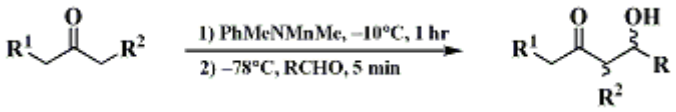
[a]Alkylation step: THF-NMP or THF-DMSO, 20°C, 1 hr. [b]Yield of isolated product. [c]Ratio of αα'/αα-disubstituted ketones.

Mn-enolates can also be hydroxyalkylated (Table III). They react easily with a vast array of aldehydes (even enolizable or α,β-unsaturated aldehydes), to give synaldol products in good yields.[12] The stereoselectivity obtained from Mn- and Li-enolates are very similar.

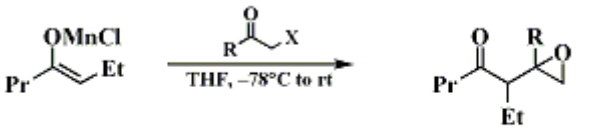
TABLE III
REACTION OF Mn-ENOLATES WITH ALDEHYDES

| Ketone | Aldehyde | Yield (%)[a] | Syn/Anti |
|---|---|---|---|
| EtCOEt | PrCHO | 83 | 66/33 |
| EtCOEt | $Et_2CHCHO$ | 86 | 77/23 |
| EtCOEt | MeCH=CHCHO | 86 | 64/36 |
| EtCOEt | Furfural | 79 | 71/29 |
| EtCOEt | PhCHO | 94 | 71/29 |
| PrCOPr | PhCHO | 88 | 88/12 |
| tert-BuCOPr | PhCHO | 81 | 99/1 |
| PrCOPr | PrCHO | 86 | 85/15 |
| BuCOBu | PrCHO | 83 | 51/49 |
| PhCOPr | PrCHO | 87 | 72/28 |

[a]Yield of isolated product.

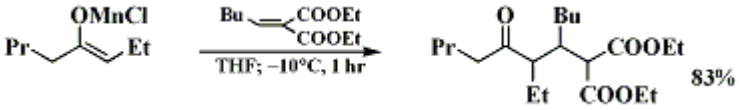



α-Halogeno ketones lead to β-keto epoxides.[12]




R = Ph; X = Br; 92%
R = Me; X = Cl; 73%

Finally, Mn-enolates are useful synthetic reagents for Michael additions.

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## References and Notes


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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Benzyl-6-methylcyclohexanone:
Cyclohexanone, 2-benzyl-6-methyl- (8);
Cyclohexanone, 2-methyl-6-(phenylmethyl)- (9); (24785-76-0)

2-Methylcyclohexanone:
Cyclohexanone, 2-methyl- (8,9); (583-60-8)

Diisopropylamine (8);
2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Dilithium tetrachloromanganate ($MnCl_2 \cdot 2\ LiCl$; $Cl_4Mn \cdot 2\ Li$):
Manganate (2-), tetrachloro-, dilithium, (I-4)- (9); (57384-24-4)

1-Methyl-2-pyrrolidinone:
2-Pyrrolidinone, 1-methyl- (8,9); (872-50-4)

Benzyl bromide:
Toluene, α-bromo- (8);
Benzene, (bromomethyl)- (9); (100-39-0)

Manganese(II) chloride:
Manganese chloride (8,9); (7773-01-5)

Lithium chloride (8,9); (7447-41-8)

2-Benzyl-2-methylcyclohexanone:
Cyclohexanone, 2-benzyl-2-methyl- (8);
Cyclohexanone, 2-methyl-2-(phenylmethyl)- (9); (1206-21-9)