

Nickel-Catalysed Conjugate Addition of Trimethylaluminum to Sterically Hindered α,β -Unsaturated Ketones

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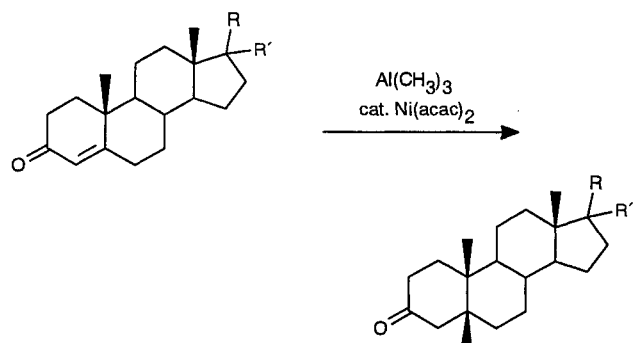
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Nickel acetylacetonate is an efficient catalyst for the 1,4-addition of trimethylaluminum to α,β -unsaturated ketones. The reaction is strongly solvent dependent and gives best results in tetrahydrofuran or ethyl acetate. The reaction is especially useful for the nucleophilic 1,4-methyl transfer to sterically hindered enones. A β -cuparenone synthesis via conjugate methyl group addition to an enone precursor is described.

Catalysed 1,4-addition reactions are an important way to achieve carbon-carbon bond formation.¹ Organoaluminum compounds are of interest due to their chemoselectivity, availability of lower alkyl ligands, easy handling of the aluminum solutions, and also their low toxicity.¹⁻⁹

Catalysed conjugate addition of trimethylaluminum (TMA) is known from the work of Ashby³ and Mole.⁴ The yields, however, were not always satisfying. As described³⁻⁸ the nucleophilicity of TMA is solvent dependent. When no catalyst was used TMA reacted very slowly with enones in tetrahydrofuran (THF). Surprisingly for an organometallic reaction, ethyl acetate (EtOAc) can also be used as solvent. We observed only a slight tendency of TMA to undergo 1,2-addition to enones in EtOAc compared to THF which can be explained by a better coordinating ability of THF for aluminum. However, the nucleophilicity of TMA for enones is low in both solvents.

Comparing our results with the findings of Mole⁴ the strong influence of the solvent on the yield becomes obvious. For the nickel-catalysed reaction of TMA with a 3-keto- $\Delta^{4,5}$ -steroid, i.e., testosteronepropionate, Mole reported a 35% yield in diethyl ether. In a similar reaction, employing a commercial TMA/hexane solution in THF or EtOAc, we obtained 66% conjugate addition product, and neat TMA in THF gave 76% yield of the desired product **16** (Scheme).



Solvent diethyl ether:⁴ R' = H, R = CO₂Et (35%); R' = H, R = C₈H₁₇ (40%); R' = H, R = Ac (30%).

Solvent THF: R, R' = (=O), **16** (76%).

Scheme

By testing the effect of metal salts as additives in the reaction of TMA with β -ionone (**3**) in THF we obtained best results with copper(I) bromide (CuBr), copper(I) cyanide and nickel(II) acetylacetonate [Ni(acac)₂] as catalysts. Reactions catalysed with copper(I) chloride, cobalt(III) acetylacetonate, cobalt(II) salicylaldehyde, cobalt(II) phthalocyanine and nickel(II) chloride (dppp) were found to be less regioselective and/or slower in rate. Manganese(II) acetylacetonate, vanadium(IV) oxide acetylacetonate and bis(triphenylphosphine)palladium(II) chloride yielded mainly the 1,2-addition product or product mixtures.

The Ni(acac)₂-catalysed conjugate addition of TMA is usually slightly less regioselective than the CuBr-catalysed 1,4-addition studied by our group,^{6,7,8} with some side product due to 1,2-addition being produced. Nevertheless, the reaction is of broad scope; TMA delivers a methyl group to α,β -unsaturated ketones and less satisfactorily also to α,β -unsaturated aldehydes⁸ in a conjugate manner under Ni(acac)₂ catalysis (Table 1).

Table 1. Ni(acac)₂-catalysed 1,4-Methyl Transfer from Al(CH₃)₃ to α,β -Unsaturated Ketones

Enone	Product	Yield ^a	Method ^b	Reaction time
		77%	A	2 h
		88%	B	2 h
		(2:1:1:1.5) ^c		
		83% ^d	A	2 h
		(5:1) ^c		
		83%	A	6 h
		(1.5:1) ^c		
		85%	A	4 h

^a Experiments were performed on a 10 mmol scale.

^b Method A was usually run at r.t., Method B at 0°C.

^c Diastereomeric ratio; determined by GC.

^d For spectroscopic data see ref. [4, 7, 19].

The most interesting feature about Ni(acac)₂-catalysed conjugate additions is their low sensitivity to steric influences.^{11–13} We report herein the nucleophilic 1,4-methyl addition of sterically hindered enones in high yields using Ni(acac)₂ and TMA (Table 2), which previously gave only unsatisfactory yields with a copper catalyst.

The Ni(acac)₂ catalyst was also tested with methylmagnesium chloride and lithium tetramethylaluminate [LiAl(CH₃)₄] on the (*S*)-4,4a,5,6,7,8-hexahydro-4a-methylnaphthalene-2(3*H*)-one (**11**) giving a 36% and 66% yield of **12**, respectively.¹⁰ The Ni(acac)₂-catalysed

reaction with a TMA/hexane solution yielded 77% of the desired product **12** and 84% with neat TMA.

Another impressive example is the synthesis of cuparenone.^{11–16} (\pm)- β -Cuparenone (**20**) was obtained in 91% yield from the enone **19** by the Ni(acac)₂/TMA method in THF. Copper-catalysed conjugate additions are reported to fail in this case.^{12,14}

The Ni(acac)₂-catalysed TMA reactions also reveal good chemoselectivity. With the Wieland–Miescher ketone **13** or the 3,17-diketo- $\Delta^{4,5}$ -steroid **15** no reaction with the saturated ketones was observed and good yields of conjugate addition were achieved. The diastereoselectivity of the reaction varied. Good selectivities were found with the highly congested enones **11** and **15** whereas the diastereoselectivity with less hindered enones was low. These findings correspond to the high reactivity of the reagents, and higher diastereoselectivities may be achieved with lower reaction temperatures or chiral catalysts.¹⁷ Usually 5 mol% of Ni(acac)₂ was employed in the reactions. Runs with 1 mol% catalyst led to a prolonged reaction time and the reaction rate decreased remarkably below 0.5 mol% catalyst. Below –30°C no reaction was observed; at 0°C a clean 1,4-addition occurred which was only slightly less selective at room temperature and above 40°C the reaction proceeded at a higher rate but led to formation of byproducts.

In general, only one out of the three methyl groups of TMA was transferred under the chosen conditions. Usually a commercial 10% solution of TMA in hexane was used; a toluene solution gave lower yields. Best results were obtained with neat TMA, although more care in handling was required since pure TMA is highly pyrophoric and an exothermic reaction occurs on dissolving in polar solvents due to formation of coordination complexes.

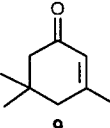
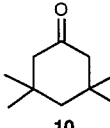
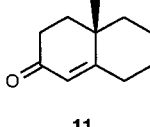
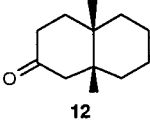
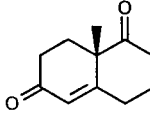
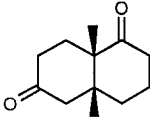
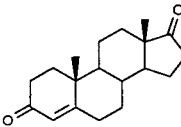
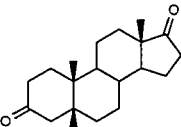
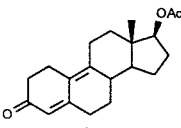
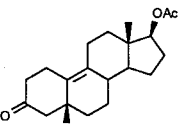
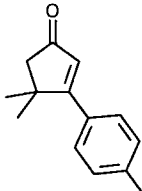
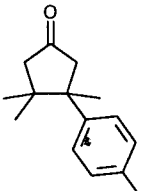
The choice of organic ligands of the organoaluminum reagents seems to be limited to ligands without a β -hydrogen.¹³ Triethylaluminum as well as triisobutylaluminum gave unsatisfactory product mixtures under nickel-catalysis.

The Ni(acac)₂-catalysed TMA reaction in THF or ethyl acetate is a simple and highly regioselective method for the nucleophilic conjugate methyl transfer to α,β -unsaturated carbonyls proceeding in good to high yields. The nickel catalyst is favourable over CuBr when steric hindrance in the substrate has to be overcome. In this way the nickel-catalysed reactions complete the 1,4-addition of TMA to enones.

All reactions were carried out under an N₂ atmosphere. Solvents and organic compounds were used in commercially available quality without further purification. The compounds **11**, (*S*)-8a-methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione (Wieland–Miescher ketone) **13**, and **19** were synthesised according to literature procedures.¹⁸

Infrared (IR) spectra were run on a Nicolet 20 SXB or Nicolet 710 spectrometer. Mass spectra (MS, 70 eV) were recorded on a TRIO 2 from Vacuum Generators. Nuclear magnetic resonance (NMR) spectral data (¹H NMR 300 MHz, ¹³C NMR 75 MHz) were obtained with a General Electric QE 300 using CDCl₃ as a solvent and were reported with tetramethylsilane as an internal standard. GC

Table 2. Ni(acac)₂-catalysed 1,4-Methyl Transfer from Al(CH₃)₃ to Sterically Hindered α,β -Enones

Enone	Major Product	Yield ^a	Method ^b	Reaction Time
		91% ^c	B	3.5 h
		77%	A	4 h
		84% (10:1) ^d	B	5 h
		72%	A	5 h
		87% (1.5:1) ^d	B	7 h
		66%	A	7 h
		76% (>95:5) ^e	B	5 h
		75% (2:1) ^d	A	7 h
		91%	B	19 h

^a Experiments were performed on a 10 mmol scale.

^b Method A was usually run at r.t., Method B at 0°C.

^c For spectroscopic data see ref. [20].

^d Diastereomeric ratio (β/α), determined by ¹H NMR (300 MHz).

^e Only 5 β -methyl was detected by ¹H NMR (300 MHz); ref.[21].

analyses were performed on a Hewlett-Packard 5890 Series II; 25 m CP Sil 19 CB (0.25/0.2), 60–260°C, 8°C/min, 0.8 bar He. TLCs and column chromatographies were effected on E. Merck silica gel (Kieselgel 60, 230–400 mesh). Rotation was measured on a Perkin-Elmer 241 Polarimeter in CHCl₃. Satisfactory microanalyses were obtained for **16** and **18**: C ± 0.4; H ± 0.03.

General Procedure:

Method A:

TMA (10% solution in hexane, 11.2 mL, 10.5 mmol) was added to a magnetically stirred solution of Ni(acac)₂ (128 mg, 0.5 mmol), dry THF (15 mL) or EtOAc (15 mL) and enone (10 mmol) at 0°C. A slightly exothermic reaction occurred and the green color of the reaction mixture turned black. After stirring for an appropriate time (see Tables; completion of the reactions was determined by TLC), the reaction was diluted with hexane (15 mL) and quenched by careful addition of sat. aq NH₄Cl (1.5 mL). Stirring was continued for 1–2 h, MgSO₄ (1 g) and silica gel (1 g) were added, and the resulting solid was filtered through a sintered glass funnel. The residue was washed with THF (3 × 30 mL). After evaporation of the combined filtrates the crude products were purified by Kugelrohr distillation or flash chromatography over silica gel (hexane/EtOAc).

Method B:

To a stirred solution of Ni(acac)₂ (128 mg, 0.5 mmol), dry THF (15 mL) or EtOAc (15 mL) and enone (10 mmol) was added TMA (1 mL, 10.5 mmol) dropwise at 0°C (Caution, neat TMA is highly pyrophoric!). After an appropriate time (see Tables), the reaction was diluted with hexane (15 mL) and quenched by careful addition of sat. aq NH₄Cl (1.5 mL) and worked up as described above.

2,3-Dimethyl-5-isopropenylcyclohexanone (2):

Purification by Kugelrohr distillation (150°C/15 mbar) gave **2** as a colorless liquid (88%, method B).⁷ The product was obtained as a diastereomeric mixture of 4 isomers (2:1:1:1.5 by GC). Major isomer:

¹H NMR (CDCl₃): δ = 1.07 (3 H, d, *J* = 6 Hz), 1.12 (3 H, d, *J* = 6 Hz), 1.45 (1 H, m), 1.72 (1 H, m), 1.75 (3 H, d, *J* = 2.5 Hz), 1.80–2.10 (2 H, m), 2.20–2.50 (2 H, m), 2.65 (1 H, m), 4.75 (2 H, m).
¹³C NMR (CDCl₃): δ = 11.5, 20.3, 20.7, 39.8, 39.9, 45.0, 46.4, 51.1, 109.4, 147.4, 212.3.

IR (neat): ν = 2960, 2920, 2870, 1710, 1450, 1370, 1210, 890 cm⁻¹.
 MS: *m/z* (%) = 167 (26), 166 (M⁺, 52), 151 (17), 123 (37), 109 (30), 95 (97), 83 (45), 65 (70), 67 (100).

4-(2,6,6-Trimethylcyclohex-2-enyl)pentan-2-one (4):

Kugelrohr distillation (165°C/15 mbar) gave a colorless liquid containing a mixture of stereoisomers (83%, method A) (5:1 by GC). Spectroscopic data are in agreement with those in references 4, 7 and 19.

2-tert-Butyl-5-methylcyclohexanone (6):

Kugelrohr distillation (135°C/15 mbar) yielded **6** as a colorless liquid (83%, method A).⁷ The *trans/cis* ratio of the diastereomeric mixture was found to be 1.5:1 by GC.

¹H NMR (CDCl₃) *trans* isomer: δ = 1.00 (9 H, s), 1.05 (3 H, s), 1.30–1.50 (2 H, m), 1.75–2.20 (5 H, m), 2.25 (1 H, m); *cis* isomer: δ = 1.35 (1 H, t, *J* = 11 Hz), 1.60 (1 H, m), 1.75–2.20 (5 H, m), 2.49 (1 H, q, *J* = 6 Hz).

¹³C NMR (CDCl₃) *trans* isomer: δ = 22.9, 27.6, 28.5, 31.6, 34.7, 36.3, 52.4, 59.3, 211.9; *cis* isomer: 19.4, 24.5, 27.9, 31.3, 32.1, 32.3, 50.3, 59.3, 212.8.

IR (neat): ν = 2960, 2920, 2870, 1710, 1460, 1360, 1120 cm⁻¹.

MS: *m/z* (%) = 168 (M⁺, 4), 153 (6), 112 (100), 97 (20).

3,3-Dimethyl-2-(pent-2-enyl)cyclopentanone (8):

Kugelrohr distillation of the crude product **8** (160°C/15 mbar) yielded a colorless liquid (85%, method A).

¹H NMR (CDCl₃): δ = 0.85 (3 H, s), 0.97 (3 H, t, *J* = 7.5 Hz), 1.20 (3 H, s), 1.65–1.80 (2 H, m), 1.90 (1 H, t, *J* = 7 Hz), 2.00–2.40 (6 H, m), 5.30–5.50 (2 H, m).

¹³C NMR (CDCl₃): δ = 14.0, 20.5, 21.6, 22.6, 29.0, 35.0, 35.8, 39.4, 60.6, 127.4, 132.0, 219.7.

IR (neat): ν = 3000, 2960, 2930, 2870, 1740, 1460, 1370, 1140 cm⁻¹.

MS: *m/z* (%) = 181 (M⁺, 22), 165 (29), 124 (48), 109 (22), 97 (100).

3,3,5,5-Tetramethylcyclohexanone (10):

Kugelrohr distillation (120°C/15 mbar) yielded a colorless liquid, which solidified on cooling (91%, method B). Spectroscopic data are in agreement with those in reference 20.

4a,8a-Dimethyloctahydronaphthalen-2(3H)-one (12):

Flash chromatography (hexane/EtOAc) yielded a colorless oil (84%, method B). Diastereomeric mixture (*cis/trans* ratio 9:1):

¹H NMR (CDCl₃): δ = 0.91 + 0.95 (3 H, s, 9:1), 1.04 (3 H, s), 1.15–1.45 (4 H, m), 1.45–2.60 (10 H, m).

Major isomer:

¹³C NMR (CDCl₃): δ = 21.4, 21.9, 21.9, 23.0, 23.4, 33.8, 34.8, 35.0, 35.4, 38.2, 38.1, 40.6, 212.7.

IR (neat): ν = 2920 (s), 1713 (s), 1460 (m), 1443 (m) cm⁻¹.

MS: *m/z* (%) = 180 (M⁺, 41), 165 (32), 137 (22), 123 (33), 109 (100).

4a,8a-Dimethyloctahydro-2(1H),5(6H)-dione (14):

Flash chromatography gave a colorless solid after evaporation (87%, method B). Diastereomeric mixture (*cis/trans* 1.5:1).

Major product:

¹H NMR (CDCl₃): δ = 0.86 (3 H, s), 1.23 (1 H, m), 1.45 (3 H, s), 1.76 (1 H, m), 1.85–2.50 (8 H, m), 2.59 (1 H, d, *J* = 15 Hz), 2.78 (1 H, m).

¹³C NMR (CDCl₃): δ = 19.1, 21.2, 21.9, 27.9, 33.4, 36.3, 37.2, 42.1, 50.1, 50.2, 210.1, 214.6.

IR (KBr): ν = 2950 (s), 1708 (s), 1700 (s) cm⁻¹.

MS: *m/z* (%) = 194 (M⁺, 72), 151 (14), 138 (62), 125 (100), 111 (43).

Minor product:

¹H NMR (CDCl₃): δ = 0.99 (3 H, s), 1.22 (3 H, s), 1.40–1.65 (2 H, m), 1.80–2.05 (4 H, m), 2.20–2.32 (1 H, m), 2.35–2.49 (3 H, m), 2.50–2.66 (2 H, m).

¹³C NMR (CDCl₃): δ = 20.8, 21.5, 22.1, 31.2, 34.1, 36.8, 38.5, 44.4, 50.4, 51.4, 211.3, 214.5.

5β-Methyl-5β-androstane-3,17-dione (16):

Flash chromatography (hexane/EtOAc) yielded a colorless solid (76%, method B).²¹ Mp 167°C, [α]_D²⁰ + 106.0° (*c* = 0.5, CHCl₃).

¹H NMR (CDCl₃): δ = 0.90 (6 H, s), 0.98 (3 H, s), 1.10–2.55 (20 H, m), 3.00 (1 H, d, *J* = 15 Hz).

¹³C NMR (CDCl₃): δ = 13.7, 17.1, 20.8, 21.7, 24.6, 26.4, 31.6, 32.0, 34.7, 35.0, 35.8, 37.4, 37.9, 41.8, 42.1, 47.4, 48.9, 51.7, 212.4, 220.5.

IR (KBr): ν = 2920 (s), 1740 (s), 1715 (s) cm⁻¹.

MS: *m/z* (%) = 302 (M⁺, 100), 287 (20), 258 (34), 231 (42), 213 (29), 175 (27), 161 (15), 149 (16), 123 (47), 107 (42).

17β-Acetoxy-5-methyloestr-9(10)-en-3-one (18):

Flash chromatography (hexane/EtOAc) yielded a colorless solid (75%, method A), diastereomeric ratio (5α/5β 1:2, determined by ¹H NMR), mp 79–105°C.

¹H NMR (CDCl₃): δ = 0.92 (3 H, s), 1.01 (1 H, s), 1.08 (2 H, s), 1.10–1.87 (10 H, m), 1.90–2.57 [11 H, m; 2.05 (3 H, s)], 2.70 (1 H, m), 2.94 (1 H, m), 4.60 (1 H, q, *J* = 8 Hz).

¹³C NMR (CDCl₃): δ = 11.4, 21.1, 23.7, 24.7, 25.6, 26.1, 27.6, 37.1, 38.4, 38.5, 39.0, 40.1, 42.4, 51.6, 56.0, 82.4, 131.1, 133.2, 171.0, 211.6, 212.0.

IR (KBr): ν = 2910 (s), 1735 (s), 1712 (s), 1445 (m), 1418 (v), 1240 (s) cm⁻¹.

MS: *m/z* (%) = 330 (M⁺, 18), 315 (3), 270 (20), 255 (34), 212 (8), 197 (11), 159 (17).

(±)-β-Cuparenone (20):

Flash chromatography (hexane/EtOAc) yielded a colorless oil after evaporation (91%, method B).

- ¹H NMR (CDCl₃): δ = 0.73 (3 H, s), 1.22 (3 H, s), 1.41 (3 H, s), 2.21–2.40 (6 H, m), 3.12 (1 H, d, *J* = 17.5 Hz), 7.17 (4 H, m).
¹³C NMR (CDCl₃): δ = 20.8, 24.1, 24.5, 26.3, 41.8, 47.8, 50.7, 52.5, 126.6, 128.7, 135.8, 141.3, 218.1.
 IR (neat): ν = 2960 (s), 1741 (s), 1515 (m), 1405 (m), 1380 (m), 1288 (m), 1205 (m) cm⁻¹.
 MS: *m/z* (%) = 216 (M⁺, 15), 199 (2), 159 (3), 132 (100), 117 (23).
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