Copper-Catalyzed Conjugate Addition of Trimethylaluminium to α,β-Unsaturated Ketones

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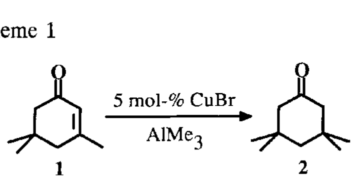
The conjugate methylation of α,β-unsaturated ketones with trimethylaluminium occurs smoothly in a very simple procedure under the catalytic effect of Cu^I salts. Scope and limitations of this process as well as the influence of solvent and catalyst on the kinetics were studied. In addition, the effect of chlorotrimethylsilane as an additive was investigated. Attack on the carbonyl group in 1,2-fashion could not be observed under the reaction conditions.

The 1,4-addition of hydrocarbon substituents to α,β-unsaturated carbonyl compounds is usually achieved by using organocuprate reagents[1,2]. Other authors demonstrated the use of organozincates[3], organomanganese reagents[4], organotitanates[5] or Grignard compounds[1,6]. Attempts to transfer organoaluminium reagents to enones were successful for the introduction of vinyl[7] and alkynyl[8] groups but only gave moderate results when using alkylaluminium reagents[9]. However, remarkable results were obtained by the reaction of trialkylaluminium with α,β-unsaturated acetals[10].

In a recent communication, our group[11] described the addition of trialkylaluminium to enones under Cu^I catalysis in high yields. In continuation of this work we have determined the scope and limitations of this method as well as the influence of various solvents and Cu^I catalysts.

Thus, when isophorone (**1**) was treated with trimethylaluminium (TMA, 10% solution in hexane) in the presence of a catalytic amount of CuBr (5 mol-%) in THF or ethyl acetate (EtOAc) at room temperature, 3,3,5,5-tetramethylcyclohexanone (**2**) was formed in 89% or 86% yield, respectively. The reaction time decreased by using chlorotrimethylsilane (TMSCl) as an additive (96% yield), or neat TMA in THF (yield 95%).

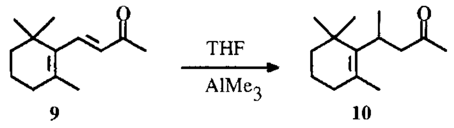
Scheme 1



THF	89%
EtOAc	86%
THF, TMSCl	96%
THF, neat $AlMe_3$	95%

The use of only 0.5 mol-% of CuBr led to incomplete consumption of the organometallic reagent within 48 hours (Figure 2). On the other hand, more reactive enones such as β-ionone (**9**) gave high yields even in the presence of reduced amounts of catalyst (96% of **10**, 0.1 mol-% of catalyst), without significantly increased reaction times (Scheme 2). The product resulting from the competing 1,6-alkylation was not detected by GC or NMR.

Scheme 2



5 mol-% CuBr	99%
0.1 mol-% CuBr	96%

As shown in Table 1, the scope of this reaction is very broad. Treatment of various cyclic and noncyclic enones with trimethylaluminium (10% solution in hexane) in THF mainly resulted in good to excellent yields of Michael-type reaction products. In some cases the addition of TMSCl may be necessary in order to complete the conversion (entry 8). In the case of 1-acetyl-2-cyclohexene (**5**) the use of EtOAc as solvent was found to be advantageous (entry 3). Especially the enolates of open-chain or macrocyclic enones resulting from 1,4-addition tended to undergo a vinylogous aldol-type condensation to unreacted starting material (Scheme 3). These difficulties were circumvented by replacement of trimethylaluminium as a solution in hydrocarbon solvents by neat trimethylaluminium[31] (entries 10–14), which are both commercially available.

As shown in Figure 1, the influence of the solvent used for the reaction is of great significance for the formation of by-products. For example, treatment of 3-nonen-2-one (**19**) with trimethylaluminium (10% solution in hexane) in nonpolar solvents such as hexane under noncatalytic conditions results in fast 1,2-addition to the carbonyl group. On the other hand, a very slow 1,2-addition reaction takes place in the presence of THF. Solvents like diethyl ether or EtOAc lead to significantly better results than hexane; however, they do not match the results obtained with THF. These results are in good agreement with the fact that THF is a highly coordinative solvent for organoaluminium compounds. Takashi[12] has published results concerning the re-

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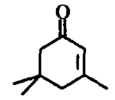
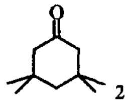
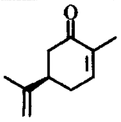
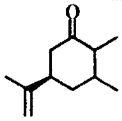
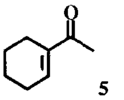
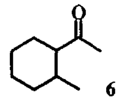
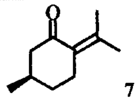
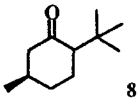
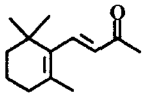
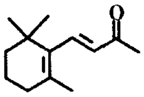
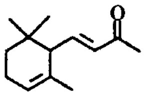
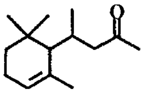
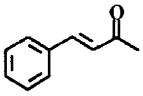
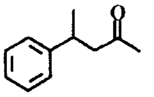
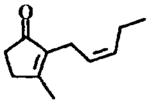
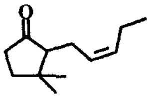
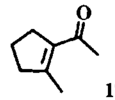
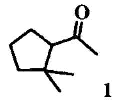
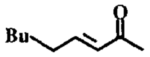
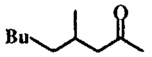
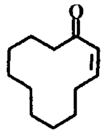
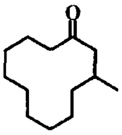
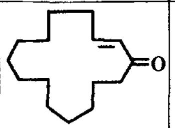
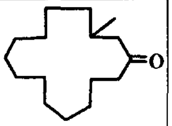
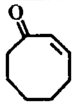
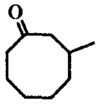
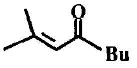
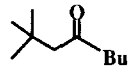
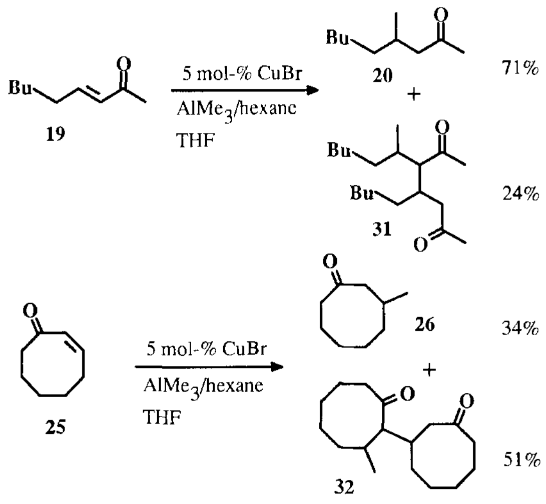
Table 1. Copper-catalyzed conjugate addition of TMA to various α,β-unsaturated ketones; methods: **A**: 5 mol-% CuBr, THF, TMA (10% solution in hexane), enone; **B**: 5 mol-% CuBr, EtOAc, TMA (10% solution in hexane), enone; **C**: 5 mol-% CuBr, THF, TMA (neat), enone; **D**: 5 mol-% CuBr, THF, TMSCl, TMA (10% solution in hexane), enone

	Enone	Product	Method	Time	Yield[a]
1	 **1**	 **2**	A B C D	9 h 9 h 5 h 4 h	89% 86% 95% 96%
2	 **3**	 **4**	A B D	0.5 h 3 h 0.5 h	92% 88% 96%
3	 **5**	 **6**	A B C D	1.5 h 5 h 2 h 1.5 h	75% 88% 81% 75%
4	 **7**	 **8**	A B D	0.5 h 1.5 h 4 h	95% 71% 93%
5	 **9**	 **10**	A C	2 h 0.5 h	99% 96%
6	 **11**	 **12**	A B D	2 h 4 h 2 h	90% 86% 87%
7	 **13**	 **14**	A B B D	1 h 4 h 48 h 0.5 h	91% 51%[h] 36%[i] 83%
8	 **15**	 **16**	A B C D	23 h 23 h 23 h 8 h	77%[e] 70%[e] 73%[e] 99%
9	 **17**	 **18**	C D	2 h 1.5 h	95% 99%
10	 **19**	 **20**	A B C D	1 h 1 h 1.5 h 0.5 h	71%[b] 45%[c] 96% 73%[d]
11	 **21**	 **22**	A C	0.5 h 2 h	54%[f] 90%
12	 **23**	 **24**	C	1.5 h	99%
13	 **25**	 **26**	A C	1 h 4 h	34%[g] 86%
14	 **27**	 **28**	C	1.5 h	99%

[a] Isolated yield, corrected by GC to the purity of substrate and product. – [b] 24% of product **31**. – [c] 47% of product **31**. – [d] 26% of product **31**. – [e] 21 to 26% of recovered starting material **15**. – [f] Yield of side product not determined. – [g] 51% of product **32**. – [h] 27% of the corresponding enol acetate **30**. – [i] 43% of the corresponding enol acetate **30**.

Scheme 3



action of triethylaluminium with various electron donors. Amines and ethers open the dimeric structure of low molecular organoaluminium compounds to form monomeric 1:1 complexes such as $R_3Al \cdot XR'$ (X = N, O). These complexes, especially those comprising ethereal ligands, showed a significantly reduced electronegativity of aluminium. The presumed ionic structure of these complexes is supported by their remarkably high electrical conductivites. The weak nucleophilicity of the organometallic reagent and its lower activity as a Lewis acid can be derived from these properties.

In an effort to determine the optimal Cu^I catalyst the reaction of isophorone (**1**) with TMA in EtOAc was studied (Table 2). As shown, CuBr is the catalyst of choice, but CuBr · SMe_2 may also be used with similar results. In fact, CuCN shows a higher catalytic activity, but its use is limited due to its toxicity[30]. The other tested catalysts were less efficient as shown in Table 2. Interestingly, we noticed a significant salt effect. The methylation was suppressed by addition of LiBr to the CuBr-catalyzed reaction; Mg salts gave similar results.

Additionally, we examined the kinetic effect of reduced amounts of CuBr catalyst on this method. With less reactive enones the reaction stops prior to complete consumption of starting material by using amounts of catalyst below 0.5 mol-%. However, amounts down to 1 mol-% were tolerated as was demonstrated by the reaction of isophorone (**1**) (Figure 2). This effect may be due to decomposition of the

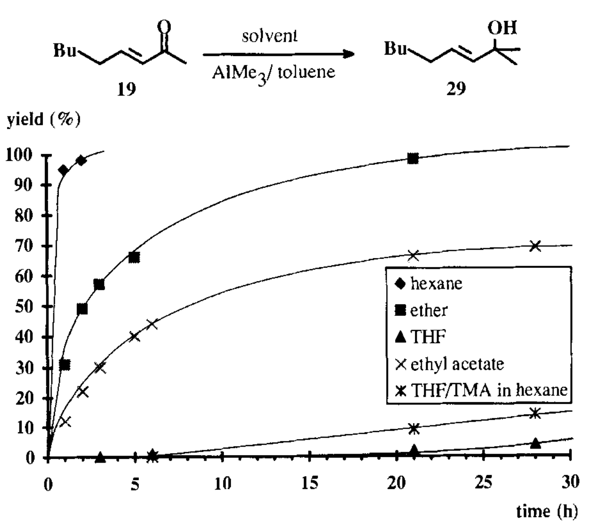


Figure 1. Kinetic influence of various solvents used in the noncatalyzed addition reaction of TMA (unless noted otherwise used as a 10% solution in toluene) with 3-nonen-2-one (**19**)

Table 2. Consumption of starting material in the reaction of isophorone (**1**) with TMA (10% solution in hexane) at room temperature; unless stated otherwise, 5 mol-% of various Cu^I catalysts was used in ethyl acetate as solvent; no reaction was obtained by using CuCl as a catalyst[30]

	CuCN	CuBr	CuBr·SMe2	CuBr (0.1 mol-%)	CuBr·2 LiBr	CuSCN	CuI
6 h	99%	96%	93%	32%	--[a]	11%	15%
24 h		99%	99%	78%	64%	51%	37%

[a] Conversion not determined.

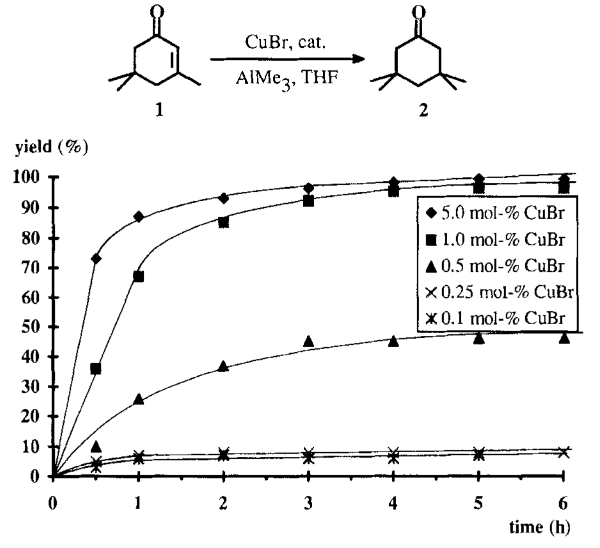


Figure 2. Kinetic influence of the amount of CuBr catalyst in the 1,4-addition reaction of neat TMA and isophorone (**1**) in THF at room temperature

catalyst during the reaction as concluded from the formation of elemental Cu^0 during long reaction times. As shown above (Scheme 2), highly reactive enones such as β-ionone (**9**) lead to quantitative yields of methylation products even in the presence of only 0.1 mol-% CuBr (96% of **10**, 0.5 h).

In summary, Cu^I-catalyzed addition of TMA to α,β-unsaturated ketones is a very efficient method of methylation. It is superior to other methods because it avoids the use of low temperatures and additives such as HMPA or TMEDA. Furthermore, there is no need for a titration protocol concerning the addition of starting material, and the workup procedure is quite simple. In addition, the use of nonstoichiometric copper compounds leads to a reduced ecological hazard. Due to these characteristics the described method is a useful alternative to previous methods, especially in view of industrial utilization.

Experimental

All experiments were performed under N_2. Glassware was not dried before use. Solvents and organic compounds were used without further purification in commercially available quality. Compounds **21**[28], **23**[24a] and **25**[25] were prepared by methods described in the literature. – IR: Nicolet 20 SXB or Nicolet 710; as capillary film (neat). – MS (70 eV): Vacuum Generator TRIO 2. – NMR (^1H: 300 MHz; ^{13}C: 75 MHz): General Electric QE 300; in $CDCl_3$ as solvent, tetramethylsilane as an internal standard. – GC: 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. – For substances purified by kugelrohr distillation the given temperatures are not the expected boiling points of the product but the chosen temperature of the oven. Yields are corrected with regard to the purity of substrate and product obtained by GC.

Method A [B]. – General Procedure for the Reaction of Enones with TMA as a Solution in Hexane: To a magnetically stirred suspension of 72 mg (0.5 mmol) of CuBr, 15 ml of THF [EtOAc] and 10.7 ml (10 mmol) of TMA (10% solution in hexane) 10 mmol of the neat enone was quickly added by means of a syringe. After the reaction mixture had been stirred for the given time (Table 1), the reaction was quenched by careful addition of 1.5 ml of a saturated aqueous NH_4Cl solution. After recooling to room temperature, the mixture was filtered through a "Duran sintered-disc filter funnel (D3)", and the residue was washed three times with 30 ml of THF. The solvent was removed from the combined filtrates under reduced pressure, and the resulting crude product was purified by kugelrohr distillation.

Method C. – General Procedure for the Reaction of Enones with Neat TMA[31]: To a stirred suspension of 72 mg (0.5 mmol) of CuBr in 24 ml of THF 1.1 ml (11.5 mmol) of TMA was added in one portion by means of a syringe. ***Caution:*** Neat TMA is a volatile, highly pyrophoric liquid; use gastight Hamilton syringes for handling! After 0.5 h, the enone (10 mmol) was added quickly by means of a syringe, and the mixture was stirred for the given reaction time (Table 1), then worked up as described in method A/B.

Method D. – General Procedure for the Reaction of Enones with TMA/TMSCl: To a suspension of 72 mg (0.5 mmol) of CuBr, 15 ml of THF and 10.7 ml (10 mmol) of TMA (10% solution in hexane) 1.52 ml (12 mmol) of TMSCl was added. Then 10 mmol of the enone was quickly added by means of a syringe, and the mixture was stirred for the given reaction time (Table 1). It was subsequently worked up as described in method A/B (2.0 ml of an NH_4Cl solution was used).

3,3,5,5-Tetramethylcyclohexanone (**2**): The pure product **2**, 1.48 g (96%, method D), was obtained by kugelrohr distillation in a Büchi apparatus (120°C/15 mbar, b.p. 79°C/12 Torr[13a]) as a colorless liquid, which crystallised on cooling. Spectroscopic data were in agreement with those reported in ref.[13].

(3R)-3-Isopropenyl-5,6-dimethylcyclohexanone (**4**): Purification was performed by kugelrohr distillation (145–150°C/12 mbar, b.p. 102–103°C/11 Torr[14]) to yield 1.60 g (96%, method D) of **4** as a colourless liquid. The known product (ref.[14]) was obtained as an diastereomeric mixture of 4 isomers (10:20:10:1 by GC). – IR: $\tilde{\nu}$ = 2960 cm^{-1}, 2920, 2870, 1710, 1450, 1370, 1210, 890. – MS: *m/z* (%) = 167 (26), 166 (52) [M$^+$], 151 (17), 123 (37), 109 (30), 95 (97), 83 (45), 65 (70), 67 (100), 55 (49). – ^{1}H NMR: δ = 4.75 (m, 2H), 2.75–2.55 (m, 1H), 2.50–2.20 (m, 2H), 2.10–1.80 (m, 2H), 1.75 (d, *J* = 2.5 Hz, 3H), 1.80–1.65 (m, 1H), 1.55–1.35 (m, 1H). 5- and 6-CH$_3$ (6H): major isomer (**a**): δ = 1.12 (d, *J* = 6 Hz), 1.07 (d, *J* = 6 Hz); second isomer (**b**): δ = 1.10 (d, *J* = 6 Hz), 1.05 (d, *J* = 6 Hz); third isomer (**c**): δ = 1.00 (d, *J* = 6 Hz), 0.84 (d, *J* = 6 Hz). – ^{13}C NMR: **a**: δ = 212.3, 147.4, 109.4, 51.1, 46.4, 45.0, 39.9, 39.8, 20.7, 20.3, 11.5; **b**: δ = 213.2, 147.5, 111.6, 48.3, 46.5, 41.0, 37.6, 34.8, 20.5, 20.5, 13.0; **c**: δ = 212.7, 147.4, 109.6, 51.5, 43.9, 40.7, 36.2, 35.1, 21.8, 13.9, 11.9.

1-Acetyl-2-methylcyclohexane (**6**): The crude product was purified by kugelrohr distillation (130–140°C/20 mbar) and isolated as a colourless liquid; yield 1.05 g (88%, method B; 8.5 mmol-scale). GC and NMR analysis showed two isomers in a *trans/cis* ratio depending on the chosen method [3:1 (A/C), 1:2 (B), 10:1 (D)]. Spectroscopic data agreed with those reported in ref.[15,19]. – Additional ^{13}C-NMR data: *trans* isomer (**a**): δ = 213.0, 59.2, 34.4, 33.7, 29.5, 28.9, 25.9, 25.6, 20.5; *cis* isomer (**b**): δ = 211.1, 54.0, 32.6, 30.6, 28.4, 24.9, 21.4, 21.0, 14.1.

(5R)-1-tert-Butyl-5-methylcyclohexanone (**8**): The crude product was distilled in a kugelrohr apparatus (130–135°C/15 mbar, b.p. 40–45°C/0.2 Torr[16]) to yield 1.50 g (95%, method A) of **8** as a colourless liquid (ref.[16]). The *trans/cis* ratio of the diastereomeric mixture depends on the reaction and workup conditions and was found to be 1.5–2:1 for method A/B/C and 6:1 for method D (GC). – IR: $\tilde{\nu}$ = 2960 cm^{-1}, 2920, 2870, 1710, 1460, 1360, 1120. – MS: *m/z* (%) = 168 (4) [M$^+$], 153 (6), 112 (100), 97 (20), 83 (15), 69 (48), 57 (32). – ^{1}H NMR: *trans* isomer (**a**): δ = 2.25 (m, 1H), 2.20–1.75 (m, 5H), 1.50–1.30 (m, 2H), 1.05 (s, 3H), 1.00 (s, 9H); *cis* isomer (**b**): δ = 2.49 (q, *J* = 6 Hz, 1H), 2.20–1.75 (m, 5H), 1.60 (m, 1H), 1.35 (br. t, *J* = 11 Hz, 1H). – ^{13}C NMR: **a**: δ = 211.9, 59.3, 52.4, 36.3, 34.7, 31.6, 28.5, 27.6, 22.9; **b**: δ = 212.8, 59.3, 50.3, 32.3, 32.1, 31.3, 27.9, 24.5, 19.4.

4-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-pentanone (**10**): Kugelrohr distillation of crude **10** (170–175°C/12 mbar, b.p. 80°C/0.03 Torr[17]) yielded 2.10 g (99%, method A) as a colourless liquid. Spectral data were in agreement with those reported by Zink et al.[17]. – Additional ^{13}C-NMR data: δ = 208.4, 141.7, 127.9, 50.6, 40.0, 36.1, 34.1, 30.3, 28.6, 27.9, 27.8, 21.5, 20.0, 19.4.

4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-pentanone (**12**): After kugelrohr distillation (150–160°C/12 mbar, b.p. 75°C/0.02 Torr[18]) 1.90 g (90%, method A) of a colourless liquid was obtained as a mixture of stereoisomers. The spectroscopic data of product **12** were identical with those of the product described in ref.[9b,18], but no ^{13}C-NMR data are given. The isomeric ratio calculated by GC depends on the reaction conditions and was found to be 1:27 for method A, 1:9 for method B and 1:99 for method D. – ^{13}C NMR: major isomer (**a**): δ = 209.1, 134.8, 121.9, 55.1, 49.2, 33.4, 30.7, 30.5, 28.3, 28.2, 28.1, 26.0, 23.9, 23.2; minor isomer (**b**): δ = 208.7, 139.8, 120.9, 55.1, 49.2, 31.9, 31.7, 30.6, 30.0, 29.9, 27.4, 27.0, 23.0, 22.7.

4-Phenyl-2-pentanone (**14**): The pure product **14** was obtained by distillation in a kugelrohr apparatus (170°C/12 mbar, b.p. 70°C/0.15 Torr[20]) as a colourless liquid; yield 1.47 g (91%, method A). Spectroscopic data were in agreement with those published in ref.[19,20].

2-(2-Penten-1-yl)-3,3-dimethylcyclopentanone (**16**): Purification was carried out by kugelrohr distillation (150–155°C/14 mbar) to yield 1.84 g (99%, method D) of **16** as a colourless liquid. Due to the used commercial starting material the product was isolated as a 8:1 mixture of *cis/trans* isomers relating to the side-chain double bond. – IR: $\tilde{\nu}$ = 3000 cm^{-1}, 2960, 2930, 2870, 1740, 1460, 1370, 1140. – MS: *m/z* (%) = 180 (4) [M$^+$], 165 (15), 124 (54), 109 (22), 96 (99), 95 (100), 81 (18), 67 (21), 55 (43). – ^{1}H NMR: δ = 5.41 (m, 2H), 2.38–2.00 (m, 6H), 1.90 (t, *J* = 7 Hz, 1H), 1.72 (m, 2H), 0.85 (s, 3H). 3′-CH$_3$ (3H): *cis* isomer (**a**): δ = 1.20 (s); *trans* isomer (**b**): δ = 1.18 (s). 10-CH$_3$ (3H): **a**: δ = 0.99 (t, *J* = 7.5 Hz); **b** = 0.98 (t, *J* = 7.5 Hz). – ^{13}C NMR: **a**: δ = 219.7, 132.0, 127.4, 60.6, 39.4, 35.8, 35.0, 29.0, 22.6, 21.6, 20.5, 14.0; **b**: δ = 219.8, 133.0, 127.6, 60.3, 39.9, 35.5, 35.1, 29.1, 28.2, 25.4, 21.6, 13.7. – $C_{12}H_{20}O$ (180.3): calcd. C 79.94, H 11.18, O 8.87; found C 79.37, H 10.87, O 9.03.

1-Acetyl-2,2-dimethylcyclopentane (**18**): The crude product was purified by kugelrohr distillation (100°C/20 mbar, b.p. 48–48.5°C/2 Torr[21a]) to yield 1.40 g (99%, method A) of **18** as a colourless liquid, spectroscopic data see ref.[21b]. – Additional ^{13}C-NMR data: δ = 211.0, 61.9, 42.6, 42.4, 31.7, 29.7, 27.3, 23.6, 22.1.

4-Methyl-2-nonanone (**20**): The crude product was distilled in a kugelrohr apparatus (140–150°C/20 mbar) to yield 1.42 g (96%, method C) of **20** as a colourless liquid (b.p. 108–112°C/39 Torr, ref.[22]). – IR: $\tilde{\nu}$ = 2960 cm^{-1}, 2920, 2875, 2860, 1715, 1460, 1360, 1170. – MS: *m/z* (%) = 156 (25) [M$^+$], 141 (17), 127 (15), 113 (13), 98 (14), 85 (43), 58 (77), 43 (100). – ^{1}H NMR: δ = 2.41 (dd, *J* = 5 Hz, *J* = 15.5 Hz, 1H), 2.22 (dd, *J* = 8 Hz, *J* = 15.5 Hz, 1H), 2.12 (s, 3H), 1.99 (m, 1H), 1.25 (m, 8H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.88 (t, *J* = 6.5 Hz, 3H). – ^{13}C NMR: δ = 208.6, 51.3, 36.9, 31.9, 30.2, 29.3, 26.5, 22.5, 19.8, 13.9.

3-Methylcyclododecanone (**22**): After distillation in a kugelrohr apparatus (180–190°C/12 mbar), 1.74 g (90%, method C) of **22** was obtained as a colourless liquid. Compound **22** is a known product[23], but no spectroscopic data are available. – IR: $\tilde{\nu}$ = 2930 cm^{-1}, 2860, 1780, 1705, 1470, 1440, 1360. – MS: *m/z* (%) = 196 (7) [M$^+$], 97 (33), 85 (32), 71 (100), 55 (52). – ^{1}H NMR: δ = 2.68 (ddd, *J* = 4 Hz, *J* = 12.5 Hz, *J* = 16 Hz, 1H), 2.40–2.12 (m, 4H), 1.92 (m, 1H), 1.53–1.12 (m, 16H), 0.99 (d, *J* = 6 Hz, 3H). – ^{13}C NMR: δ = 212.0, 49.8, 39.7, 31.4, 28.2, 25.1, 24.3, 24.0, 24.0, 22.5, 22.4, 22.0, 20.5.

3-Methylcyclopentadecanone (**24**): Kugelrohr distillation (140–150°C/0.06 mbar, b.p. 145°C/0.9 Torr[24a]) yielded 1.55 g (99%, method C) of the natural product muscone (**24**) as a colourless oil. The spectral data were in agreement with those reported in ref.[24].

3-Methylcyclooctanone (**26**): The pure product **26**, 1.16 g (86%, method C), was obtained by distillation in a kugelrohr apparatus (135–145°C/12 mbar). The colourless liquid is a known product[25], but only poor spectroscopic data were published. – IR: $\tilde{\nu}$ = 2960 cm^{-1}, 2930, 2880, 1700, 1470, 1460, 1450, 1210. – MS: *m/z* (%) = 140 (7) [M$^+$], 112 (12), 98 (26), 84 (18), 69 (100), 55 (70). – ^{1}H NMR: δ = 2.50–1.10 (m, 13H), 1.02 (d, *J* = 6 Hz, 3H). – ^{13}C NMR: δ = 215.6, 48.8, 42.6, 35.2, 32.7, 27.3, 24.3, 23.7, 22.8.

2,2-Dimethyl-4-octanone (**28**): Kugelrohr distillation (110–115°C/50 mbar, b.p. 69°C/13 Torr[26]) yielded 1.06 g (99%, method C; 8.5 mmol-scale) of a colourless liquid. – IR: $\tilde{\nu}$ = 2960 cm^{-1}, 2870, 1780, 1470, 1360. – MS: *m/z* (%) = 156 (20) [M$^+$], 99 (17), 85 (26), 71 (34), 57 (83), 43 (100). – ^{1}H NMR: δ = 2.39 (t,

J = 7.4 Hz, 2H), 2.30 (s, 2H), 1.53 (quint, J = 7.4 Hz, 2H), 1.31 (sext, J = 7.4 Hz, 2H), 1.02 (s, 9H), 0.91 (t, J = 7.4 Hz, 2H). – ^{13}C NMR: δ = 211.0, 54.9, 30.9, 29.7, 25.7, 22.3, 13.7.

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[30] Under reaction conditions as described by method C, CuCN shows a much lower catalytic activity; using CuCl as catalyst, up to 10% conversion of starting material was obtained.

[31] Additional remark: The referees criticized the use of neat TMA in some cases to obtain high yields. In our group the use of TMA as an ethereal stock solution (diethyl ether or THF) was examined to work well. However, such solutions are currently not commercially available for laboratory use, but may be available by ordering bulk scales from WITCO, Germany.

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