Control of Regioselectivity in the Transition-Metal-Catalysed Conjugate Additions of Alkylaluminium Compounds and Methyltitanium Ate Complexes to Androsta-1,4-diene-3,17-dione

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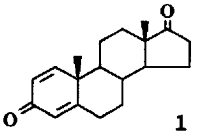
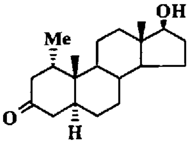
By a variation of the nature of the reagent system conjugate addition to the cross-conjugated steroidal dienone **1** occurs selectively either at C-1 or at the sterically hindered C-5. With Me_3Al or Me_4AlLi in the presence of catalytic amounts of Cu^I salts, a high regioselectivity (up to 97:3) in favour of position 1 is achieved. Application of ate complexes of aluminium and titanium in the presence of $Ni(acac)_2$ as catalyst, however, leads to a reversal of the regioselectivity in favour of position 5 (up to 11:89). Aluminium and titanium ate complexes are efficient reagents in the $Ni(acac)_2$-catalysed conjugate addition to sterically hindered enones.

The addition of organometallic compounds to enones is a useful and often highly selective alkylation method. A number of studies have been carried out with enones with the aim of discovering the parameters which control the 1,2 and 1,4 selectivity of this reaction[1]. The situation with cross-conjugated dienones is slightly more complicated, because steric factors may play an important role in additions to each of the double bonds of the dienone system of androsta-1,4-diene-3,17-dione (**1**). The dienone **1** is a starting material for many syntheses of steroidal drugs. The introduction of a 1-methyl group is a first step in the synthesis of mesterolone (**2**), a steroidal compound used for the treatment of the androgen-deficiency disease[2].



1

androsta-1,4-diene-
3,17-dione



2

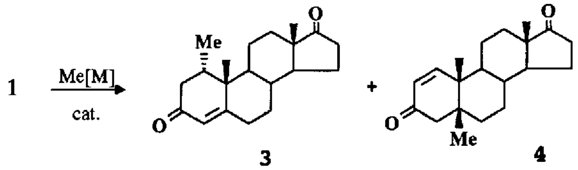
mesterolone

In order to investigate catalysed additions to 1,4 conjugated systems we found that **1** is a model compound suitable for studying the regioselectivity of different reagents. The steroid **1** containing two carbonyl groups and two enone structures displays high sterical hindrance in 1,4 addition reactions at C-5.

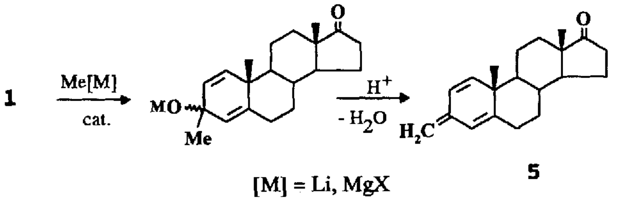
The introduction of a methyl group into the 1-position of **1** by a Michael-type reaction can be carried out with molar amounts of Me_2CuLi[3]. Due to the highly nucleophilic character of alkylmagnesium halides or alkyllithiums in copper catalysed reactions, the 1,2 addition is, as we found, the dominant reaction mode of doubly unsaturated dienones of type **1** even in the presence of accelerating agents like trimethylsilyl chloride (TMSCl) or boron trifluoride etherate[4].

Results and Discussion

In this paper we describe the results of our regioselectivity studies with transition-metal catalysts. We tested organometallic reagents of aluminium and titanium with less nucleophilic properties and compared them with the classical Grignard and alkyllithium reagents used in transition-metal-catalysed conjugate addition reactions. In our recent work, we have found that trimethylaluminium (Me_3Al) in the presence of catalytic amounts of CuBr or CuCN is a very efficient system for conjugate additions of alkyl groups with a high degree of regioselectivity[4]. In reaction with the steroid **1** the yield of **3** was up to 93% with TMSCl as an accelerating additive. The ratio of **3** to **4** was 97:3 (entry 1, Table 1).



The addition of Me_3Al with catalytic amounts of CuBr gives a higher yield and higher regioselectivity than Me_2CuLi (entries 4 and 5 in Table 1). Et_3Al transfers an ethyl group in 94% yield (entry 2, Table 1). The use of monomethylcopper (MeCu) in the presence of TMSCl also results in a good regioselectivity (entry 3). Using lithiumtetramethylaluminium (Me_4AlLi) and 5 mol-% of CuCN as catalyst (entry 6), we observed the formation of the isomers **3** and **4** in a ratio of 90:10, which is comparable with that when a molar amount of the cuprate reagent Me_2CuLi (entry 4) is employed. The system is significantly more nucleophilic than the system Me_3Al/CuBr (cat.). This results in a higher degree of 1,2 addition, which, after aqueous workup, affords compound **5** bearing an 3-exomethylene group (entry 6).



The reaction of MeMgBr in the presence of 5 mol-% of CuBr yielded mainly the 1,2 addition product **5** after workup (entry 7). With MeTi(O*i*Pr)$_4$Li in the presence of CuJ · 2 LiCl[5], the addition to the carbonyl group was the main reaction route (entry 9). The results we obtained with molar copper reagents and copper-catalysed reactions are summarised in Table 1.

Table 1. Regioselectivity in 1,4-addition reactions to the dienone **1** in catalytic and stoichiometric copper reactions

entry	R[M] (eq) and additive (eq)	catalyst [a]	T (°C)	solvent	% 1	3+4 (%) [b]	ratio 3 : 4 [c]	% 5
1	Me_3Al (1.1) + TMSCl (1.2)	CuBr	r.t.	THF	<2	96	97:3	< 2
2	Et_3Al (1.1) + TMSCl (1.2)	CuBr	r.t.	THF	<3	94	96:4[d]	< 3
3	MeCu (1.4) + TMSCl (1.2)	-	r.t.	THF	15	80	96:4	5
4	Me_2CuLi (1.8)	-	0	CH_2Cl_2	<2	82	93:7	13
5	Me_2CuLi (1.8)	-	0	THF	10	67	88:12	23
6	Me_4AlLi (1.2)	CuCN	-10/0	THF	12	73	92:8	14
7	MeMgBr (1.2)	CuBr	-50/0	THF	5	10	86:12	80
8	MeTi(OiPr)$_4$MgBr (1.2)	CuCN	-10/0	THF	12	8	85:15	74
9	MeTi(OiPr)$_4$Li (1.2) + TMSCl (1.2)	CuJ·2LiCl	-50/0	THF	20	<10	80:20	70

[a] Entry 1: 2 mol-% CuBr, 30 mmol **1**; entry 2, 6–9: 5 mol-% catalyst, experiments were performed on a 10 mmol scale. – [b] Isol. yields. – [c] The **3/4** ratio was estimated by GC analysis. – [d] The product is the 1-Et compound of type **3**.

When we tested Me_3Al in the presence of Ni(acac)$_2$ as a catalyst, we found that the two isomers **3** and **4** are formed in a 64:36 ratio. As we observed that the solvent plays an important part in this reaction[7]. Meisters et al.[6] described the addition of trimethylaluminium to 3-oxo-Δ^4-steroids in the presence of Ni(acac)$_2$ affording 5β-methylsteroids in 30–40% yield. We found that in addition to **1** the yield of **3** and **4** increased from 51% in diethyl ether to 92% in ethyl acetate (entries 1 and 2, Table 2). The use Co(acac)$_2$ as catalyst furnished the isomers **3** and **4** in a 30:70 ratio (entry 4).

The 1,4 addition of aluminium ate complexes is also catalysed by Ni(acac)$_2$. The ate complex Me_4AlLi, which was prepared from Me_3Al and MeLi, yielded in addition to **1** a 38:62 ratio of the regioisomers **3** and **4** (entry 3).

We found that the methyl ate complexes of titanium in combination with a nickel catalyst are useful reagents for 1,4 additions to sterically hindered enones[8]. In adapting this method to the conjugate addition to the steroid **1**, the use of MeTi(O*i*Pr)$_4$Li/cat. Ni(acac)$_2$ gave rise to a preferred attack at C-5 affording **3** and **4** in a ratio of 11:89 (entry 8). This selectivity is different from the copper rections in Table 1. The conditions of the Ni(acac)$_2$-catalysed reactions with ates and none-ates are listed in Table 2.

The ate complexes of MeLi are generally more selective in addition reactions at C-5 than those of MeMgX. The ate complexes of aluminium and titanium are generated in situ.

The ate complex $Me_3AlOArM$ was prepared from dimethylaluminium-2,6-di-*tert*-butylaluminium-4-methylphenoxide (DAD) as described by Yamamoto et al.[10] by treatment with MeLi or MeMgX. The reaction of MeMgX/cat. with Ni(acac)$_2$ and Me_2AlOAr or Ti(O*i*Pr)$_4$ (entries 6 and 7, Table 2) ate complexes are formed, which yielded a different result than MeMgCl (entry 9).

The results of the Ni(acac)$_2$-catalysed reactions compiled in Table 2 are different from those obtained by copper reagents in Table 1. Lowering of the Lewis acidity of the organometallic reagents (from none-ates to ates) leads to a change in regioselectivity and an attack from the more sterically deshielded side. Also more bulky reagents did not lead to an attack from the less hindered side to produce the preferred **3**. This indicates that also Lewis acids are involved in the nickel-catalysed 1,4-addition reactions and that the type of organometallic reagent used is important for the regioselectivity.

Most applications of organotitanium reagents are 1,2-addition reactions to carbonyl compounds[11a]. Less is known about 1,4 additions with titanium reagents[11b]. Titanates are very useful for selective $S_{N2'}$ allylation reactions. Conjugate additions of these are also accelerated by silyl chlorides or silyl triflates in the presence of a copper catalyst[5].

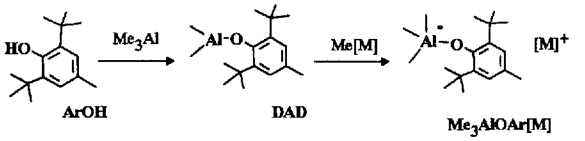
As shown in the conversion of **6** to **7**, Ni(acac)$_2$-catalysed reactions are also useful for the methylation of the sterically deshielded 5-position in **6**. Using 1 equiv. of Me_3Al as a 10% solution in hexane in ethyl acetate as solvent, we converted the steroid **6** to the 5β-methylsteroid **7** in 76% yield.

When we used MeTi(O*i*Pr)$_4$MgCl in the presence of 5 mol-% of Ni(acac)$_2$, we realized a clean conversion to the 5β-methyl steroid **7** in 73% yield. This shows that the systems are significant to synthetic applications for the conjugate addition of a methyl group to sterically hindered enones[7,8,12]. The experiment with Me_2CuLi gave the product **7** in moderate 19% yield. The methylation at C-5 of testos-

Table 2. $Ni(acac)_2$-catalysed 1,4-addition reactions to the dienone **1**

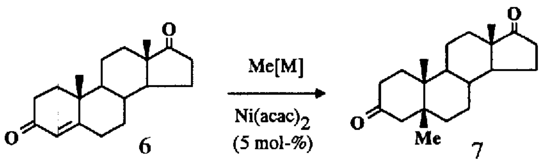
entry	Me[M](equiv.)	catalyst [b]	T (°C)	solvent	% 1	3+4 (%)[c]	ratio 3 : 4[d]	% 5
1	Me_3Al (1)	$Ni(acac)_2$	-20/0	AcOEt	-	92	64:36	< 2
2	Me_3Al (1)	$Ni(acac)_2$	-20/r.t.	ether	5	51	66:34	25
3	Me_4AlLi (1.2)	$Ni(acac)_2$	-20/0	THF	-	90	38:62	2
4	Me_3Al (1)	$Co(acac)_2$	0	AcOEt	20	69	30:70	10
5	$Me_3AlOArLi$(1.2) [a]	$Ni(acac)_2$	-30/0	THF	2	90	**15:85**	5
6	$Me_3AlOArMgBr$ (1.2)[a]	$Ni(acac)_2$	-30/0	THF	6	89	33:67	-
7	$MeTi(OiPr)_4MgCl$ (1.2)	$Ni(acac)_2$	-30/0	THF	10	85	34:66	< 5
8	$MeTi(OiPr)_4$ Li (1.2)	$Ni(acac)_2$	-30/0	THF	5	87	**11:89**	3
9	MeMgCl (1)	$Ni(acac)_2$	-50/0	THF	10	10	48:52	75

[a] OAr = 2,6-di-*tert*-butyl-4-methylphenoxide was used as ligand. – [b] 5 mol-% $Ni(acac)_2$ was used in the experiments without any previous activation of the catalyst[9]. – [c] Experiments were performed on a 10-mmol scale, yields are isolated. – [d] The ratio **3**/**4** was estimated by GC-analysis.



$$Ti(OiPr)_4 \xrightarrow{Me[M]} MeTi(OiPr)_4[M]$$

[M] = Li, MgCl, MgBr



Me[M] =	Me_3Al	76 %	(AcOEt)
	$MeTi(OiPr)_4MgCl$	73 %	(THF)
	Me_2CuLi	19 %	(THF)

terone 17-acetate with methylmagnesium iodide in the presence of cupric acetate as a catalyst was reported to proceed 17-hydroxy-5β-methylandrostan-3-one in 20% yield[13a]. The Luche method of conjugate addition of organozinc reagents is also suitable for conjugate additions to highly substituted enones[13b]. Also the conjugate addition reactions of silane-activated cuprates with 10-methyl-$\Delta^{1,9}$-2-octalone revealed the applicability of the feasibility in conjugate addition to sterically demanding enone structures[13c].

Conclusion

The use of organoaluminium compounds in the presence of a copper(I) catalyst leads to the formation of **3** from the dienone **1** with a high degree of selectivity. Nickel-catalysed reactions of organoaluminium compounds yield predominantly the isomer **4** resulting from an increased addition to the sterically hindered 5-position in comparison to the copper-catalysed reactions. Preferred attack at C-5 in **1** occurs when methyl ate complexes of Al and Ti are used as reagents.

Experimental

All reactions were carried out in capped vials by using the reagents described above. Products **3** and **4** were isolated from the reaction mixture by preparative chromatography on silica gel Merck F 254s with ethyl acetate/hexane as eluent. – The analysis of the reaction mixtures was carried out with a gas chromatograph fitted with a 25 m × 0.2 mm CP Sil 19 CB fused capillary column. The detector signal was integrated. The column temperature was programmed from 150°C to 250°C at 10°/min. Under these conditions, the retention times for **1**, **3**, and **4** were 17.1, 16.6, and 15.6 min, respectively. – Trimethylaluminium was obtained from commercial sources (Witco); MeLi, MeMgCl, MeMgBr, $Ni(acac)_2$, CuBr, and CuCN were purchased from Aldrich, $Ti(O\textit{i}Pr)_4$ was purified by distillation. – All solvents were used as commercially available without any further purification.

a) Preparation and Conversion of Me_4AlLi or $MeTi(OiPr)_4Li$: Under nitrogen, 12 mmol of trimethylaluminium (10.5 ml of a 15% toluene solution) [or 12 mmol of $Ti(O\textit{i}Pr)_4$ in 10 ml of dry THF] is cooled at −30°C and treated with 12 mmol of methyllithium (7.5 ml of a 1.6 M solution of MeLi in ether) and stirred for 15 min at this temperature. Then 128 mg (0.5 mmol) of $Ni(acac)_2$ is added followed by a solution of 2.84 g of steroid **1** (in 10 ml of THF). The mixture is then warmed up to 0°C over a period of 1 h and stirred for further 4 h at this temp. The reaction is controlled by thin-layer chromatography (TLC) on silica gel with ethyl acetate/hexane (1:1) as eluent. The relative retention is 0.3 for **1**, 0.42 for **3**, 0.5 for **4**, and 0.85 for **5**. The reaction is quenched with NH_4Cl/water and the products are extracted with ethyl acetate and dried over $MgSO_4$.

b) Preparation of Me_3AlOAr and Conversion with **1**: To 12 mmol of Me_3Al (10.5 ml of a 15% toluene solution) 12 mmol of 2,6-di-*tert*-butyl-4-methylphenol is added. When the formation of methane is completed, the solution is cooled to −30°C. 12 mmol of methyllithium (7.5 ml of a 1.6 M solution in ether) is added followed by 0.5 mmol (128 mg) of $Ni(acac)_2$ and 10 mmol (2.84 g) of the dienone **1**. The reaction is quenched in a similar way as described in the above example.

For preparation of the magnesium bromide salts, MeMgBr is used in a similar manner instead of MeLi in the ate-forming step. $Ti(O\textit{i}Pr)_4$ was purchased from Aldrich and is freshly distilled.

1α-Methylandrost-4-ene-3,17-dione (**3**) *from* **1** *with $Me_3Al/CuBr$* (Entry 1, Table 1): 8.52 g (30 mmol) of androsta-1,4-diene-3,17-dione (**1**) and 86 mg (0.6 mmol) of CuBr are dissolved in 70 ml of tetrahydrofuran and the solution is stirred under nitrogen. 28.4 ml

(33 mmol) of a 10% solution of Me_3Al in toluene is added at 20 °C. To this solution, 3.92 g (36 mmol) of trimethylsilyl chloride is added. The reaction mixture is stirred for 2 h at room temp. The reaction is quenched with 3 ml water, the inorganic material is filtered off and washed twice with ethyl acetate. GC analysis reveals that the reaction mixture contains the products **3** and **4** in a ratio of 97:3. The crude mixture is purified by chromatography on silica gel with a mixture of hexane/ethyl acetate as eluent. The first fraction contains the 5β-methyl isomer **4** (0.27 g, 2.6%). After evaporation of the solvent, the second fraction yielded 8.32 g of 1α-methylandrost-4-ene-3,17-dione (**3**) (93%), m.p. 154 °C, $[\alpha]_D^{20} = -205.6$ (c = 1 in $CHCl_3$). – ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.95 (s, 3H, 19-CH_3), 0.97 (d, 3H, ^2J = 7 Hz, 1α-CH_3), 1.35 (s, 3H, 18-CH_3), 1–2.75 (m, 17H), 5.73 (s, 1H, 4-H).

5β-Methylandrost-1-ene-3,17-dione (**4**) (Entry 8, Table 2): A solution of 12 mmol (3.4 g) of freshly distilled $Ti(OiPr)_4$ in 10 ml dry tetrahydrofuran (THF) is cooled to −30 °C and treated with 7.5 ml (12 mmol) of a 1.6 M MeLi ether solution. The reaction mixture is stirred for 10 min. To this, 0.5 mmol (128 mg) of $Ni(acac)_2$ and a solution of 10 mmol (2.84 g) of androsta-1,4-diene-3,17-dione (**1**) in 15 ml of THF are added at −30 °C. The solution is stirred for 2 h and warmed up during this time to room temp. The reaction is quenched with 10 ml of a NH_4Cl solution and the mixture is extracted with ethyl acetate. GC analysis reveals that the crude product consists of a mixture of **3** and **4** in a ratio of 11:89. It is purified by chromatography on silica gel with a hexane/ethyl acetate mixture to give after evaporation of the solvent 2.33 g of 5β-methylandrost-1-ene-3,17-dione (**4**) (77.5% yield), m.p. 135 °C. – ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.91 (s, 3H, 5β-CH_3), 0.96 (s, 3H, 19-CH_3), 1.15 (s, 3H, 18-CH_3), 1–2.75 (m, 16H), 5.93 (d, 1H, 1-H), 6.65 (d, 1H, 2-H).

3-Methylideneandrosta-1,4-dien-17-one (**5**) (Entry 7, Table 1): A solution of 10 mmol (2.84 g) of androsta-1,4-diene-3,17-dione (**1**) in 20 ml of THF is treated with 0.5 mmol (72 mg) of CuBr. The mixture is cooled to −50 °C and 1.3 g (12 mmol) of TMSCl is added. The mixture is stirred for 15 min. At −50 °C 4 ml (12 mmol) of a 3 M solution of MeMgCl in THF is added. Stirring is continued for 30 min. The reaction is quenched with 20 ml NH_4Cl. The product is extracted with ethyl acetate and purified by flash chromatography on silica gel to yield 2.3 g of 3-methylidenandrosta-1,4-dien-17-one (**5**) (80% yield), m.p. 137 °C. The content of **3** and **4** in the reaction is <10%. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.93 (s, 3H, 19-CH_3), 1.2 (s, 3H, 18-CH_3), 1.0–2.6 (m, 15H), 4.7 (d, 2H), 5.9 (d, 1H, 1-H, 6.0 (s, 2H, 4-H), 6.17 (d, 1H, 2-H).

1α-Ethylandrost-4-ene-3,17-dione from **1** *with Et_3Al/CuBr* (Entry 2, Table 1): 2.84 g (10 mmol) of androsta-1,4-diene-3,17-dione (**1**) and 72 mg (0.5 mmol) of CuBr are dissolved under nitrogen in 15 ml of tetrahydrofuran. To this solution 3.92 g (36 mmol) of trimethylchlorosilane is added. At 10 °C, 12 mmol of triethylaluminium (12 ml of a 1 M solution in toluene) are added at 20 °C. The reaction mixture is stirred for 2 h at room temp. and than treated with 10 ml of 1 N HCl. The product is extracted twice with ethyl acetate and the combined extracts are purifiedpurified by chromatography on silica gel with hexane/ethyl acetate as eluent. Evaporation of the solvent gave 2.79 g of 1α-ethylandrost-4-ene-3,17-dione in 90% yield (m.p. 168 °C). – ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.88 (t, 3H, 1α-CH_2CH_3, J = 7.5 Hz), 0.95 (s, 3H, 19-CH_3), 1.33 (s, 3H, 18-CH_3), 1.0–2.68 (m, 17H), 5.72 (s, 1H, 4-H).

5β-Methylandrostane-3,17-dione (**7**) *from* **6**: A solution of 12 mmol (3.4 g) of freshly distilled $Ti(OiPr)_4$ in 10 ml of dry tetrahedrofuran is treated at −30 °C with 12 mmol of methyllithium (7.5 ml of a 1.6 M solution in ether). The reaction mixture is stirred for 10 min. To this, 0.5 mmol (128 mg) of $Ni(acac)_2$ is added followed by a solution of 2.7 g (10 mmol) androst-4-ene-3,17-dione (**6**) in 10 ml of THF at −30 °C. The mixture is stirred for 2 h with warming up to room temperature and treated with 20 ml of a 1 N HCl solution. The product is extracted twice with ethyl acetate and the combined extracts are purified by chromatography on silica gel with ethyl acetate/hexane as eluent. After evaporation of the solvents, the yield of 5β-methylandrostane-3,17-dione is 2.25 g (73%). The product is recrystallized from diisopropyl ether to afford colorless needles (m.p. 167 °C; ref.[7] 167 °C). – ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.90 (s, 3H, 5β-CH_3), 0.92 (s, 3H, 19-CH_3), 0.98 (s, 3H, 18-CH_3), 1.10–2.25 (m, 20H), 3.0 (d, 1H, J = 15 Hz).

5β-Methylandrostane-3,17-dione (**7**) *from* **6** *and Me_2CuLi:* To 15 mmol of $Me_2CuLi \cdot LiI$ [prepared from 2.86 g (15 mmol) of CuI in 10 ml dry THF and 30 ml (18.75 mmol) methyllithium as a 1.6 M solution in ether] a solution of 2.7 g (10 mmol) of androst-1-ene-3,17-dione (**6**) in 10 ml of THF is dropped at −50 °C. The mixture is stirred for 30 min. at −50 °C and for additional 2 h with warming up to 0 °C. The reaction is quenched with 20 ml of a 2 N HCl solution. The product is extracted twice with ethyl acetate and the combined extracts are dried over Na_2SO_4. The product is chromatographed on silica gel with ethyl acetate/hexane (25:75) as eluent. After evaporation of the solvents, the yield of 5β-methylandrostane-3,17-dione (**7**) is 0.54 g (19%). Later chromatographic fractions contain unchanged **6** (0.4 g; 15%) and a mixture of the diastereomeric 3-hydroxy-3-methylandrostan-17-one (1.5 g; 52%).

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