Unprecedented Stereoselectivity in the Addition of Organoiron(II) Reagents to Cyclohexanone Derivatives

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Various organoiron(II) reagents undergo Grignard-type additions to substituted cyclohexanone derivatives, C–C bond formation occurring stereoselectively from the equatorial direction (97–100% selectivity).

The problem of equatorial *versus* axial attack in nucleophilic addition reactions of cyclohexanone derivatives continues to be of theoretical[1] and synthetic[2–10] interest. Generally, small nucleophiles such as hydride ions add selectively from the axial direction, whereas organometallic compounds tend toward equatorial attack.[2,3] Nevertheless, the degree of diastereoselectivity is not uniformly satisfactory. In the case of the model ketone 4-*tert*-butylcyclohexanone, classical reagents such as PhMgBr, MeMgI, PhLi, MeLi and Bu^{n}Li afford mixtures of axial and equatorial alcohols, the diastereoisomer ratios ranging between 49:51 and 79:21. An excess of MeLi–Me_2CuLi[4] or of MeLi–$LiClO_4$[5] leads to an improvement in diastereoselectivity (92–94% equatorial

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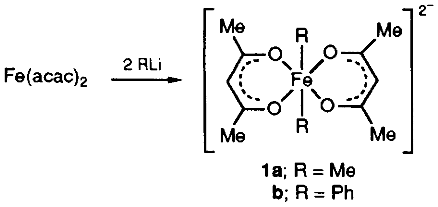
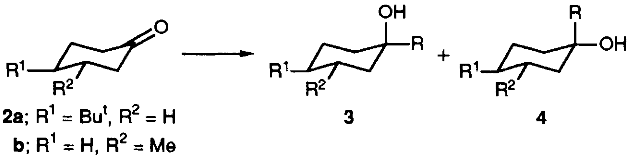


Scheme 1



Scheme 2

attack), although the yield is not always reported. Reversal of diastereoselectivity is possible using bulky aluminium reagents as Lewis acid in combination with RMgX or RLi.[6]

Another strategy is the transmetallation of MeLi with $ClTi(OPr^i)_3$ generating the bulky reagent $MeTi(OPr^i)_3$,[7] which affords 90–94% of the axial alcohol.[8] However, the generality of these approaches has not been demonstrated. Recent work involving the transmetallation of organolithium reagents with magnesium tosylates and pivalates shows that reagents of the type PhMgOTs (Ts = p-$MeC_6H_4SO_2$) and $PhMgOC(O)Bu^t$ add selectively from the equatorial direction (90–94% axial alcohol), but in the case of analogous methylmagnesium reagents, 60 : 40 mixtures of diastereoisomers are obtained.[9] Conversely, methylmanganese pivalate, $MeMnOC(O)Bu^t$, but not the phenyl analogue, reacts stereoselectively (90–93% equatorial attack).[10] We now report that methyl-, *n*-butyl- and phenyl-iron(II) reagents add to a variety of cyclohexanone derivatives with unprecedented degrees of diastereoselectivity and good yields.

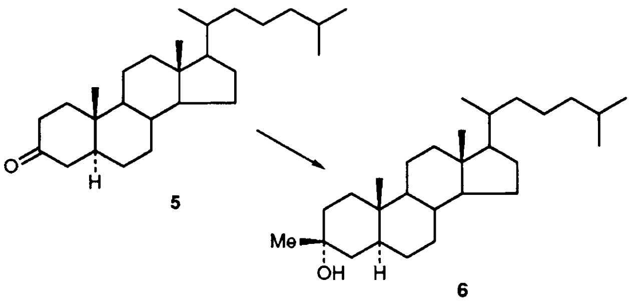
Upon reaction of $FeCl_3$ with 2, 3 or 4 mol. equiv. of MeLi, reduction of the metal occurs with formation of methyl–iron(II) reagents.[11] Although their structure is currently not known, we employed them in subsequent carbonyl addition reactions in an *in situ* manner. Such a one-pot reaction mode was also utilized in the case of transmetallation using the iron(II) salts[12] $Fe(OEt)_2$ and $Fe(acac)_2$ (Hacac = pentane-2,4-dione). We speculate that in the latter case the structure of the reagents may involve an octahedral arrangement around the metal (*cf.* **1**).

The organoiron(II) compounds were first treated with 4-*tert*-butylcyclohexanone **2a** and 3-methylcyclohexanone **2b** (Table 1).‡ The results show that the methyliron reagents add solely from the equatorial direction. Although n-alkyliron(II) reagents might be expected to undergo undesired β-hydride elimination, recent work shows that Grignard-type additions are in fact possible.[11] Indeed, in the case of ketone **2a** the reagent $3\,Bu^nLi$–$FeCl_3$ led to a single diastereoisomer (**3**, $R^1 = Bu^t$, $R^2 = H$, $R = Bu^n$) in 52% isolated yield. In this reaction about 30% reduction of the ketone was observed. In contrast, the combination $3\,Bu^nMgCl$–$FeCl_3$ afforded mainly (>90%) reduction product (*ca.* 2 : 1 diastereoisomer ratio). Interestingly, by using $2\,Bu^nMgCl$–$Fe(acac)_2$ no reduction occurred, the ratio of diastereomeric Grignard-type adducts being 88 : 12 (79% isolated yield). Significantly, even the 'flat' phenyl group, which normally causes great problems in such reactions,[2,10] can be introduced with 97% equatorial selectivity! In the case of phenyl addition, the precursor organometallic was also varied: PhLi delivers better results than PhMgBr in the transmetallation–carbonyl addition sequence.

Table 1 Addition reactions of organoiron(II) reagents with ketones **2** in THF[a]

Ketone	Reagent	R	Temp./°C	Yield[b] (%)	3 : 4[c]
2a	$2MeLi$–$FeCl_3$	Me	−78 → 22	63	98 : 2
2a	$3MeLi$–$FeCl_3$	Me	−78 → 22	98 (85)	99 : 1
2a	$4MeLi$–$FeCl_3$	Me	−78 → 22	99 (86)	98 : 2
2a	$MeLi$–$Fe(acac)_2$	Me	−78 → 22	31	99 : 1
2a	**1a**	Me	−78 → 22	85 (80)	99 : 1
2a	$3Bu^nLi$–$FeCl_3$[d]	Bu^n	−78 → −15	60 (52)	99 : 1
2a	$2Bu^nMgCl$–$Fe(acac)_2$[e]	Bu^n	−78 → 5	86 (79)	88 : 12
2a	$MeLi$–$FeCl_3$–$2PhLi$[f]	Ph	−78 → 0	64 (60)	93 : 7
2a	$MeLi$–$FeCl_3$–$2PhMgBr$[f,g]	Ph	−78 → 0	90 (70)	82 : 18
2a	**1b**	Ph	−78 → 22	76 (68)	97 : 3
2b	$3MeLi$–$FeCl_3$	Me	−78 → 22	96 (89)	99 : 1
2b	**1a**	Me	−78 → 22	79 (71)	99 : 1

[a] Reaction time in all cases: 4 h. [b] The numbers refer to conversion as determined by GC, those in parentheses to isolated yields. [c] Determined by GC analysis of the crude reaction mixture. [d] About 30% reduction of the ketone was observed. [e] No reduction of ketone was observed. [f] MeLi was used for the reduction $Fe^{III} \rightarrow Fe^{II}$, then PhLi or PhMgBr was added. [g] About 10% reduction of the ketone was observed.



Scheme 3

Finally, cholestanone **5**, which reacts with MeMgX[13] and MeLi to form 1 : 1 to 3 : 1 mixtures of the axial and equatorial alcohol, underwent addition reaction with $3\,MeLi$–$FeCl_3$ (−78 → 22 °C during 4 h) to provide a 78% yield (isolated) of the pure axial alcohol **6**. The crude product prior to purification showed a diastereoselectivity of 99 : 1. Reagent **1a** resulted in similar selectivity (98 : 2 ratio), although conversion turned out to be lower (36%; −78 → 10 °C during 16 h).

Another feature of the new iron(II) reagents described here is chemoselective aldehyde addition in the presence of ketone functionality. For example, reagent **1a** reacted with a 1 : 1 mixture of benzaldehyde and acetophenone to afford a >99 : <1 mixture of secondary and tertiary alcohol (−78 → −15 °C during 4 h; 88% isolated yield of 1-phenylethanol).

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‡ *Typical procedures.* Starting from $FeCl_3$: to a stirred solution of $FeCl_3$ (730 mg, 4.5 mmol) in 20 ml of absolute tetrahydrofuran (THF), methyllithium (8.5 ml, 1.6 mol l^{-1} in Et_2O, 13.6 mmol) was added at −78 °C under an Ar atmosphere.[11] After stirring for 1 h, ketone **2a** (4.5 ml, 1 mol l^{-1} in THF, 4.5 mmol) was added. The mixture was stirred for 4 h, during which it was allowed to reach 22 °C, hydrolysed with saturated NH_4Cl (aq) solution (2 ml), diluted with diethyl ether (150 ml), washed with water (3 × 20 ml), dried ($MgSO_4$), evaporated to dryness and chromatographed on silica gel (hexane–ether, 8 : 1) to give 650 mg (85%) of pure **3** (R = Me). Starting from $Fe(acac)_2$: to a stirred solution of $Fe(acac)_2$[12] (760 mg, 3 mmol) in absolute THF (10 ml), methyllithium (3.75 ml, 1.6 mol l^{-1} in Et_2O, 6 mmol) was added at −78 °C. After 1 h stirring at the same temperature, **2a** (3 ml, 1 mol l^{-1} in THF 3 mmol) was added, the mixture was allowed to reach 22 °C, hydrolysed with 6 mol dm^{-3} HCl, diluted with diethyl ether (100 ml), washed with H_2O (5 × 20 ml), dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed as above to give 410 mg (80%) of **3** (R = Me).

This is similar to the previously reported reactions of reagents derived from RLi–$FeCl_3$.[11]

In summary, methyl-, n-butyl- and phenyl-iron(II) reagents lead to unprecedented degrees of diastereoselectivity in addition reactions of substituted cyclohexanone derivatives. Essentially complete stereocontrol in the formation of axial alcohols is possible for the first time.

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