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$_2$CuLi[4] or of MeLi–LiClO$_4$[5] leads to an improvement in diastereoselectivity (92–94% equatorial

1a; R = Me
b; R = Ph

Scheme 1

2a; R¹ = Buᵗ, R² = H
b; R¹ = H, R² = Me

Scheme 2
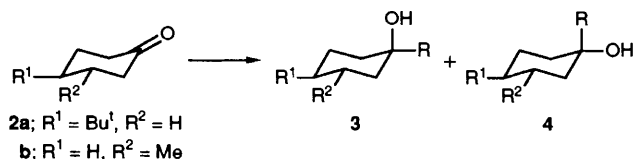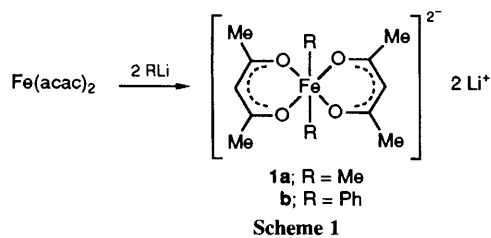
attack), although the yield is not always reported. Reversal of diastereoselectivity is possible using bulky aluminium reagents as Lewis acid in combination with RMgX or RLi.[6]

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 = $p\text{-}MeC_6H_4SO_2$) and PhMgOC(O)Buᵗ 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)Buᵗ, 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

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–FeCl₃	Me	−78→22	63	98:2
2a	3MeLi–FeCl₃	Me	−78→22	98(85)	99:1
2a	4MeLi–FeCl₃	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	3BuⁿLi–FeCl₃[d]	Buⁿ	−78→−15	60(52)	99:1
2a	2BuⁿMgCl–Fe(acac)₂[e]	Buⁿ	−78→5	86(79)	88:12
2a	MeLi–FeCl₃–2PhLi[f]	Ph	−78→0	64(60)	93:7
2a	MeLi–FeCl₃–2PhMgBr[f,g]	Ph	−78→0	90(70)	82:18
2a	1b	Ph	−78→22	76(68)	97:3
2b	3MeLi–FeCl₃	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 Feᴵᴵᴵ → Feᴵᴵ, then PhLi or PhMgBr was added. [g] About 10% reduction of the ketone was observed.

Scheme 3
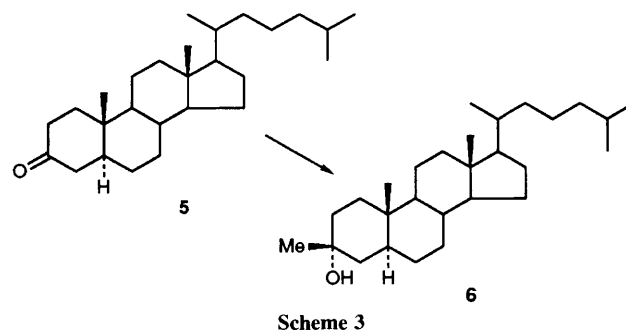
solely from the equatorial direction. Although n-alkyliron(II) reagents might be expected to undergo undesired β-hydride elimination, recent work shows that Grignard-type additions are in fact possible.[11] Indeed, in the case of ketone 2a the reagent 3 BuⁿLi–FeCl₃ led to a single diastereoisomer (3, R¹ = Buᵗ, R² = H, R = Buⁿ) in 52% isolated yield. In this reaction about 30% reduction of the ketone was observed. In contrast, the combination 3 BuⁿMgCl–FeCl₃ afforded mainly (>90%) reduction product (*ca.* 2:1 diastereoisomer ratio). Interestingly, by using 2 BuⁿMgCl–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.

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–FeCl₃ (−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).

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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