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Selective Addition of Organolithium Reagents to BF_2-Chelates of β-Ketoesters

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ABSTRACT

A short, mild, and highly chemoselective addition of organolithium reagents to a BF_2 complex of 3-oxopropanoates has been developed. The methodology allows straightforward preparation of various 1,3-dioxa-BF_2 complexes and subsequently leads to the formation of 1,3-diketones starting from the corresponding 3-oxopropanoates.

Carbon−carbon bond formation is one of the foremost topics in organic synthesis. There have been numerous methods developed to date, each of them having their own advantages and disadvantages. Among these methods, ones characterized by high functional group tolerance are most desired. It has been known for many years that coordination of the Lewis basic carbonyl group by Lewis acids enhances the electrophilic character of the carbonyl carbon. This phenomenon has played a crucial role in the development of mild nucleophilic reagents for carbon−carbon bond formation.[1] In the 1970s, Smith and Spencer described the formation of 2-alkylidene ketones employing BF_2 complexes of 2-formyl ketones and organometallic reagents.[2] In the past few years, we have been interested in the reactivity of β-diketonatoboron difluorides and their applications as a starting materials for the regioselective enamine formation[3] as well as construction of several heterocycles.[4] Additionally, Christoffers et al. demonstrated regioselective enamine formation from oxonia-boranuida-betaines and their application in the asymmetric Michael reaction.[5] Garcia-Garibay et al. used difluorodioxaborinines as a tool for the enantiomerically pure synthesis of natural products (+)- and (−)-α-cuparanone.[6] Recently, different 1,3-dioxa-BF_2-chelate systems have been shown to be remarkably efficient probes for tumor hypoxia imaging[7] and as near-infrared probes for in vivo detection of amiloid-β deposites.[8] Additionally, materials with the 1,3-dioxa-BF_2-chelate functionality possess n-type semiconducting properties, recently discovered by Ono et al.[9]

The long-known and readily prepared boron difluoride complexes of alkyl and aryl 3-oxopropanoates (e.g., **2**) seemed to offer an attractive alternative method for the synthesis of asymmetrically substituted 1,3-diketonatoboron difluorides if the electrophilicity at the ester moiety of the

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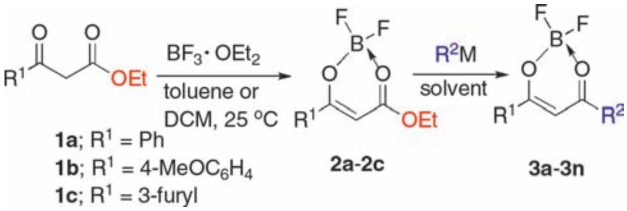
complex **2** is dominated over the other functionalities present. Furthermore, formed 1,3-diketonatoboron difluorides **3** can be subsequently transformed into the corresponding 1,3-diketones and other amino derivatives under mild reaction conditions.[4−6] Accordingly, an investigation of the reactions of the BF_2 complex of type **2** with selected organometallic reagents was undertaken (Scheme 1, Table 1).

As is evident from Table 1, a BF_2 complex of 1,3-diketoesters favors the addition of organolithium reagents to ester functionality, affording the corresponding asymmetric 1,3-diketonatoboron difluorides (Scheme 1).

Scheme 1. Reaction of BF_2 Complex of Ethyl 3-Oxopropanoates with Organometallic Reagents



Initially, we chose derivative **2a** as the model substrate for surveying reaction parameters in the model reaction (Table 1). The initial screening of several *n*-Bu-organomethalic reagents revealed that only *n*-BuLi adds successfully to the activated carboxylic group in complex **2a** deriving the desired product **3a** in very promising yield (Table 1, entry 1). On the other hand, analogue organozinc and higher order organocuprates[10] (Table 1, entries 3 and 4) did not lead to the formation of the desired product. Instead, in both cases, ethyl 3-phenyl-3-oxopropanoate was isolated almost quantitatively. The result suggests that most likely softer organometallic reagents react on the boron moiety of the complex **2a**, via the ate complex, thus deriving the corresponding 1,3-ketoester. However, when *n*-BuMgCl was used as a reagent under the same reaction conditions, the desired product in low yield (9%) together with ethyl 3-phenyl-3-oxopropanoate was obtained.

Next, a variety of experimental variables, such as reaction temperature, choice of solvent, and reagent (*n*-BuLi) loading were systematically examined. After thorough investigation, we found that the best results were accomplished using 1.1 equiv of the organolithium reagents at −78 °C in THF followed by quenching of the reaction mixture at the same temperature and subsequent extraction of the product into dichloromethane (see Table 1). Reacting **3a** at −78 °C in THF with phenyllithium for 30 min followed by quenching of the reaction mixture at the same temperature resulted in recovery of the starting material **3a** in 87% yield together with 4% of the mixture of corresponding alcohols. This result indicates that β-diketonatoboron difluorides are less reactive under the applied reaction conditions comparing to analogous BF_2 complexes of 1,3-diketoesters. Limiting the organolithium reagent to 1.1 equiv, control of the reaction temperature and lower reactivity of the products seems to prevent the reaction yielding the overaddition products.

Table 1. Reaction of **2a** with R^2M at Different Reaction Conditions

entry	R^2M (equiv)	solvent	temp (°C)	yield of **3**^{a} (%)
1	*n*-BuLi (1.1)	THF	−78	73
2	*n*-BuMgCl (1.1)	THF	−78	9
3	*n*-Bu_2Zn (1.1)	THF	−78	NO^b
4	(*n*-Bu)$_2Cu(CN)Li_2$ (1.1)	THF	−78	NO^b
5	*n*-BuLi (1.1)	Et_2O	−78	43
6	*n*-BuLi (1.1)	PhMe	−78	21
7	*n*-BuLi (1.5)	THF	−78	71
8	*n*-BuLi (1.1)	THF	−78 to 25	70
9	*n*-BuLi (1.5)	THF	−78 to 25	43

^{a} Isolated yields are given, ^{b} NO (not observed), ethyl 3-phenyl-3-oxopropanoate was isolated instead.

With our optimized reaction conditions in hand, the scope of organolithium reagent addition to several difluoroboron complexes **2** was investigated. In general, the yields of the reaction were good (40−97%). *t*-BuLi also underwent successful addition albeit with modest yield, which can be attributed to its steric hindrance and rather strong basicity. Phenyllithium was also found to undergo successful transformation in good yield subsequently broadening the scope of the transformation. In addition to alkyl- and aryllithiums, the applicability of more challenging and synthetically useful alkynyl and heteroarylorganolithiums was examined (Table 2, entries **e**−**g**,**l**,**m**).

As is evident from Table 2, 2-furyl- and 2-thioazolyllithium prepared according to the literature procedures[11] gave

Table 2. Reaction of **2** with R^2Li Reagents

starting material **2**	R^1	R^2	yield of **3**^{a} (%)
a	Ph	Me	**3a** (97)
b	Ph	*n*-Bu	**3b** (73)
c	Ph	*t*-Bu	**3c** (39)
d	Ph	Ph	**3d** (82)
e	Ph	PhC≡C	**3e** (98)
f	Ph	2-furyl	**3f** (69)
g	Ph	2-thiazolyl	**3g** (74)
h	4-methoxyphenyl	Ph	**3h** (55)^b
i	3-furyl	Me	**3i** (43)^b
j	3-furyl	*n*-Bu	**3j** (41)^b
k	3-furyl	Ph	**3k** (61)
l	3-furyl	PhC≡C	**3l** (81)
m	3-furyl	2-furyl	**3m** (77)
n	3-furyl	2-thiazolyl	**3n** (69)^b

^{a} Isolated yields are given, ^{b} 5−10% of the corresponding 1,3-diketone was isolated.

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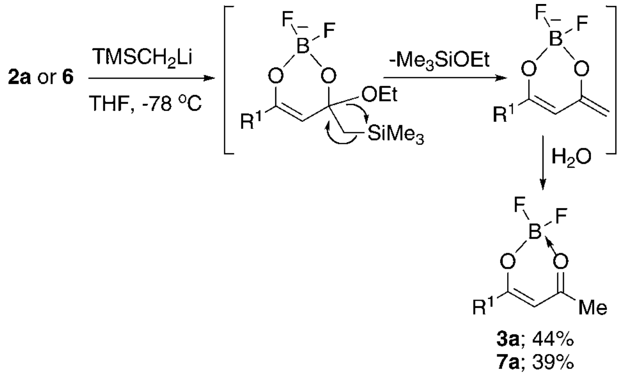
[10] *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994.

the desired products in synthetically useful yields. At this point, it is appropriate to note that in some cases a minor percentage of the corresponding 1,3-diketone was detected in the crude reaction product arising from hydrolytic reaction during reaction workup. The amount of the uncoordinated 1,3-diketone was higher under the basic reaction workup and prolonged stirring of the workup mixture (30 min).

Interestingly, when $TMSCH_2Li$ was employed as a reagent, compounds **3a** and **7a** were isolated as in the case of using methyllithium. The rationale of this transformation is depicted in Scheme 2.

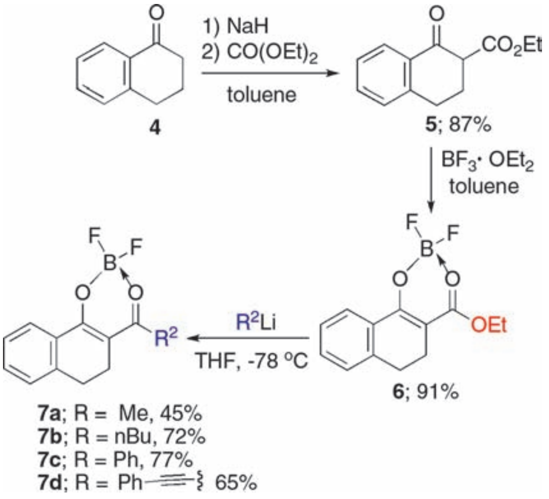
Scheme 2. Reaction of BF_2 Complexes **2a** and **6** with $TMSCH_2Li$



The addition of $TMSCH_2Li$ to the ester moiety of complex **2a** or **6** is most probably followed by the elimination of Me_3SiOEt. The formed intermediate, which was never isolated or detected in the crude product, must undergo rapid protonation during the reaction workup resulting in the formation of final products **3a** and **7a** (Scheme 2).

We then set out to apply the above-discussed chemistry to the ethyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate derivative with representative organolithium reagents. The starting 1,3-ketoester **5** was synthesized according to the literature procedure in good yield.[12] Treatment of **5** with 2 equiv of $BF_3{\cdot}Et_2O$ in toluene at room temperature gave the desired BF_2 complex **6** as a bluish-fluorescence material (Scheme 3). Treatment of the latter under the optimized reaction conditions derived the corresponding 1,3-diketoboron difluoride complexes **7a**−**d** in reasonable yields. Interestingly enough, compounds **7c** and **7d** possess strong fluorescence[13] for which a solvatochromic effect was observed for **7d** (Figure 1). In the fluorescence spectra in dichloromethane, **7c** and **7d** showed emission maxima at 417 nm (excited at 359 nm) and 540 nm (excited at 401 nm), respectively. The absolute fluorescence quantum yields of **7c** and **7d** in dichloromethane at room temperature were determined as $\Phi_F = 0.45$ and 0.87, respectively.

Scheme 3. Reaction of BF_2 Complex of Ethyl 1-Oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**6**) with R^2Li Reagents



Detailed optical, electrochemical and the solid-state emission properties of this and related compounds are currently under investigation and the results are going to be published in due course.

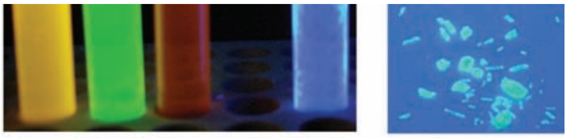

7d; hexane/CH_2Cl_2/Toluene **7c**; CH_2Cl_2 **7c**; solid

Figure 1. Fluorescence properties of **7c** and **7d**.

In principle, two mechanistic rationales could be postulated for the observed transformation of **2** and **6** to **3** and **7**. The first would be the simple nucleophilic attack of C-nucleophile via the Bürgi−Dunitz trajectory[14] and subsequent elimination of lithium alkoxide. The second, which is in our opinion more probable, is the initial formation of the ate complex between Lewis basic borondifluoride center and the Lewis acidic lithium of organolithium species (most probably corresponding oligomers) followed by the attack of the C-centered nucleophile of the organolithium aggregates[15] to the activated ester functionality, forming a tetrahedral intermediate which subsequently undergoes elimination of lithium alkoxide, thus yielding the more stable 1,3-diketoboron difluoride complex (see Scheme 4).

In conclusion, we have demonstrated that treatment of readily accessible and stable borondifluoride complexes of

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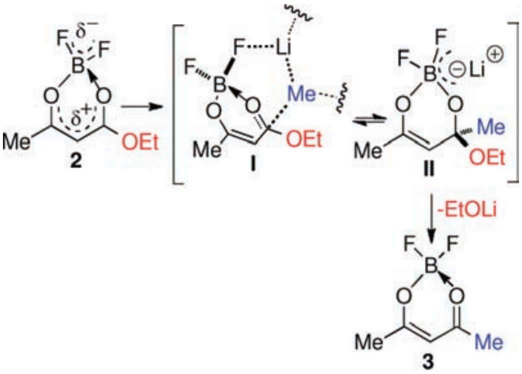
Scheme 4. Proposed Reaction Mechanism for the Transformation of **2** and **6** to **3a−n** and **7a−d**



1,3-ketoesters with a variety of organolithiums at −78 °C in THF can lead to the formation of the corresponding 1,3-diketoborondifluoride analogues. The latter can be simply transformed to the synthetically valuable asymmetrically substituted 1,3-diketones. On the other hand, the presented methodology enables straightforward access to the variety of attention-grabbing fluorescent dyes. However, to the best of our knowledge, the presented transformation is herein discussed for the first time.

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Supporting Information Available: Synthesis of the starting materials, general experimental methods, characterization of all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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