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On the Reactivity of Lithium β-ketocarboxylates: the Role of Lithium salts

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ABSTRACT: Lithium β-ketocarboxylates **1**(COOLi), prepared by the reaction of lithium enolates **2**(Li^+) with carbon dioxide, readily decarboxylate in THF solution unless in the presence of lithium salts, in which case they are indefinitely stable at room temperature in inert atmosphere. The availability of stable THF solutions of lithium β-ketocarboxylates **1**(COOLi) in the absence of carbon dioxide allowed reactions to take place with nitrogen bases and alkyl halides **3** to give α-alkyl ketones **1**(R) after acidic hydrolysis. The sequence thus represents the use of carbon dioxide as a removable directing group for the selective monoalkylation of lithium enolates **2**(Li^+). The roles of lithium salts in preventing the decarboxylation and disproportionation reactions of lithium β-ketocarboxylates **1**(COOLi), and in determining the course of the reaction with bases and alkyl halides **3**, are discussed.

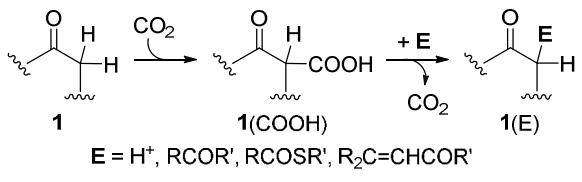
Introduction

Enzymes involved in polyketides and fatty acids synthesis use carbon dioxide as a removable activating group for performing C-C bond formation reactions at the α position of a carbonyl group under mild conditions (Scheme 1).[1] Organic chemists have successfully applied this strategy to develop useful synthetic procedures such as classic malonic and acetoacetic synthesis,[2] enantioselective organocatalytic decarboxylative aldol, Mannich and Michael reactions,[3] and transition-metal catalyzed decarboxylative C-H bond functionalization.[4] The role of β-ketocarboxylic acids **1**(COOH) and their salts **1**(COOM) (M: counterion) as key intermediates in these reactions has prompted research into the carboxylation of ketones **1** with CO_2[5] and the decarboxylation of β-ketoacids,[6-9] since both steps are involved in the synthetic sequence (Scheme 1).

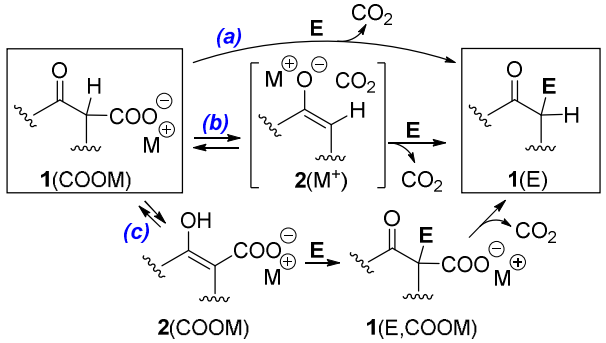
The reactions of β-ketocarboxylates **1**(COOM) with electrophiles **E** (Scheme 1) have been debated around three alternative pathways whose decarboxylation step has a different timing in relation to C-C bond formation (Scheme 2)[1,3] namely, a) electrophilic substitution concerted with decarboxylation; b) decarboxylation and capture of enolate **2**(M^+) by the electrophile, and c) enolization, capture of enol intermediate **2**(COOM) by the electrophile, and decarboxylation. The actual reaction course in each case may, however, depend on the specific reagents and conditions used.

The sequence shown in Scheme 1 has been scarcely applied to alkyl halides **3** (**E** = R-I or R-Br in Schemes 1 and 2). Notwithstanding, it provides a formal path for the α-alkylation of starting ketone **1**, which may circumvent the tendency to polyalkylation of ketone enolates

Scheme 1. Carbon dioxide as removable activator for the α-position of ketones **1**. Electrophiles **E**: RCOSR', RCOH, R_2C=CHCOR', H^+, among others.



Scheme 2. Reaction paths proposed for the reaction of β-ketocarboxylates **1**(COOM) (M = counterion) with electrophiles **E**.[3]



2(M^+).[10] The reaction of ketones **1** with magnesium methyl carbonate and alkyl halides (the Stiles reaction)[11] actually follows this approach and has found applications in synthesis. Yet it proceeds under harsh conditions (10-fold excess reagent, dimethylformamide as the solvent, and high temperatures), and thus fails to take full advantage of the activation provided by the 1,3-dicarbonyl moiety. Conversely, organocatalytic decarboxylative C-C bond forming reactions[3] have not been described for alkyl halides as electrophiles. The importance of β-ketocarboxylates **1**(COOM) as synthetic and biosynthetic intermediates, and of the CO_2-capture reactions and products with potential applications in synthesis,[3,5] prompted us to explore the reaction of lithium β-ketocarboxylates **1**(COOLi) with alkyl halides **3** in tetrahydrofuran (THF) as the solvent to disclose its reaction paths, intermediates and scope.

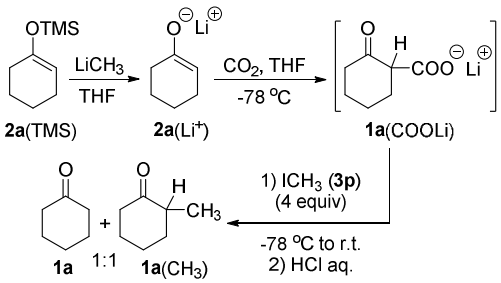
Herein we report the preparation of stable THF solutions of lithium β-ketocarboxylates **1**(COOLi), and the reactions of these intermediates with nitrogen bases and alkyl halides **3**. The results reported herein illustrate the reactivity of lithium β-ketocarboxylates **1**(COOLi) and open up new opportunities for their synthetic application.

Results and Discussion

The disproportionation. Lithium β-ketocarboxylates **1**(COOLi) were prepared *in situ* by adding a THF solution of the lithium enolate **2**(Li^+), generated by the reaction of the corresponding silylenolether **2**(TMS) with methyllithium in anhydrous THF, to a saturated solution of CO_2 in THF at -78 °C (Scheme 3). Reactions were performed using lithium 2-oxocyclohexane-1-carboxylate **1a**(COOLi) as a model substrate and adamantane as the internal standard. The experimental procedures are included in the experimental section and the Supporting Information. The reaction of ketones **1** with lithium diisopropylamide proved unsuitable to prepare starting enolate **2**(Li^+) as diisopropylamine (DIPA) interfered with the ensuing carboxylation reaction.[12]

The reaction of enolate **2a**(Li^+) with CO_2 in THF at -78 °C led to the immediate formation of a white solid.

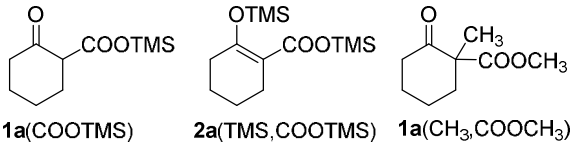
Scheme 3. Reaction paths proposed for the reaction of β-ketocarboxylates **1**(COOM) (M = counterion) with electrophiles **E**.



Methyl iodide (**3p**) in excess (4 equiv) was added at -78 °C, and the reaction mixture was gently purged with argon and allowed to warm up in an inert atmosphere. The solution became clear at *ca.* -20 °C and subsequently formed a white solid that remained unchanged up to room temperature. The reaction mixture was quenched with aqueous hydrogen chloride and analyzed by gas chromatography (GC) and mass spectrometry (MS) to show a *ca.* 1:1 mixture of cyclohexanone (**1a**) and 2-methylcyclohexanone [**1a**(CH_3)], exclusively.

The control experiments aimed to capture the intermediate species involved, allowed to ascertain the reaction course under these conditions. First, the reaction mixture from the carboxylation reaction was quenched with excess chlorotrimethylsilane (TMSCl) at -78 °C in CO_2 atmosphere. The nuclear magnetic resonance (NMR) analysis of a deuterochloroform solution of the residue after the evaporation of the volatiles showed a mixture of (Chart 1) trimethylsilyl β-ketocarboxylate **1a**(COOTMS) (keto:enol forms *ca.* 1:1) (83 %) and trimethylsilyl 2-(trimethylsilyloxy)-cyclohex-1-ene-1-carboxylate [**2a**(TMS,COOTMS)] (17 %).

Chart 1. Products from the capture of the reaction intermediates with TMSCl and dimethyl sulfate/HMPA.



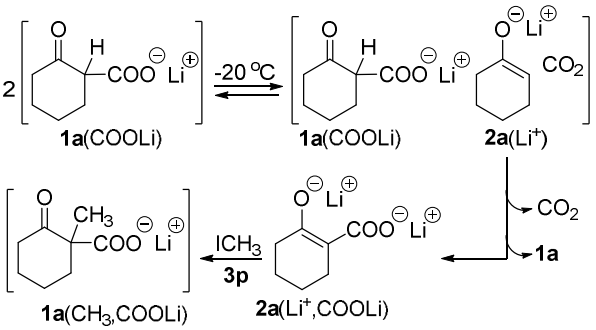
Second, the reaction mixture was warmed to room temperature and centrifuged. The solid was treated with excess chlorotrimethylsilane in anhydrous THF in CO_2 atmosphere, and the mixture was evaporated under vacuum. The NMR analysis of the residue showed a *ca.* 1:1 mixture of **2a**(TMS,COOTMS) (47 %) and trimethylsilyl β-ketocarboxylate [**1a**(COOTMS)] (53 %) (Chart 1). The analysis of the sample by GC-MS showed that trimethylsilyl β-ketocarboxylate [**1a**(COOTMS)] decomposed under the analysis conditions to give the corresponding ketone **1a**.

Third, the heterogeneous mixture from the carboxylation reaction was treated with methyl iodide (**3p**) (2 equiv) for 90 min. at room temperature, and was quenched with dimethylsulfate (2 equiv) and hexamethylphosphoramide (HMPA) (5 equiv). The analysis of the supernatant by GC-MS showed the presence of a *ca.* 1:1 mixture of cyclohexanone (**1a**) and methyl 2-methyl β-ketocarboxylate [**1a**(CH_3,$COOCH_3$)] (Chart 1).

These results established that lithium β-ketocarboxylate **1a**(COOLi) in THF solution disproportionates at -20 °C in the presence of CO_2 to give ketone **1a** and the lithium enolate of lithium β-ketocarboxylate **2a**(Li^+,COOLi) [henceforth dianion **2a**(Li^+,COOLi)] (Scheme 4). The reaction can proceed through the decarboxylation of **1a**(COOLi) to give enolate **2a**(Li^+), which

undergoes a faster acid-base reaction with unreacted lithium β-ketocarboxylate **1a**(COOLi) than the competing substitution with alkyl halide **3p** in excess in solution. In agreement with this, the carboxylation reaction performed by flowing CO_2 (1 bar) through a cold THF solution of enolate **2a**(Li^+), under which conditions lithium β-ketocarboxylate **1a**(COOLi) forms in the presence of unreacted enolate **2a**(Li^+), produced a 1:1 mixture of dianion **2a**(Li^+,COOLi) and ketone **1a** which remained unchanged for 4 h at room temperature in CO_2 atmosphere. Dianion **2a**(Li^+,COOLi) would then be the actual nucleophile to react with methyl iodide (**3p**) to give lithium α-methyl-β-ketocarboxylate **1a**(CH_3,COOLi), which produces the corresponding α-methyl ketone **1a**(CH_3) in the acidic hydrolysis step. Remarkably, the non enolizable lithium α-alkyl-β-ketocarboxylate **1a**(CH_3,COOLi) was stable in solution under these reaction conditions.

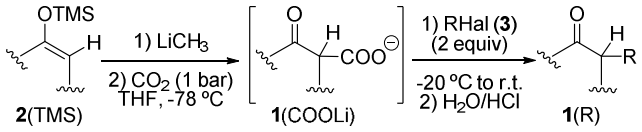
Scheme 4. Disproportionation of lithium β-ketocarboxylate **1a**(COOLi) and reaction with ICH_3 (**3p**).



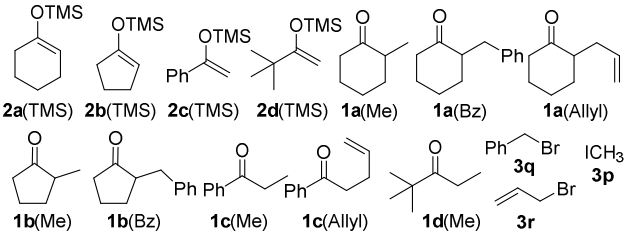
In order to verify the impact of the substrate structure on the reaction course, we explored these reactions for the enolates **2**(Li^+) that derived from cyclohexanone (**1a**), cyclopentanone (**1b**), acetophenone (**1c**) and pinacolone (**1d**). The carboxylation of enolates **2**(Li^+) was performed at -78 °C, as described above. The reaction mixtures were placed in an salt-ice bath at -20 °C for 30 min, were treated with a 2-fold excess of alkyl halide **3** under gentle argon flow, and were then allowed to warm to room temperature upon standing for 15 h. The reaction mixtures were analyzed by GC-MS after acidic hydrolysis. The results are shown in Table 1. The analysis by GC-MS of the aliquots withdrawn from the solutions and quenched with TMSCl prior to alkyl halide **3** addition showed the formation of doubly silylated derivatives **2**(TMS,COOTMS) in all the cases.

The reaction was general for a variety of lithium β-ketocarboxylates **1**(COOLi) and led to 2-alkylketone **1**(R) exclusively except for five-membered ring derivative **1b**(COOLi), in which case the formation of polyalkylation products suggested that secondary alkylated lithium β-ketocarboxylate **1b**(R,COOLi) decarboxylated to give

Table 1. Reaction of trimethylsilylenol ethers **1** with methyllithium, CO2, and alkyl halides **3**, followed by acid hydrolysis.[a]



Run	2(TMS)	3	Product distribution 1(R)	1(R) %	1	1 (%)
1	**2a**(TMS)	3p	**1a**(Me)	48	1a	52
2[c]	**2a**(TMS)	3q	**1a**(Bz)	60	1a	37
3	**2a**(TMS)	3r	**1a**(Allyl)	7	1a	93
4	**2b**(TMS)	3p	**1b**(Me)	67	1b	33
5[c]	**2b**(TMS)	3q	**1b**(Bz)	64	1b	34
6[c]	**2c**(TMS)	3p	**1c**(Me)	64	1c	34
7	**2c**(TMS)	3r	**1c**(Allyl)	34	1c	66
8	**2d**(TMS)	3p	**1d**(Me)	3	1d	97



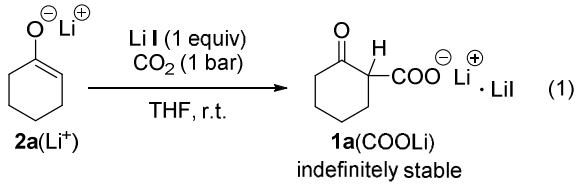
[a] The carboxylation was performed by adding a THF solution of enolate **2**(Li) and adamantane as internal standard to a saturated solution of CO_2 in THF at -78 °C. The alkyl halide **3** (2 equiv) was added at -20 °C. The enolate **2**(Li) formed quantitatively from the silyl enol ether **2**(TMS) in all the cases. [b] Determined from GC analysis of the reaction mixture. The values were not corrected for the respective response factors. [c] Minor amounts of dialkylation products were observed.

enolate **2b**(R,Li^+), which reacted with alkyl halide **3** or the ketone **1b**(CH_3) present in the reaction medium. The low reactivity observed for dianion **2d**(Li^+,COOLi) can be attributed to the steric hindrance posed by the *tert*-butyl group.

These results revealed that lithium β-ketocarboxylates **1**(COOLi) underwent facile disproportionation in THF solution, even at low temperature and in a CO_2 atmosphere, and that dianions **2**(Li^+,COOLi) are the actual nucleophilic species to react with the alkyl halide **3** in excess in the solution. A similar behavior has been described[13] for copper and palladium β-ketocarboxylates **1**(COOM) (M = Cu, Pd) in dimethylformamide solution at high temperatures. The disproportionation reaction severely hampered the application of intermediates **1**(COOLi) in synthesis as it depleted *ca.* half the starting reagent to give ketone **1**.

The role of lithium salts. The reaction exhibited a rather different course when performed in the presence of

lithium iodide.[14] For instance, the NMR analysis of THF-d_8 solution of lithium enolate **2a**(Li^+) and lithium iodide (2 equiv) treated with a flow of CO_2 (1 bar) at room temperature for 2 h, and quenched with TMSCl at 0 °C, showed the presence of trimethylsilyl β-ketocarboxylate **1a**(COOTMS) exclusively, as a *ca.* 1:2 keto:enol mixture. The solution of lithium β-ketocarboxylate **1a**(COOLi) and lithium iodide (2 equiv) in THF-d_8 proved to be indefinitely stable at room temperature, even after a prolonged purging of the solution with argon, and was unreactive toward methyl iodide (**3p**) (4 equiv), even upon standing at room temperature for 48 h. The control experiments established that 1 equiv of lithium iodide sufficed to stabilize lithium β-ketocarboxylate **1a**(COOLi) in THF toward its disproportionation into ketone **1a** and dianion **2a**(Li^+,COOLi) (Eq. 1). This value may change in each case depending on the variable amounts of lithium salts in the methyllithium solutions from the reagent's synthesis or decomposition upon standing.



This puzzling behavior is akin to a variety of anomalies described[15] for reactions that involve organolithium reagents in the presence of lithium salts.[16] The impact of lithium salts on the stability of lithium β-ketocarboxylates **1a**(COOLi) in THF solution can be attributed to the oxophilic and strongly coordinating character of lithium ions[15,16] which may alter some key factors related to the decarboxylation reaction, namely: i) the coordination of the additional lithium cations with the carboxylate anion stabilizes its negative charge density and renders it less prone to decarboxylation;[6] ii) lithium ions disaggregate β-ketocarboxylate **1a**(COOLi) in solution,[16a,b] which thus diminishes its competitiveness as a proton donor toward the enolate **2a**(Li^+) that formed in the decarboxylation step, in relation to the recapture of CO_2 (Scheme 4);[7] iii) the additional lithium ions favor either the enol form of **1a**(COOLi) or the conformations with the σ-bond to the carboxylate group placed off the perpendicular to the carbonyl's plane, which do not undergo decarboxylation due to stereoelectronic factors.[8,9] Note that the reactions of dianions **2**(Li^+,COOLi) with alkyl halides **3** described above (Table 1) produce lithium halides that may contribute to the stability of the lithium α-alkyl-β-ketocarboxylate **1a**(CH_3,COOLi) formed as a product observed in the experiments reported in Table 1 (Scheme 4). The impact of the halide anion on these reactions was not ascertained in this work.[14]

The reaction with nitrogen bases. The stability of the THF solutions of lithium β-ketocarboxylate **1a**(COOLi) and lithium iodide, purged with argon or nitrogen to strip off CO_2, opens up new opportunities to explore the reactivity and applications of these intermediates in synthesis. For instance, absence of CO_2 facilitates the reaction of **1a**(COOLi) with nitrogen bases to generate the dianion **2a**(Li^+,COOLi) required for the alkylation reaction. Otherwise, CO_2 would interfere by forming carbamic acid derivatives[12] or establishing strong Lewis acid-base interactions with the nitrogen base.[17] Note that the alkylation of lithium β-ketocarboxylate **1a**(COOLi) requires a quantitative acid-base reaction with the base, unlike the base-catalyzed addition of **1a**(COOLi) to carbonyls, imines or α,β-unsaturated carbonyls in the aldol, Mannich or Michael reactions,[3] where the base is regenerated in the last proton transfer step which renders the addition product.

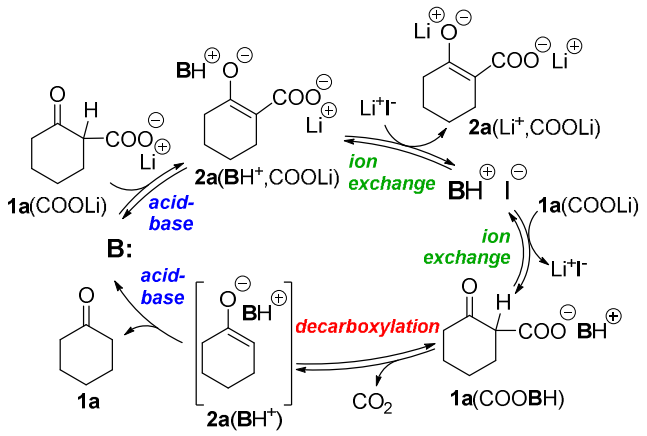
Addition of diisopropylamine (DIPA), hexamethyldisilazane (HMDS) and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), to a 0.2 M solution of lithium β-ketocarboxylates **1a**(COOLi) and lithium iodide (1 equiv) in THF purged with argon at room temperature gave a white solid in all cases, except for HMDS. The reactions were monitored at different times by withdrawing aliquots which were quenched with TMSCl and analyzed by GC. The reaction with HMDS was performed in THF-d_8, and the solution was analyzed by NMR after quenching with TMSCl under the same conditions.

The results showed a nearly quantitative formation of dianion **2a**(Li^+,COOLi) after 1-10 min in all cases, followed by its progressive depletion to give a 1:1 mixture of ketone **1a** and dianion **2a**(Li^+,COOLi). The counterion in the dianion species, Li^+ or BH^+ [**2a**(Li^+,COOLi) or **2a**(BH^+, COOLi)] was not ascertained. Notwithstanding, we will use the notation **2a**(Li^+,COOLi) for the dianion formed in the acid-base reaction of **1a**(COOLi) with the base based on the assumption that presence of lithium iodide in the reaction medium promotes the ion-exchange in **2a**(BH^+,COOLi) to give **2a**(Li^+,COOLi) and BH^+I^-.

The fastest disproportionation was observed for HMDS (1 h). DIPA promoted a more extensive depletion of β-ketocarboxylate **1a**(COOLi) upon standing for long periods (14 h) to give ketone **1a** and lithium diisopropylcarbamate(iPr)$_2$NCOOLi. This result indicates that the secondary amine reacts with the CO_2 that evolved from the disproportionation to give the corresponding carbamic acid (iPr)$_2$NCOOH,[12] which contributes to further neutralize the reaction intermediates. The reaction with DBU led to a fast and nearly quantitative (91 %) formation of dianion **2a**(Li^+,COOLi) which remained in solution for *ca.* 5 h before starting to slowly deplete to give the ketone **1a**.

These results show that nitrogen bases promote the disproportionation of lithium β-ketocarboxylate **1a**(COOLi) even in the presence of lithium iodide, by probably performing the role of a proton carrier between the intermediate species. The reaction may proceed (Scheme 5) through an initial acid-base reaction of **1a**(COOLi) and Li^+/BH^+ exchange to give dianion **2a**(Li^+,COOLi) and salt BH^+I^-, followed by the Li^+/BH^+ ion exchange of unreacted **1a**(COOLi), decarboxylation of the resulting **1a**(COOBH) promoted by H-bonding within the ion pair,[7] and the subsequent annihilation of enolate

Scheme 5. Disproportionation of lithium β-ketocarboxylate 1a(COOLi) catalyzed by nitrogen bases B.

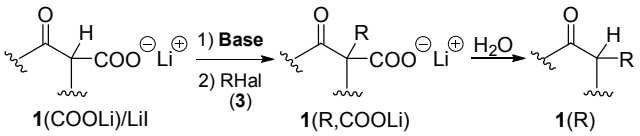


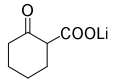
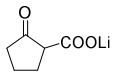
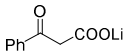
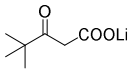
2a(BH^+). The Li^+/BH^+ ion exchange in β-ketocarboxylate **1a**(COOLi) would be the key step in this process as it promotes the loss of CO_2 which triggers the internal acid-base reaction of enolate **2a**(BH^+) (Scheme 5). Accordingly, the disproportionation reaction was the fastest for HMDS and the slowest for DBU, the weakest and strongest bases in the series, respectively, with the most and least soluble conjugate salts, $HMDSH^+I^-$ and $DBUH^+I^-$, respectively.

The reaction with alkyl halides 3. The reactions of lithium β-ketocarboxylates **1**(COOLi) with alkyl halides **3** were performed by adding the base (1.2 equiv) to a 0.2 M THF solution of **1**(COOLi) and lithium iodide purged with argon, and by treating the reaction mixture with alkyl halide **3** (1 equiv) for 15 h, at room temperature. The reaction mixture was monitored by withdrawing aliquots which were quenched with TMSCl and analyzed by gas chromatography. The reaction mixture was treated with hydrochloric acid and the organic phase was analyzed by GC-MS. The reaction was optimized for a series of ketone enolates **2**(Li^+) and the results are shown in Table 2.[18] The experimental procedures are described in the Supplementary Material.

The results in Table 2 illustrate the reactivity of lithium β-ketocarboxylates **1**(COOLi) to nitrogen bases and alkyl halides **3** and the application of CO_2 as a removable directing group to control the reactivity of lithium enolates **2**(Li^+). The reactions proceeded under mild conditions and required 1 equiv of alkyl halide **3**. Some significant trends related to the presence of lithium iodide in the reaction medium were observed in these experiments. First, alkyl bromides **3** react with lithium iodide to form the corresponding iodides, which facilitates the S_N2 reaction of dianion **2**(Li^+,COOLi). Second, the acid-base reaction of lithium β-ketocarboxylates **1**(COOLi) with the nitrogen base, and the disproportionation reaction become slower as the lithium salt concentration increases. These observations can be attributed to the coordination

Table 2. Reaction of lithium β-ketocarboxylates **1**(COOLi) with bases **4** and alkyl halides **3**, in THF in the presence of LiI.[a]



Run	Substrate 1(COOLi)	3	LiI (equiv)	Base	Product 1(R)	Yield (%)[b]
1		**3p**	2	DBU	**1a**(Me)	84
2		**3q**	2	DBU	**1a**(Bz)	80
3	**1a**(COOLi)	**3r**	2	DBU	**1a**(Allyl)	82
4		**3p**	2	DBU	**1b**(Bz)	82[c]
5		**3p**	5	DIPA	**1b**(Me)	93
6	**1b**(COOLi)	**3q**	5	DIPA	**1b**(Bz)	95
7		**3r**	5	DIPA	**1c**(Allyl)	87
8		**3r**	2	DBU	**1c**(Allyl)	58[d]
9		**3p**	1	DBU	**1c**(Me)	72
10	**1c**(COOLi)	**3q**	1	DBU	**1c**(Bz)	81
11		**3r**	1	DBU	**1c**(Allyl)	83
12		**3p**	2	DBU	**1d**(Me)	85
13		**3q**	2	DBU	**1d**(Bz)	93
14	**1d**(COOLi)	**3r**	2	DBU	**1d**(Allyl)	93

[a] Reactions performed by adding 1.2 equiv of base, and 1 equiv of **3** (except for **3p**: 4 equiv) to a 0.2 M solution of **1**(COOLi) (except for **1b**(COOLi): 0.16 M) and LiI in THF, with adamantane used as the internal standard, at r.t. and in an inert atmosphere, for 15 h. [b] Determined by the GC analysis of the reaction mixture. Values were not corrected for the respective response factors. Ketones **1**(R) and **1** were the only products except where noted. [c] **1b**(R,R): 12 %. [d] **1c**(R,R) 12 %.

of lithium cations to the base and β-ketocarboxylate **1**(COOLi),[16] which hampers both the proton abstraction by the base, and the Li^+/BH^+ ion exchange of **1**(COOLi) required for the decarboxylation and disproportionation steps. Third, excess lithium salts in solution prevents the reaction of the base with alkyl halide **3** through competition of the lithium cations with **3** for the basic and nucleophilic nitrogen atom.[16] The role of alkali cations as inhibitors of the acid-base reactions of nitrogen bases has been established for the carboxylation of ketones with CO_2 promoted in the presence of alkali salts,[5h,j,k] and even for the hydrolysis of lithium amides.[19]

The intrinsic reactivity of lithium β-ketocarboxylate **1**(R, COOLi), formed as the primary reaction product, and the complex interplay of the different factors and processes involved, required the optimization of the reaction conditions for each case. The reactions of our model lithi-

um β-ketocarboxylate **1a**(COOLi) were performed in the presence of 2 equiv of lithium iodide with DBU as the base (Entries 1-3, Table 2). The reaction of five-membered cyclic lithium β-ketocarboxylate **1b**(COOLi) under the same conditions led to the formation of doubly alkylated cyclopentanone **2b**(R,R) with a 13 % yield (Entry 4, Table 2). This result suggested that β-ketocarboxylate **1b**(R,COOLi) decarboxylates faster than the corresponding six-membered derivative **1a**(R,COOLi), probably due to stereoelectronic factors being more favorable to decarboxylation in the former.[8,9] DIPA was used as the base in this case as its ammonium salt, which is more soluble in the reaction medium than that of DBU (Entries 5-7, Table 2), facilitated the proton transfer to the enolate **2b**(Li^+, R) that formed after decarboxylation. The reaction required a 5-fold excess lithium iodide to minimize the reaction of DIPA with alkyl halide **3**.[20]

The reaction conditions established for our model substrate **1a**(COOLi) (Entry 1, Table 2) were not suitable either for acetophenone derivative **1c**(COOLi) (Entry 8, Table 2) since the enolizable secondary β-ketocarboxylate **1c**(R,COOLi) underwent the same reactions as the starting material to give the dialkylated product. Reactions were then performed with DBU in the presence of 1 equiv of lithium iodide (Entries 9-11, Table 2) which promoted a fast acid-base reaction and rendered dianion **2c**(Li^+,COOLi) quantitatively thus removing the base from the reaction medium. DIPA rendered similar results in this case. Conversely, the lithium β-ketocarboxylate **1d**(COOLi) that derived from pinacolone (**1d**), underwent the alkylation reaction under the reaction conditions established for our model substrate **1a**(COOLi) (Entries 12-14, Table 2). In this instance the bulky *tert*-butyl substituent prevented further reactions of secondary β-ketocarboxylate **1d**(R,COOLi).

Conclusions

The reaction of lithium enolates **2**(Li^+) with CO_2 provides stable THF solutions of lithium β-ketocarboxylates **1**(COOLi) when performed in the presence of lithium iodide, otherwise lithium β-ketocarboxylates **1**(COOLi) disporportionate at low temperature in the presence of excess CO_2 to give ketone **1** and dianion **2**(Li^+,COOLi). The availability of stable THF solutions of lithium β-ketocarboxylates **1**(COOLi) in the absence of CO_2 allowed us to explore the reaction of these intermediates with nitrogen bases and alkyl halides **3**. The complete transformation represents the selective monoalkylation of enolates **2**(Li^+) by using CO_2 as a removable directing group. The study described herein discloses the rather complex behavior of lithium β-ketocarboxylates **1**(COOLi) in THF, and the role of lithium ions as Lewis acids in ion pairing and the aggregation of basic species in solution,[15,16] and the decarboxylation reaction. The availability of stable solutions of a variety of lithium β-ketocarboxylates **1**(COOLi) in THF opens up new opportunities to apply these intermediates in organic synthesis.

Experimental Section

General. Reagents were purified following standard procedures. All the reactions were performed by Schlenk techniques using flame-dried glassware. The reported yields were determined by gas chromatography (GC) with a (5%-phenyl)-methylpolysiloxane capillary column (length 30 m, internal diameter 0.25 mm, film thickness 0.25 μm). Adamantane was used as the internal standard. The conversion and yield values were not corrected for the response factors of the different products. Detailed experimental procedures and spectra are provided in the Supporting Information.

Reactions in the presence of lithium salts (Table 2). General procedure. Lithium enolate **2a**(Li^+) was prepared by adding dropwise 0.75 mL of a 1.6 M solution of methyllithium in diethyl ether (1.2 mmol) to a stirred solution of 1-(trimethylsilyloxy)cyclohexene (**2a**(TMS)) (0.195 mL, 1.0 mmol) and adamantane (0.068 g, 0.5 mmol) as the internal standard in THF (2.75 mL) cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and to stand for 1 h. This solution was added dropwise through a PTFE cannula to a stirred solution of lithium iodide (0.268 g, 2.0 mmol) in 1.5 mL of THF which had been previously saturated with CO_2 by cooling to -78 °C in a CO_2 atmosphere (1 bar) for 1 h. After 5 min at -78 °C under stirring the reaction mixture was warmed to 0 °C and argon was gently bubbled through for 30 min. Afterwards the solution was allowed to reach room temperature. The reaction mixture was treated with DBU (0.179 mL, 1.2 mmol) for 30 min, and then with benzyl bromide (0.119 mL, 1.0 mmol) under stirring. The reaction advance was monitored by withdrawing 0.1 mL aliquots and quenching them with chlorotrimethylsilane (TMSCl) (0.013 mL, 0.1 mmol) at room temperature; samples were diluted with 1 mL of diethyl ether, filtered (PTFE filter, pore size: 0.2 μm), and analyzed by GC. Once the reaction was complete (15 h) the reaction mixture was treated with 0.5 mL of concentrated hydrochloric acid, diluted with 1 mL of diethyl ether, and dried over anhydrous $MgSO_4$. The GC and GC-MS analyses showed 2-benzylcyclohexan-1-one **1a**(Bz) (80 %) and cyclohexanone **1a** (20 %) as the only products. The reaction mixtures that contained lithium iodide gave 4-iodo-1-butanol as a side product that derived from the solvent.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, NMR spectra, and GC-MS data for the crude reaction mixtures in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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ABBREVIATIONS

THF, tetrahydrofuran; GC, gas chromatography; MS, mass spectrometry; NMR, nuclear magnetic resonance; HMPA, hexamethylphosphoramide; DIPA, diisopropilamine; HMDS, hexamethyldisilazane; DBU, 1,8-diazabicyclo(5.4.0)undec-7-ene.

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18) Alkyl halide **3** competes with the conjugate acid BH^+ for the nucleophilic and basic species **2**(Li^+, COOLi) (Scheme 5). The alkylation reaction removes dianion **2**(Li^+,COOLi) from the solution and, thus, contributes to prevent the disproportionation path (Scheme 5). For this reason we performed these reactions with reactive alkyl halides **3p-r**. The use of less reactive alkyl halides **3** will require further adjustment of the reaction conditions.

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SYNOPSIS TOC