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i-Pr₂NMgCl·LiCl Enables the Synthesis of Ketones by Direct Addition of Grignard Reagents to Carboxylate Anions

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Supporting Information Placeholder

ABSTRACT: The direct preparation of ketones from carboxylate anions is greatly limited by the required use of organolithium reagents or activated acyl sources that need to be independently prepared. Herein, a specific magnesium amide additive is used to activate and control the addition of more tolerant Grignard reagents to carboxylate anions. This strategy enables the modular synthesis of ketones from CO₂ and the preparation of isotopically-labelled pharmaceutical building blocks in a single operation.

Ketones (**1**) are one of the cornerstones of organic chemistry, being a fundamental class of products and essential synthetic intermediates. Aromatic ketones are particularly relevant drugs and fragrances, and they are key to the synthesis of heterocyclic cores in valuable products.¹ As a result, extensive research has been dedicated to obtain ketones from raw carboxylic acids (**2**) and CO₂ (**3**). However, the addition of localized carbon nucleophiles to carboxylic acids is a key transformation that remains challenging after decades of research (Scheme 1A). Most approaches elaborate carboxylic acids **2** into more electrophilic derivatives **4**, such as acyl chlorides,² anhydrides,³ thioesters,^{2f,4} cyanides,⁵ ketimines,⁶ imides,⁷ amides⁸ and Weinreb amides.⁹ Special carbon nucleophiles **5** with lower reactivity like cuprates,¹⁰ organozincs,^{4,11} and boronates,^{2g,3b,7,12} are often used to avoid the rapid over-addition to the resulting ketone products **1**. Alternatively, the direct coupling of carbon nucleophiles with unactivated carboxylic acids requires unstable organolithium reagents, often in excess.^{13,14} These addition reactions to lithium carboxylate anions **Li-6** benefit from the stability of the addition complex **Li-7**, but are limited by competing metalation reactions, carbonyl reduction, and the narrow functional scope of the lithium organometallics.¹⁴ Grignard reagents (**8**) are preferred nucleophiles for their enhanced stability and functional-group tolerance, particularly in large-scale processes.^{15,16} Unlike organolithiums, Grignard reagents (**8**) are poorly reactive towards carboxylate anions (**6**), and the resulting addition intermediates are unstable, giving rise to tertiary alcohol over-addition by-products.^{13d,14}

The addition of aromatic Grignard reagents to benzoates would give rise to important benzophenone compounds,^{1b} but it is particularly problematic due to the lower reactivity of aromatic carboxylates and aryl Grignard reagents. To the best of our knowledge, this reaction has only been studied using chelate-assisted heteroaryl substrates,¹⁷ or lithium propylamide as additive (Scheme 1B).¹⁸ However the application of these processes in organic synthesis is severely limited by the narrow scope, and the inhibition in the presence of tetrahydrofuran,¹⁸ which is the most common solvent to synthesize, store and distribute Grignard reagents.^{16,19} Overcoming the challenges associated with the direct addition of Grignard nucleophiles (**8**) to carboxylate anions (**6**) is key to enable an extended modular synthesis of ketones from CO₂ (**3**).^{13d} Carboxylates **6** are readily obtained from aryl Grignard reagents (**8**) and CO₂ (**3**),²⁰ and these anions could ideally undergo coupling with a second organomagnesium nucleophile. The enhanced scope bestowed by Grignard reagents¹⁶ would enable access to diversely functionalized ketones in a single operation.^{13d} The use of CO₂ also offers a more sustainable alternative for scale-up than current methods based on CO, CO-sources and/or expensive transition-metal catalysts,^{12,21} particularly for the synthesis of isotopically carbon-labelled pharmaceuticals used in bio-distribution studies and trace analysis.²²

We have recently discovered the differential behavior of Grignard reagents in combination with the hindered *turbo*-Hauser base *i*-Pr₂NMgCl·LiCl (**9a**)²³ in the context of Pummerer reactions.²⁴ We hypothesized that the enhanced “ate” character^{19a,25}

of the *turbo*-organomagnesium amides thus formed, could (1) enhance the nucleophilicity of the initial Grignard reagent to overcome the low electrophilicity of the carboxylate anion, (2) stabilize the addition complex through strong coordination^{2e,9a} and/or rapid intramolecular enolization, and in a broader sense (3) address the efficiency and selectivity problems that are associated with classic organometallic "ate" reagents $[R_3M]^-$ ($M=Mg, Cu, Zn$).^{10,11,25}

Scheme 1. State-of-the-art in the synthesis of ketones and our approach using Grignard reagents.

In agreement with the general notion in the literature,^{10,13a,13d,17-18,26} our exploratory studies (Table 1) revealed that no addition of phenylmagnesium bromide (**8a**) occurs to the sodium carboxylate (**Na-6a**; entry 1), and a similar result is obtained in the presence of $PrNHLi$ (**9b**; entry 2), probably due to the THF in the commercial Grignard solution.¹⁸ In stark contrast, $i\text{-}Pr_2NMgCl \cdot LiCl$ (**9a**) has a dramatic effect at enhancing the conversion and selectivity of the reaction, obtaining the ketone **1a** as the major product (entry 3). After extensive experimentation, we found that the more soluble magnesium carboxylate **MgCl-6a** further suppresses the formation of the over-addition product **10a** (entry 4). Interestingly, only little conversion is observed when omitting the premixing of **8a** and **9a** (entry 5). Ultrasonic homogenization of this mixture decreases the formation of the addition-reduction by-product **11a** in small-scale experiments (entry 6; for details see Scheme 4), but is not required in large scale reactions as stirring proves sufficient (Scheme 2). Interestingly, subtle changes in the steric hindrance of the *turbo*-Hauser base have a noticeable effect on the

efficiency of the reaction (entry 7). $LiCl$ is essential in the Hauser base to achieve high conversion (entry 8), probably indicating its role in the aggregation²⁷ of the *turbo*-organomagnesium amide formed upon mixing of the Grignard **8a** and **9a** (for discussion, see Scheme 4).²⁸ Control experiments in the absence of $i\text{-}Pr_2NMgCl \cdot LiCl$ (**9a**; entry 9) confirm its critical role at promoting the addition reaction to the magnesium carboxylate. Furthermore, related lithium amides **9e,f** or $LiCl$ alone were deemed ineffective (entries 10-12), thus indicating the singular activating effect of the magnesium amide $LiCl$ complex **9a** in the addition to the carboxylate anion. To the best of our knowledge, organomagnesium amides have only been used as bases in challenging deprotonation reactions,^{28c} and the performance of their $LiCl$ -adducts as carbon nucleophiles has not been explored before our work.²⁴

Table 1. Activation and control of Grignard reagents by $i\text{-}Pr_2NMgCl \cdot LiCl$ (**9a**).

#	M	additive (9)	composition (%) ^a			
			2a	1a	10a	11a
1	Na	—	94	0	0	0
2	Na	$PrNHLi$	97	0	0	0
3	Na	$i\text{-}Pr_2NMgCl \cdot LiCl$ (9a)	9	77	14	0
4	$MgCl$	$i\text{-}Pr_2NMgCl \cdot LiCl$ (9a)	0	92	0	5
5	$MgCl$	$i\text{-}Pr_2NMgCl \cdot LiCl$ (9a) ^b	67	28	0	5
6	$MgCl$	$i\text{-}Pr_2NMgCl \cdot LiCl$ (9a) ^c	26	49	3	25
7	$MgCl$	$TMPMgCl \cdot LiCl$ (9c)	72	26	0	0
8	$MgCl$	$i\text{-}Pr_2NMgCl$ (9d)	55	36	4	4
9	$MgCl$	—	64	18	15	0
10	$MgCl$	$i\text{-}Pr_2NLi$ (9e)	70	22	4	8
11	$MgCl$	$TMPLi$ (9f)	61	25	3	8
12	$MgCl$	$PrNHLi$ (9b)	65	21	14	0
13	$MgCl$	$LiCl$ (9g)	57	15	28	0

Conditions: **2a** (0.1 mmol), NaH or $t\text{-}BuMgCl$ (0.1 mmol), toluene, 0 °C; $PhMgBr$ (**8a**, 0.12 mmol) and **9** (0.12 mmol), 0 °C, ultrasound; r.t., 7 h. ^aDetermined by $^1H\text{-NMR}$ using 1,1,2,2-tetrachloroethane as internal standard. ^bNo pre-mixing of **8a** and **9a**. ^cNo ultrasound. TMP, 2,2,6,6-tetramethylpiperid-1-yl.

With these optimized conditions in hand we next studied the substrate scope, that benefits from the enhanced tolerance of Grignard nucleophiles (Scheme 2).¹⁶ Readily available carboxylic acids are coupled with phenylmagnesium bromide to produce ketones **1a-c** in high yields. A range of aromatic Grignard reagents bearing oxygen- (**1d**), sulfur- (**1e**) or nitrogen-based substituents (**1f**) provide ketones in good to excellent yields. Notably, the localized Grignard reagents allow the regioselective preparation of *meta*-substituted electron-rich products that would be problematic through Friedel-Crafts acylation (**1e,f**). Electron-poor nucleophiles bearing halogens (**1g**) and π -deficient heterocycles (**1h**) are also tolerated. It is important to underscore the integration with the *in situ* telescoped C–H

metalation of phenylpyridine (**1h**), and the compatibility with bromine-containing carboxylic acids (**1h,i**) without engaging in halogen-magnesium exchange by-processes. Furthermore, heterocyclic moieties can be introduced from both coupling partners (**1h-l**), enabling for instance the expedient preparation of important thiazolyl-ketones.^{1g} Unlike previous reports,¹⁷ the presence of a nitrogen-center *ortho*- to the reacting site is not required (**1l**). Interestingly, the naphthol-derived ketone **1m** can be prepared without protection of its phenol function (*vide infra*). To our delight, aliphatic Grignard reagents also readily engage in this transformation, provided that two equivalents of the *turbo*-organomagnesium amide are used. Thus, electron-rich and electron-poor acids are coupled to provide valerophenones **1n-q** in excellent yields. Using benzyl and homobenzyl nucleophiles the corresponding α - and β -arylated ketones are obtained (**1r,s**). The latter (**1s**), is a key intermediate in the synthesis of the anti-hypertensive propafenone (Arythmol®).^{1d,1e} Moreover, Grignard reagents containing an alkene (**1t,v**) or a free alcohol functionality (**1u**) can be introduced in high yields. Remarkably, the electron-rich, unprotected *meta*- and *ortho*-salicylic acids, including hydroxy-naphthoic acid, are excellent

substrates for this reaction, thus enabling the preparation of medicinally relevant phenolic and/or morpholine-derivatives **1s,v-x**. Likewise, the alcohol-containing ketone **1y**, an intermediate to the essential anti-psychotic haloperidol (Haldol®),^{1c} is prepared in excellent yield. Secondary alkyl nucleophiles can be used as well to prepare electron-deficient ketones **1x,z-ac** in high yields, in combination with trifluoromethyl- and halogenated benzoic acids. Unprotected anthranilic acids are also compatible (**1ad**), thus providing valuable intermediates for the preparation of benzodiazepine pharmaceuticals.^{1m-o} Upon scale-up, sonication is unnecessary, as illustrated by the gram-scale synthesis of the fluorinated ketones **1c** and **1z**. The generality demonstrated by this method, and the edge of *i*-Pr₂NMgCl·LiCl (**9a**) over the previously developed lithium propylamide additive (**9b**)¹⁸ is remarkable (see **1a,g,j,l,m,o,r,w,y,ad**). Still, tertiary alkyl Grignard reagents do not engage in this reaction, which we use to our advantage in the selective deprotonation of the carboxylic acid substrates (**2**) with *t*-BuMgCl. Interestingly, aliphatic acids are recovered unreacted under these conditions due to their fast enolization,^{13e} a limitation that we are currently investigating.

Scheme 2. Synthesis of ketones through *turbo*-Hauser-base-enabled Grignard addition to carboxylic acids.

See SI for experimental conditions; ultrasound only required on small-scale. Isolated yields. ^areaction temperature 65 °C. ^b*t*-BuMgCl (2.0 equiv.) was used. ^cMeMgCl (2.0 equiv.) was used instead of *t*-BuMgCl.

Carboxylate anions (**6**) can also be readily obtained from the reaction of Grignard reagents (**8**) with carbon dioxide (**3**).^{20a} The combination of this process with the transformation uncovered herein enables a modular synthesis of ketones from two carbon nucleophiles, using CO₂ as a safe and available source of the central carbonyl group (Scheme 3).^{13d} This way,

functionalized Grignard reagents, prepared *in situ* by halogen-magnesium exchange^{19a} or direct metalation,²³ enable the direct use of aryl halides or arenes in the one-pot synthesis of complex ketones.¹⁶ As such, dichloropyridine is directly combined with CO₂ and different Grignard reagents to provide **1ae,af** in excellent yields. Likewise, the ketone **1ag** is obtained directly from

an ester-containing thiophene substrate and furane. This method also allows for the preparation of isotopically-labelled ketones simply by using carbon dioxide, the most available source of labelled carbon. The ^{13}C -labelled [^{13}C]-**1y,ah** are obtained in excellent yields, which are precursors of the isotopically-labelled pharmaceuticals haloperidol ([^{13}C]-**12**) and ketoprofen ([^{13}C]-**13**), respectively.^{1c,22,29}

Scheme 3. Modular synthesis of radiolabelled ketones from functionalized Grignards and CO_2 .

See SI for experimental conditions. Isolated yields. ^aCommercial Grignard solution in THF (Et_2O can also be used).

The excellent selectivity observed towards the ketone products indicates that the post-addition intermediate must be stable until the reaction is quenched. In the presence of **9a** under the standard reaction conditions (Scheme 4A), the model benzophenone **1ai** undergoes rapid addition of an aryl Grignard (**10ai**; entry 1). However, extensive reduction (**11ai**) takes place when using an aliphatic Grignard reagent (entry 2). Control experiments revealed that the reduction side-product **11ai** can be obtained using only $i\text{-Pr}_2\text{NMgCl}\cdot\text{LiCl}$ (**9a**; entry 3). Interestingly, LiCl is essential to observe this reduction (entry 4), which we observe in trace amounts in our ketone synthesis. We reason that the reduction products stem from a Meerwein-Ponndorf-Verley-type (MVP) hydride-transfer from the magnesium amide (see **14**). These results support the stability of the addition intermediates, as early release of the ketone product **1** would lead to significant over-addition and reduction by-products. Furthermore, deuteration experiments reveal that the enolate of the product **15a** is formed when using aliphatic nucleophiles (Scheme 4B), which opens the door for further functionalizations *in situ*. The deprotonation of the product also explains the need for two equivalents of the reagents to synthesize enolizable ketone products from alkyl Grignard reagents (Scheme 2). Based on these results, we propose the mechanism shown on Scheme 4C. We reason that the crucial pre-mixing of **8** and **9a** before addition to the carboxylate anion **6**, and the noticeable effect of the structure of the amide ligand (see Table 1) are consistent with the aggregation of **8** and **9a**. Given the data available on the structure of *turbo*-Hauser bases²⁷ and organomagnesium amides,^{28b,28c} we presume that a *turbo*-organomagnesium amide (**16**) is formed. Unlike conventional Grignard reagents or their LiCl complexes (Table 1, entry 13), **16** is sufficiently

nucleophilic to add to magnesium carboxylates (**6**) without the limitations of organometallic "ate" reagents.^{10,11,25} The concur of lithium, magnesium and a singular bulky amide base have proven essential for this activation (Table 1). When using aromatic nucleophiles, we propose that the resulting intermediate **17** is stabilized through coordination with the amide ligand, while in the case of aliphatic Grignard reagents we have demonstrated that the addition intermediate **18** evolves into enolate **15**. The stability of the putative intermediates **15,17** until the reaction is quenched explains the high selectivity obtained towards the ketone products **1**. Otherwise by-products stemming from over-addition (**10**) and reduction (**11**) would dominate, as it has been demonstrated above (Scheme 4A).

Scheme 4. Mechanistic studies and proposal.

A addition intermediate is stable & MPV-reduction of ketones with $i\text{-Pr}_2\text{NMgCl}\cdot\text{LiCl}$

B enolization occurs in the reaction using alkyl Grignards

C proposed mechanism

See SI for details. ^aDetermined by ^1H -NMR using 1,1,2,2-tetrachloroethane as internal standard. M = $\text{Li}_x\text{Mg}_y\text{L}_n$.

In summary, the *turbo*-Hauser base $i\text{-Pr}_2\text{NMgCl}\cdot\text{LiCl}$ (**9a**) activates and controls the addition of Grignard reagents to carboxylate anions. This reaction likely proceeds through organomagnesium amide intermediates featuring enhanced nucleophilicity and the capacity to stabilize the resulting addition products. The wide scope of this transformation in both coupling partners allows swift synthesis of relevant aromatic ketones on a preparative scale. Integration with Grignard carbonation enables the sequential assembly of ketones using CO_2 as

carbonyl equivalent, thus facilitating the synthesis of isotopically-labelled pharmaceuticals.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, optimization details, and characterization data (file type, i.e., PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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