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Direct Addition of Grignard Reagents to Aliphatic Carboxylic Acids Enabled by Bulky *turbo*-Organomagnesium Anilides

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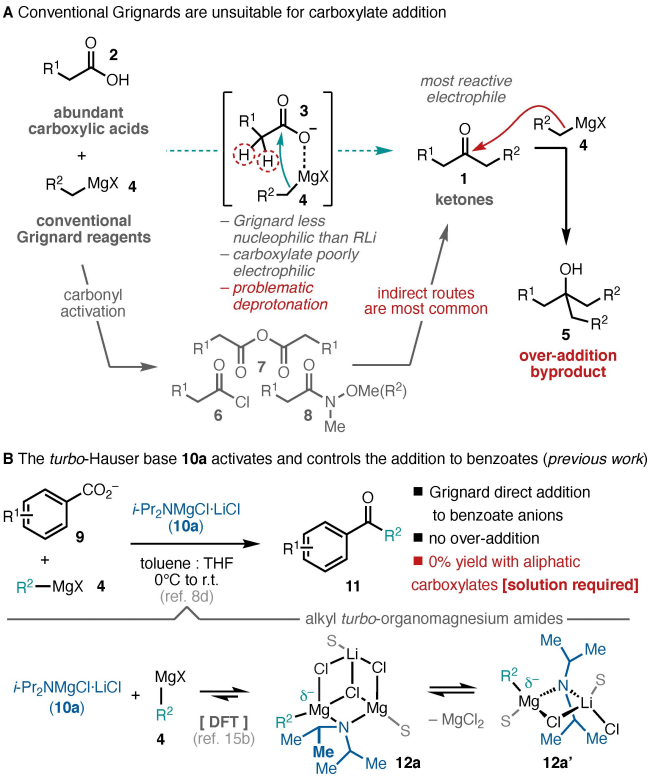
Dedicated to R. E. Mulvey on the occasion of his 62nd birthday

Abstract: The synthesis of ketones through addition of organometallic reagents to aliphatic carboxylic acids is a straightforward strategy that is limited to organolithium reagents. More desirable Grignard reagents can be activated and controlled with a bulky aniline-derived *turbo*-Hauser base. This operationally simple procedure allows the straightforward preparation of a variety of aliphatic and perfluoroalkyl ketones alike from functionalized alkyl, aryl and heteroaryl Grignard reagents.

Ketones **1** have a privileged role in organic chemistry and are prevalent in pharmaceuticals,[1] fragrances,[2] and synthetic intermediates,[3] to mention just a few. The synthesis of ketones from carboxylic acids **2** is particularly attractive due to their abundance in raw materials and building blocks (Scheme 1A). However, the direct addition of main group organometallics to carboxylic acids has traditionally been a challenging process.[4] Issues arise both from the low electrophilicity of carboxylate anions **3** that lead to low conversions with Grignard reagents **4**, and the high electrophilicity of the resulting ketones **1** towards over-addition side reactions that produce tertiary alcohols **5**. Typically, these issues are circumvented by using weaker nucleophiles,[5] combined with the pre-activation of the carboxylic acid **2** into a more reactive electrophile such as acyl chlorides **6**, anhydrides **7**[6,5b] or (Weinreb) amides **8** that also stabilize the addition intermediate.[7] These strategies enable mild and functional group tolerant Grignard reagents **4** as widely available nucleophiles at the expense of an activation step. A direct addition of carbon nucleophiles to carboxylic acids would be desirable, but the reported methods are still limited to particular substrates and/or organolithium nucleophiles.[8]

Recently, our group has demonstrated a direct addition of Grignard reagents **4** to magnesium benzoates **9** enabled by a *turbo*-Hauser base **10**[9] to yield acetophenone derivatives **11** (Scheme 1B).[8d] This additive enhances the nucleophilicity of the Grignard reagent **4** and stabilizes the addition intermediate towards further over-addition side reactions. While this protocol accommodates a wide range of carboxylic acid and Grignard



Scheme 1. A) Direct and indirect addition of Grignard reagents to carboxylate anions, and B) our recent work on benzoates using *turbo*-organomagnesium amide aggregates.

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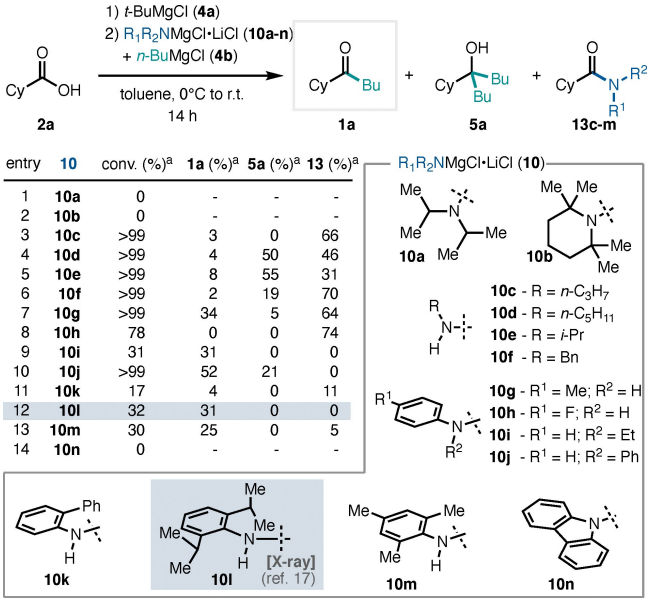
substrates **2**, **4**, it was found to be incompatible with enolizable aliphatic acids (i.e., **2a**, Scheme 2). To enable coupling with enolizable substrates, we hypothesized that the basicity and steric properties of the reagent could be tuned with an appropriately designed amine. Our previous studies on the reagents **12a**[8d,15] evidenced the critical influence of the amine structure in the reactivity and selectivity of the resulting species. For example, reagents derived from diisopropylamine (DIPA; **12a**) were remarkably reactive whereas those derived from 2,2,6,6-tetramethylpiperidine (TMP; **12b**) only produced traces of the desired compounds. We have rationalized these results based on the different aggregation state of these reagents, which we have studied thoroughly in the case of those derived from DIPA (**12a**).[15b]

Given the similar electrophilicity of benzoate and aliphatic carboxylate anions, the nucleophilicity of *turbo*-organomagnesium amides was unlikely to be behind their low performance (Scheme 1B).[8d] Instead, this mixture of organometallics and bases were known to promote irreversible enolization reactions.[10] Deprotonation of the carbonyl substrate in the α-position is not only known with carboxylates,[11] but also with activated derivatives such as acyl halides[6a,12] or amides.[13] The enolate dianions formed from aliphatic carboxylates cannot engage in addition reactions. This problem has been alleviated with lanthanide additives in some additions to carbonyls other than carboxylates.[11,13—14] Instead, we explored the use of alternative *turbo*-Hauser base additives to modify the basicity/nucleophilicity balance of the corresponding organomagnesium aggregates, and to stabilize the addition product at once.

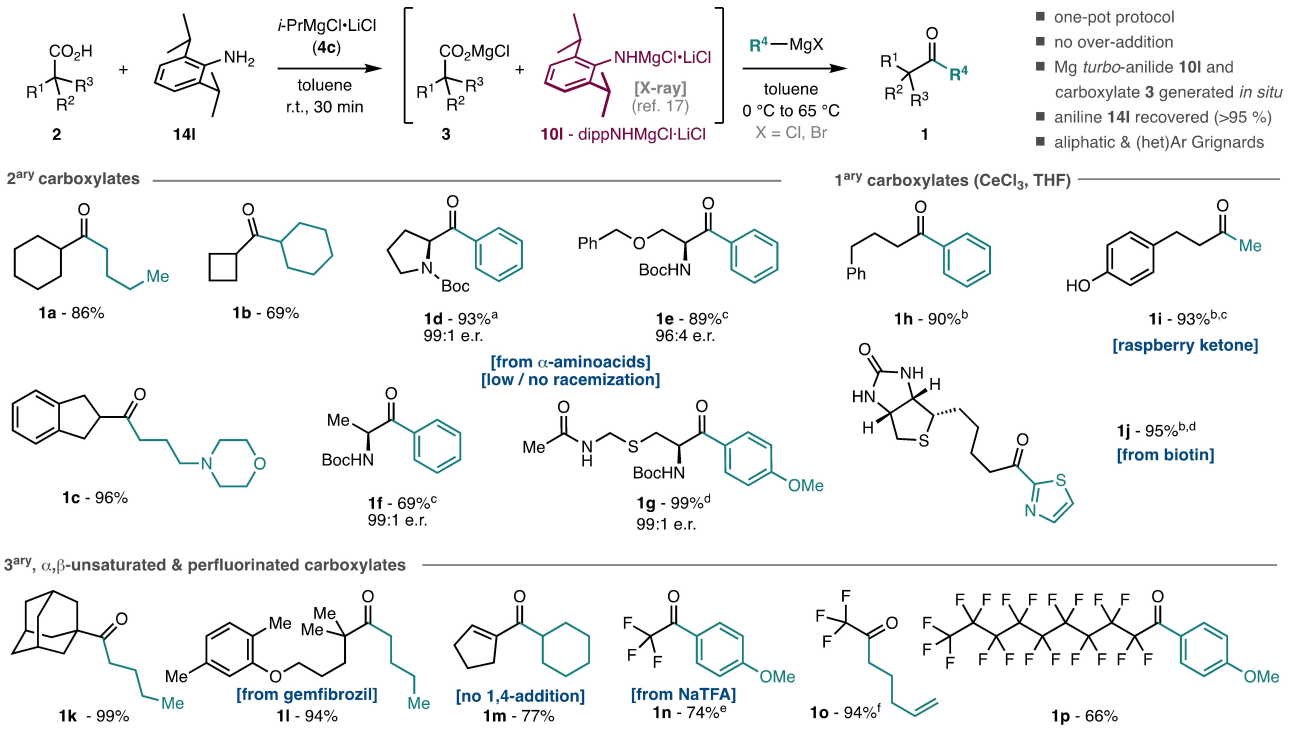


entry	10	conv. (%)[a]	1a (%)[a]	5a (%)[a]	13 (%)[a]
1	10a	0	-	-	-
2	10b	0	-	-	-
3	10c	>99	3	0	66
4	10d	>99	4	50	46
5	10e	>99	8	55	31
6	10f	>99	2	19	70
7	10g	>99	34	5	64
8	10h	78	0	0	74
9	10i	31	31	0	0
10	10j	>99	52	21	0
11	10k	17	4	0	11
12	10l	32	31	0	0
13	10m	30	25	0	5
14	10n	0	-	-	-

Scheme 2. Effect of different *turbo*-Hauser base additives **10** in the reactivity and the selectivity of a model Grignard reagent. Conditions: **2a** (0.1 mmol), toluene (1.5 mL), *t*BuMgCl (**4a**, 0.1 mmol), 0 °C, 15 min; *then* base **10** (0.2 mmol) pre-mixed with *n*BuMgCl (**4b**, 0.2 mmol, see the Supporting Information for details); sonication, 0 °C, 15 min, *then* r.t., 14 h. [a] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

Different *turbo*-Hauser bases **10** were studied by using the aliphatic carboxylic acid **2a** in the standard conditions of our previous protocol (Scheme 2). In all cases, the magnesium carboxylate **3** was conveniently generated in situ in small scale from the substrate **2a** using *t*BuMgCl (**4a**). This reagent has the advantage of not interfering with the addition of other Grignards due to its low nucleophilicity. Then, the *turbo*-Hauser base **10** and the Grignard solution **4b** were mixed and subsequently added to the magnesium carboxylate solution.[8d] We previously noted that the premixing of these two reagents is essential for the reaction, further suggesting the formation of a key organomagnesium amide nucleophile **12** (Scheme 1B). To tune the basicity/reactivity balance of this putative reagent, *turbo*-Hauser bases **10** derived from various amines were investigated (Scheme 2). Conventional secondary magnesium amides derived from DIPA **10a** and TMP **10b**, that were successful in our earlier work, provided no conversion (entries 1, 2).[8d] The base derived from propylamine **10c**, a primary aliphatic amine, led mostly to the formation of amide **13c** in our system (entry 3). The apparent discrepancy of this result with seminal work by Asaoka[8a] could be explained by the presence of LiCl, which seems to increase the nucleophilicity of the metal amide.[16] Other primary amides **10d–f** with increasing steric bulk produced amides, with increasing amounts of the tertiary alcohol **5a** (entries 4–6) that stems from the double addition of the reagent. These results indicate that the relative rate of addition and amide formation can be modulated by the nitrogen ligand, and also the nucleophilicity of the latter reasonably decreases with increasing steric bulk. Remarkably, the base derived from *p*-toluidine **10g** led to the desired ketone **1a** in 34% yield and only minimal over-addition **5a**, but formed 64% of the amide **13g** (entry 7). Other primary and secondary aniline bases **10h–k** resulted in variable yields and selectivities (entries 8–11). We reasoned that increasing the steric hindrance of the nucleophilic aniline fragment might prevent amide formation and favor the desired reactivity. Indeed, the bases derived from 2,6-diisopropylaniline (**10l**, entry 12) and 2,4,6-trimethylaniline (**10m**, entry 13) provided ketones with high selectivity, albeit in low yields. Thus, we selected the readily available 2,6-diisopropylaniline based reagent, thereafter termed dippNHMgCl·LiCl (**10l**), for further optimization. Importantly, organomagnesium amides derived from **10l** have been reported and fully structurally characterized.[17] However, these bases have never been used in combination with organometallic reagents to enhance and control their reactivity as far as we know.

Further optimization work with dippNHMgCl·LiCl (**10l**) revealed that gentle warming to 65 °C allowed to reach 84% yield of the desired ketone **1a** with complete selectivity in 14 h (Scheme 3). Higher temperatures (100 °C) or substantially much prolonged reaction times (24 h) can be used but these modifications result in increased formation of the tertiary alcohol by-product **5a** (see the Supporting Information). Other aromatic or ether solvents led to lower conversion (see the Supporting Information), pointing at an optimal aggregation of the organomagnesium amide[8d,15] in toluene. Importantly, the higher acidity of the 2,6-diisopropylaniline (**14l**) compared to



Scheme 3. Scope of the addition of alkyl and aryl Grignard reagents to aliphatic carboxylate anions enabled by dippNHMgCl·LiCl (**10l**). Isolated yields are shown. Conditions: **2** (0.1 mmol), solvent (1.5 mL), 2,6-|(*i*-Pr)$_2$-aniline (**14l**, 0.2 mmol), *i*PrMgCl·LiCl (**4c**, 0.3 mmol), r.t., 30 min; *then* R^{3}MgX (**4**, 0.2 mmol) at 0 °C, *then* sonication, 0 °C, 15 min, *then* 65 °C, 1–14 h. [a] 40 °C and premixing of the base **10l** and the Grignard was used to obtain optimal *ee* of the product (see the Supporting Information). [b] $CeCl_3$ (0.2 mmol) used as additive and THF as solvent. [c] 1 equiv. extra **4c** was used to ensure deprotonation of any acidic functions. [d] 2 equiv. extra **4c** were used to ensure deprotonation of any acidic functions. [e] Commercial sodium trifluoroacetate was used as starting material. [f] Crude yield determined by ^{1}H NMR due to the volatility of the product.

the diisopropylamine used in our previous work allowed the use of *i*PrMgCl·LiCl[16b,c] (**4c**) to generate both the magnesium carboxylate **3** and the *turbo*-Hauser base **10l** simultaneously in situ (Scheme 3). Then, the desired Grignard nucleophile **4**, is added and the reaction warmed to 65 °C. This protocol does not require the independent preparation of the base and carboxylate, nor the mixing of base and Grignard separately. As a side note, we have observed that solutions of **10l** decompose upon exposure to sunlight and thus it is advisable to protect the reaction vessel from light to obtain optimal and reproducible results.

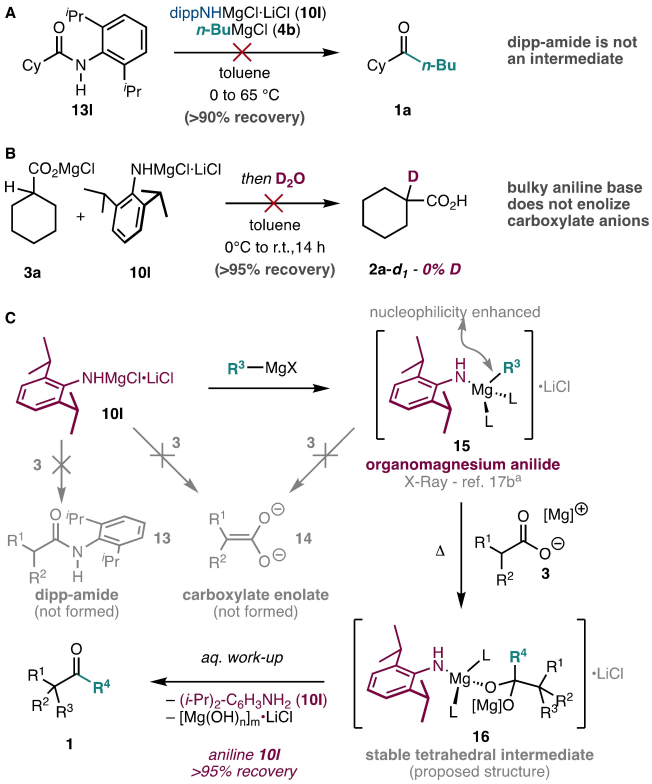
With these practical conditions in hand, we set out to study the scope of this reaction using different carboxylic acids **2** and Grignard reagents **4** (Scheme 3). Ketones **1** with various cyclic substituents including strained rings (**1b**) and potentially enolizable benzylic positions (**1c**) are obtained in good yields. More advanced aliphatic Grignard reagents bearing heterocyclic substituents were seamlessly tolerated and generated the 2-indanyl ketone **1c** in 96% yield. As a major class of natural products, amino acids would be valuable substrates for this reaction, allowing the rapid, straightforward preparation of otherwise challenging chiral α-aminoketones.[19] In this case, it is preferable to use a sequential addition protocol instead of the one-pot procedure, with careful monitoring of both temperature and reaction time. The Boc-protected proline proves to be an excellent substrate, giving rise to the corresponding phenyl ketone **1d** in 93% yield. Boc-L-serine(Bn) and Boc-L-Alanine are also efficiently arylated to produce **1e,f**. A cysteine derivative containing a potentially more sensitive amide protecting group forms **1g** in virtually quantitative yield. Despite the strongly basic conditions, the absolute stereochemical information is conserved (**1d,g**), thus confirming the absence of enolization using the mild base additive **10l**. Control experiments in the case of Boc-L-proline and Boc-L-alanine revealed that the addition of **10l** is not essential due to the strong coordinative assistance of the Boc group.[20] This observation may be of interest in process-scale synthesis of these derivatives, but it is specific to them. The addition reactions to chiral amino acids can complement existing organolithium methods[21] at addressing the current multistep procedures that are required to prepare chiral α-aminoketones.[22]

At first, primary acids remained largely unreactive in these optimized conditions, probably due to their easier enolization compared with their secondary counterparts. We investigated the potential of lanthanide additives (**8**) to lower basicity of the *turbo*-organomagnesium amide nucleophiles. To our delight, both $CeCl_3$ and $LaCl_3$ improved the outcome of the reaction, requiring THF as solvent due to the poor solubility of the lanthanide salts in toluene[14d,e] (see the Supporting Information). These conditions led to a 90% yield of ketone **1h**, and they could be implemented in both sequential and one-pot protocols with identical results. The unprotected 4-hydroxy-

hydrocinnamic acid produces the important raspberry ketone (**1 i**)[2b,18] in a single step. Likewise, biotin (vitamin B7) is efficiently converted to thiazolylketone[1c] **1 j** without protection of the urea moiety, highlighting the tolerance of these conditions for sensitive polar substrates.

Finally, non-enolizable substrates like tertiary aliphatic carboxylic acids are also compatible with this method. This allows to obtain the adamantyl-ketone **1 k** in quantitative yield. In a more complex example, the pharmaceutical gemfibrozil is efficiently functionalized to provide ketone **1 l**. Even an α,β-unsaturated acid can be used to obtain ketone **1 m** in 77% yield without 1,4-addition side-products. Moreover, (per)fluoroalkyl ketones can also be prepared with this strategy, providing **1 n–p** in good to excellent yields. These valuable building blocks typically require longer synthetic routes.[1e] These results are remarkable given the extreme electrophilicity of these ketones, which make them particularly sensitive to over-addition side reactions. Moreover, the trifluoromethyl ketone **1 n** was prepared from sodium trifluoroacetate, revealing a process-friendly synthesis of trifluoromethyl ketones.

Given that the use of other organomagnesium amides **10 c–h,k,m** resulted in amide products **13** (Scheme 2), we questioned whether this process was operating through amide intermediates that may be involved in the stabilization of the tetrahedral intermediate. However, the amide **13 l** under standard conditions proved to be unreactive ruling out this possibility (Scheme 4A). Also, we confirmed that



Scheme 4. Mechanistic studies and proposed model. [a] $R^3 = n$Bu; L,L = TMEDA (no LiCl). TMEDA, *N,N,N′,N′*-tetramethylethylenediamine.

dippNHMgCl·LiCl (**10 l**) was not sufficiently basic to deprotonate enolizable carboxylate anions such as **3 a** (Scheme 4B). Therefore, we ascribe the success of dippNHMgCl·LiCl (**10 l**) at promoting Grignard addition to carboxylate anions to a combination of: a) the high nucleophilicity of the organometallic ligand in the *turbo*-organomagnesium anilide aggregates **15** (Scheme 4C) that enables addition to the poorly reactive electrophiles **3**; b) the low nucleophilicity of the anilide that prevents sterically the formation of amides **13**; c) the low basicity of the aggregates **15** that prevents the formation of dianionic carboxylate enolates **14**. The role of the aromatic amide and LiCl in the stabilization of the tetrahedral intermediate **16** to prevent over-addition by-products is yet unclear.

In conclusion, a new synthesis of ketones **1** from carboxylic acids has been developed. It relies on the combination of Grignard reagents **4**, carboxylate anions **3**, and an unusual aromatic and hindered *turbo*-Hauser base additive, dippNHMgCl·LiCl (**10 l**). Importantly, these components can be generated in situ from carboxylic acids and 2,6-diisopropylaniline. The method engages a wide variety of aromatic and aliphatic Grignard reagents and various primary, secondary, tertiary, α,β-unsaturated, and (per)fluorinated carboxylic acids. These can be decorated with heterocycles, unprotected alcohols, and ureas. Even amino acids can be used to prepare chiral α-amino ketones in a single step and with excellent conservation of the absolute configuration. Altogether, the addition of Grignard reagents activated and controlled by bulky magnesium anilides simplifies access to ketones from abundant carboxylic acids, and demonstrates the potential of these additives to enhance the nucleophilicity without increasing the basicity of common organometallics.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Magnesium · ketones · acylation · metalation · Grignard reaction

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