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A practical one-pot process for α-amino aryl ketone synthesis

Karen Conrad,* Yi Hsiao and Ross Miller

Department of Process Research, Merck Research Laboratories, Merck & Co. Inc., Rahway, NJ 07065, USA

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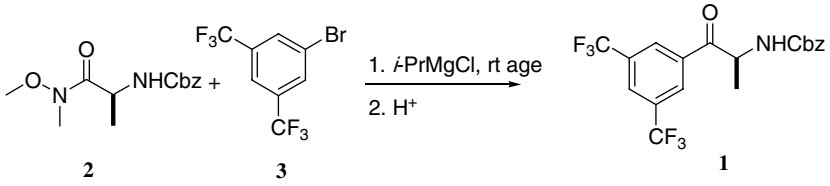
Abstract—An efficient, convenient, high-yielding synthesis of α-amino aryl ketones is described, involving the one-pot deprotonation–transmetallation–arylation of a Weinreb amide while retaining chirality of the original amide.

α-Amino ketones are important building blocks for many biologically active compounds. There are many different synthetic routes to α-amino ketones reported in the literature,[1] and Weinreb amide arylation/alkylation via Grignard addition is one of the most utilized methods.[1d,e]

In general, to prepare an α-amino ketone by this method, the Weinreb amide is derived from a *N*-protected amino acid (Boc or Cbz)[1d,e] and the Grignard reagent is prepared from the corresponding halide using Mg metal or *i*-PrMgCl.[2,3] The *N*-protected Weinreb amide contains one exchangeable proton and excess base is required for the deprotonation, which is normally accomplished by using an extra equivalent of the prepared Grignard[4] or *i*-PrMgCl.[5] Therefore, the reaction involves a two-pot process; the deprotonation of the Weinreb amide and the Grignard formation performed in two separate vessels, followed by transferring the Grignard into the deprotonated *N*-protected Weinreb amide solution. This method is useful for small scale synthesis to kilogram scale, however, the requirement of two anhydrous reaction vessels as well as a transfer of the moisture-sensitive Grignard reagent at sub-zero temperature not only lowers the productivity but also can lessen the robustness of the process.

Recently, during the investigation of the synthesis of an α-Cbz-amino ketone (**1**), we surprisingly discovered that the widely accepted Weinreb amide pre-deprotonation step is not necessary. In contrast to alkylation reagents where transmetallation is faster than the deprotonation, we theorized that the deprotonation would not only be faster than the Grignard addition to the Weinreb amide[5] but also the transmetallation of the bromide. In fact, the reaction proceeded smoothly when *i*-PrMgCl (2.5 equiv) was directly added into a mixture of Weinreb amide (**2**) and 3,5-bis (trifluoromethyl)bromobenzene (**3**) at −10 °C. (Scheme 1) After aging at room temperature overnight, the desired product was obtained at 92% HPLC assay yield and 99% ee. From these results, it was obvious that the rate of deprotonation dominated at first stage of the reaction. To confirm these results, the addition of isopropylmagnesium chloride to a solution of the Weinreb amide (**2**) and the bromide was followed by HPLC. The appearance of the debrominated



2 **3** **1**

Scheme 1.

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* Corresponding author. Tel.: +1 732 594 5129; fax: +1 732 594 1499; e-mail: karen_conrad@merck.com

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1,3-bis(trifluoromethyl)benzene (resulting from the quenched aryl grignard) does not occur until at least 0.95 equiv of the Grignard has been added. Thus, the Weinreb amide is deprotonated first, then the aryl Grignard is generated in situ using Knochel's procedure.[2]

The major side reaction is the addition of the isopropylmagesium chloride directly to the Weinreb amide, forming the isopropyl adduct. This by-product was controlled at <4–5%, and can be easily removed during the crystallization. We have also found that the typical acid quench at the end of the reaction causes the racemerization of the product. However, a reverse quench using HCl can minimize this problem, resulting in crude ketone **1** of 95% ee, and a crystallization from heptane upgraded the ee to 99%. Using our new one-pot protocol, this reaction was successfully operated on multikilogram scale.[10]

With these encouraging results, a variety of other aryl halides were examined to determine the scope of the reaction (see Table 1).

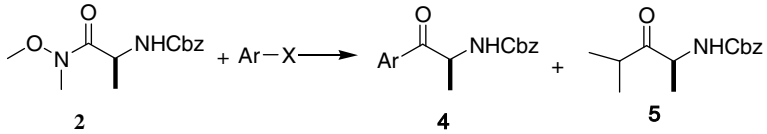
The reaction works very well with aryl bromides containing electron-withdrawing groups,[6] as shown in entries **3**–**6**, and **15**–**17**. As previously mentioned, the main side reaction is the formation of the isopropyl adduct of the Weinreb amide. We have found that the amount of this adduct generated is dependent on the rate of transmetallation. If the aryl Grignard forms quickly, little to no adduct is produced. On the other hand, if the aryl Grignard forms slowly or not at all, the adduct formation can become a competitive reaction. Transmetallation does not occur or occurs very slowly when there are electron-donating groups or no substituents on the aryl bromide, as with bromobenzene **8**, 4-methoxybromobenzene, and 4-bromotoluene. However, simply changing the bromide to the corresponding iodide will allow the reaction to proceed, as with iodobenzene **9**, methoxyiodobenzene **10**–**11**, and iodotoluene **12**–**14**. Thiazole **15** will also transmetallate at the same position as 2-bromothiazole **16** and produce ketone product at an acceptable yield, due to the acidic nature of the hydrogen at the 2-position.

There also appears to be a substitution effect on the Grignard reactivity. *o*-Substituted aryl halides have a lower yield than the *m*- or *p*-substituted analogs. For example, 3,5-difluoro-1-bromobenzene **5** has a higher yield than 2,5-difluoro-1-bromobenzene **4**. Similarly, 2-iodotoluene **14** has a lower yield than 3- or 4-iodotoluene (**12** and **13**). However, this trend is opposite with the iodomethoxybenzenes **10** and **11**. *o*-Methoxyiodobenzene has the higher yield, possibly through the coordination of the oxygen with the Mg metal to form a more stable intermediate.[6b,7]

The % ee was determined by chiral HPLC assay of the isolated ketone compared to an authentic sample of the racemic ketone, synthesized using the same chemistry as previously described. As previously discussed, the % ee of the ketone product is dependant on the acid quench, as well as the isolation. With optimization of both procedures for the individual substrates, we would expect the % ee to improve for these examples.

We have also examined the use of a morpholine amide in our reaction (Scheme 2), as the *N*,*O*-dimethylhydroxylamine used to synthesize Weinreb amide can be prohibitively expensive for scale-up.[8] Morpholine amide[9] performs similarly in our one-pot reaction. However, the yields are approximately 5–10% lower under the

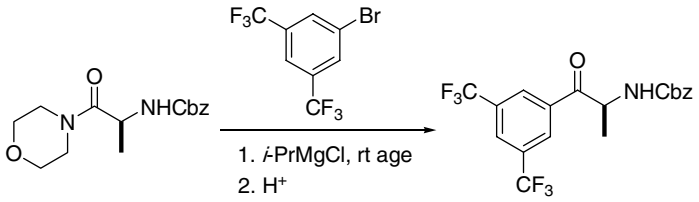
Table 1. Grignard reaction of **2** with aryl halides



2 **4** **5**

Entry	Halide	Assay yield, %[a]		
		Ketone **4**	Adduct **5**	ee %[b]
3	3,5-Bis(trifluoromethyl)bromobenzene	93.7	4.0	99
4	1-Bromo-2,5-difluorobenzene	86.6	7.7	89
5	1-Bromo-3,5-difluorobenzene	98.7	1.3	91
6	3-Bromopyridine	79.1	3.3	90
7	3-Bromo-5-methoxypyridine	97.1	3.3	88
8	Bromobenzene	0	>90	0
9	Iodobenzene	90.5	0	99
10	3-Iodoanisole	84.3	1.2	96
11	2-Iodoanisole	92.9	0.4	99
12	4-Iodotoluene	84.7	0.6	98
13	3-Iodotoluene	96.6	1.4	97
14	2-Iodotoluene	83.6	9.7	91
15	Thiazole	83.4	0	94
16	2-Bromothiazole	90.7	0	94
17	4-Bromobenzonitrile	88.7	15.7	82

[a] Assay yield of α-amino ketone product determined by HPLC using purified standards of desired products.
[b] ee determined by chiral HPLC assay of product compared to authentic sample of racemic ketone using Chiralpak AD-H (250 × 4.6 mm) column.



Scheme 2.

same experimental conditions (1.25 equiv bromide, 2.5 equiv *i*-PrMgCl in THF, age at ambient temp), and we have found that the completed unquenched reaction is unstable with extended age time.

In conclusion, we have discovered a novel one-pot process for α-amino ketone synthesis via the arylation of Weinreb amides, which require no pre-deprotonation of the Weinreb amide, dramaticaly simplifies the operation, and increases the productivity. The procedure clearly demonstrates that the Knochel magnesiztions are kinetically slower than deprotonations in contrast to organolithium transmetallations.

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Supplementary data

Full characterization of compounds and experimental details. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.183.

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10. Typical experimental procedure: Weinreb amide **2** (10.0 g, 37.4 mmol) and 3,5-bis(trifluoromethyl)bromobenzene **3** (13.75 g, 46.9 mmol) were dissolved in 40 ml THF, and the solution was degassed ($K_f < 500$ ppm). The solution was cooled using an acetone/dry ice bath (**2** precipitates out of solution at −10 °C), and *i*-PrMgCl in THF (40 ml, 2 M, 80 mmol) was slowly added to the reaction so that the internal temperature ⩽−5 °C. At the end of the addition, the external cooling was removed, and the reaction was aged at ambient temperature overnight (reaction usually completes within 6 h). HCl (5 N, 23 ml) was charged to a separate vessel and cooled to 0 °C, and the reaction mixture was then charged so that the internal temperature was ⩽5 °C. MTBE (20 ml) was added, mixed, and the layers separated. The pH of the aqueous layer was 4.1 (typical range 3.7–4.4). The MTBE layer was then washed with water (20 ml) and saturated aq NaCl (20 ml), and then concentrated via vacuum distillation to approximately 20 ml at 26–28 in. Hg and internal temperature of 25–30 °C. Heptane (100 ml) was added, and the solution was distilled to 65 ml, with the internal temperature 45–60 °C and 26–28 in. Hg. The solution was slowly cooled to 35 °C, and then seeded (approx. 1 wt %). The slurry was then slowly cooled to 10 °C over 2.5 h. The solids were filtered, washed with 20 ml cold heptane, and the cake was dried on the filter, 69% isolated yield, >99% ee. The experimental procedure as described for **1** through the satd aq NaCl wash was used for the remainder of the examples. The MTBE was then evaporated and the residue chromatographed on silica gel, eluting with hexanes/ethyl acetate. The purified product was then used as a standard to determine reaction yield by HPLC.