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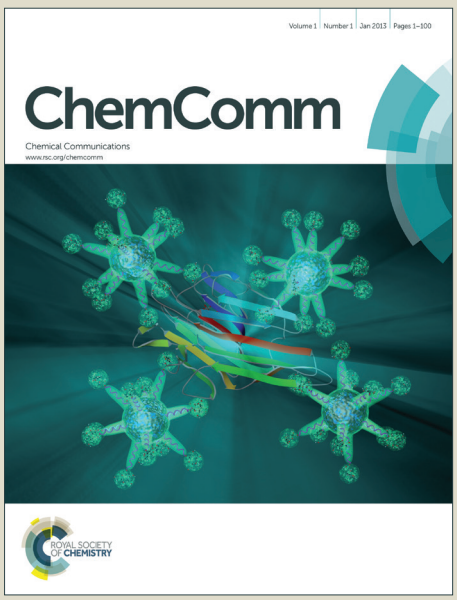

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Tertiary α-diarylmethylamines derived from diarylketimines and organomagnesium reagents

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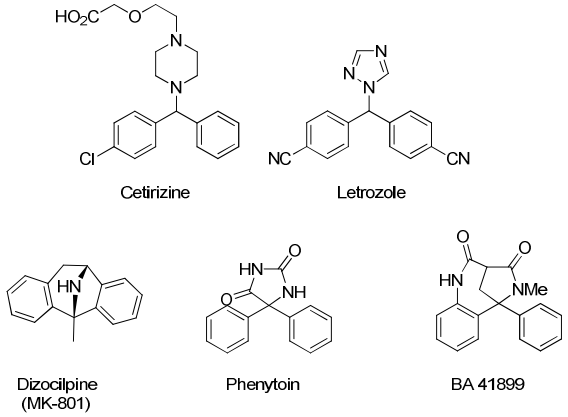
Organomagnesium reagents enable swift and versatile derivatisation of diarylimines to the corresponding α-substituted diarylmethylamines in excellent yields, through fast and clean reactions. Where it occurs, 1,2-reduction can be circumvented using readily accessible dialkylmagnesium reagents.

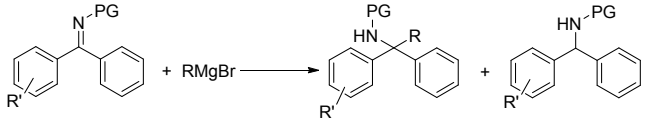
Benzhydrylamine (or diphenylmethylamine) derivatives are a class of hydrophobic polar molecules that are present in a number of marketed and research-stage drugs such as Cetirizine[1] and Letrozole[2] (Scheme 1). In stark contrast, their α-trisubstituted counterparts are relatively underrepresented despite interest in the biological activity they show, *e.g.*, Dizocilpine,[3] a non-competitive NMDA receptor antagonist used in research laboratories, Phenytoin,[4] a potent antiepileptic drug, and BA-41899,[5] a calcium-sensitizing agent studied for treatment of heart failure.



Scheme 1: Selected diarylamethylamine compounds of interest

While much effort has been directed to tackle the formation of α-trisubstituted amines from alkyl and aryl/alkyl imines – including access to diarylmethylamine derivatives [6] – benzophenone imines have received relatively little attention as substrates.[7] The synthesis of diarylmethylamine scaffolds from benzophenone imines via direct 1,2-addition of organometallic nucleophiles is an attractive and efficient approach, as the parent ketones, and reagents, are either commercially available, or quickly accessed from numerous synthetic routes. The remarkably low reactivity of such *bis*-aromatic ketimines, however, renders this task daunting and may in part be the reason for the dearth of synthetic methods available and, as a consequence, drug candidates incorporating this scaffold. A few examples of such transformations with organomagnesium or organolithium reagents have appeared in general studies on imines over the past century, mostly employing *N*-alkyl- and *N*-aryl imines.[8] The single recent account of a specific study on 1,2-addition of organometallic nucleophiles to diarylimines, using 4 eq. of trialkylaluminum reagents, underlines the need for further developments in this area.[9]

In the course of our investigations on 1,2-additions of Grignard reagents to unsaturated compounds,[10] we embarked on the development of a versatile method to access libraries of α-trisubstituted diarylmethylamines from readily accessible benzophenone imines.



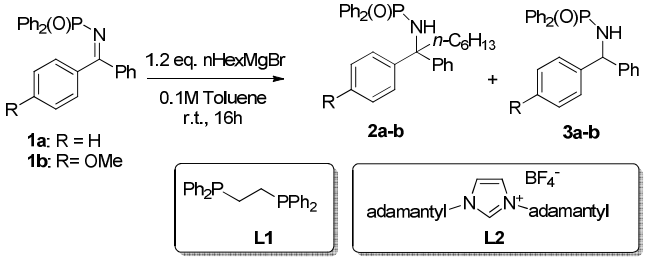
Here we show that readily accessible benzophenone imines can undergo smooth 1,2-addition with organomagnesium reagents. This synthetic route provides corresponding diarylmethylamines with excellent yields through fast and clean reactions and using low reagent loading.

Despite the demonstrated efficiency of trialkylaluminum reagents in 1,2-addition to imines, such a transformation would benefit from the use of less pyrophoric, easily accessible and versatile organomagnesium compounds – but these reagents also present the inherent risk of competitive 1,2-reduction *via* β-hydride elimination. We thus envisioned using diarylimines bearing a strongly electron-withdrawing diphenylphosphoryl (DPP) protecting group, and a range of additives. Conditions screened initially are summarized in Table 1.

Reaction of 1.2 eq. of *n*-hexylmagnesium bromide, in toluene (0.1M) at room temperature (Table 1, entry 1), with substrate **1a** gave a crude reaction mixture composed of **1a** (41%), desired addition product **2a** (41%) and 1,2-reduction product **3a** (18%). The role of Lewis acidic metal additives was investigated to optimise the results in the presence and absence

of a diphosphine ligand **L1** (entries 2-5). Catalytic amounts of copper(I) salts showed improvement of desired product to starting material ratio, but without complete conversion or suppression of 1,2-reduction, despite exploring different copper sources. NHC-Ligand **L2** did not show significant improvement (entries 6-7). When using 5 eq. of Grignard reagent, 64% conversion to the desired product could be achieved, albeit with 20% of reduction product **3a** (entry 8). We then turned our attention to a more activated substrate (entries 9-20), imine **1b**. Without any additive, this substrate delivered 68% of the addition product **2b**, and 16% reduction product **3b** (entry 9). Lewis acids were studied to increase conversion to the desired amine **2b**. Copper(I) bromide dimethylsuflide complex (entries 10-11) was detrimental to the reaction. Using nickel(II) chloride as an additive (entries 13-14), compound **3b** was still present in the crude reaction mixture, while with silver(I) triflate (entries 15-16) inhibition of the reaction was observed. With boron trifluoride diethyl etherate (entry 17) complete reduction of the starting material was observed.

Table 1: Preliminary screening of reaction conditions for 1,2-additions to diarylketimine **1a** and **1b**

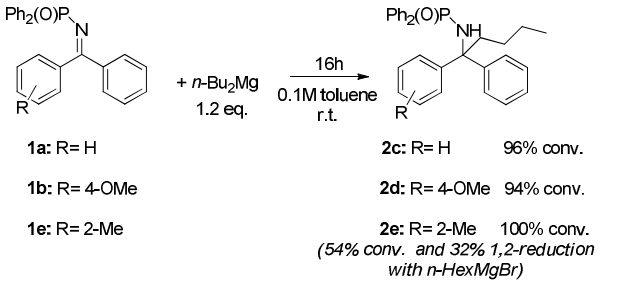


Entry	Imine	Additive, 1.2 eq.	1	2	3
1	**1a**	-	41%	41%	18%
2	**1a**	$CuBr.SMe_2$/**L1** (1:1) [a]	18%	51%	31%
3	**1a**	$CuBr.SMe_2/PPh_3$ (1:2) [a]	18%	54%	28%
4	**1a**	$CuF.(PPh_3)_3$/**L1**(1:1) [a]	46%	41%	13%
5	**1a**	$(CuOTf)_2.C_6H_6$/**L1** (1:1)[a]	18%	47%	35%
6	**1a**	$CuBr.SMe_2$/**L2** (1:1) [b]	34%	48%	18%
7	**1a**	**L2** [b]	20%	57%	23%
8 [c]	**1a**	-	16%	64%	20%
9	**1b**	-	16%	68%	16%
10	**1b**	$CuBr.SMe_2$	82%	15%	3%
11	**1b**	$CuBr.SMe_2$ / **L1** (1:1)	60%	30%	10%
12	**1b**	**L1**	-	84%	16%
13	**1b**	$NiCl_2$	~3%	82%	15%
14	**1b**	$NiCl_2$ / **L1** (1:1)	-	84%	16%
15 [d]	**1b**	AgOTf	90%	4%	6%
16 [d]	**1b**	AgOTf / **L1** (1:1)	76%	15%	9%
17	**1b**	$BF_3.OEt_2$ (2eq)	-	-	100%
18 [e]	**1b**	-	~2%	86%	12%
19 [e]	**1b**	-	-	86%	14%
20 [e,f]	**1b**	-	-	89%	11%

Conditions: 0.1 mmol imine **1**, 1 mL dry toluene, N_2 atmosphere, r.t., overnight. *n*-HexMgBr (1.2 eq, 2.0M in Et_2O) was added in one portion. Relative ratios were determined from ^1H NMR spectra of the crude reaction mixture. *a:*.Reactions performed with 5 mol% of the additive. *b:* Reaction performed with 10 mol% additive and 1.4 eq Grignard reagent *c:* 5eq Grignard reagent was used. *d:* Reactions were shielded from light with aluminum foil. *e:* 2 eq. nHexMgBr was used. *f:* Reaction performed at 0.5M concentration.

Increasing the amount of reagent to 2 eq. (entry 18) yielded more of the desired amine **2b**, but still with 12% of **3b** present in the crude product mixture. Increasing the concentration of imine **1b** to 0.5 M (entry 19) led to 86% of amine **2b**.The combination of these latter two conditions gave as high as 89% of **2b**, but also delivered 11% of **3b** (entry 20).

With the goal of suppressing the competing reduction of the imine, we explored the possibility of using dialkylmagnesium reagents, as their increased reactivity might outcompete the 1,2-reduction process (Scheme 2).



Scheme 2: Organomagnesium reagent evaluation

Indeed, imine **1a** was fully converted to 96% of the corresponding tertiary amine **2c** and only 4% of reduction product. Similarly, imine **1b** gave amine **2d** with high efficacy. Surprisingly, *ortho*-substituted imine **1e** gave full conversion to the desired tertiary amine without neither starting material nor side-product detected. This latter imine yielded a high amount of 1,2-reduction side product when reacted with 2 eq. of *n*-HexMgBr, probably due to the steric hindrance of the *ortho* substituent that tilts the balance of reduction versus addition towards the former, undesired reaction. These examples clearly show the advantage of the much more reactive dialkylmagnesium reagents when β-hydride-induced reduction is of concern.

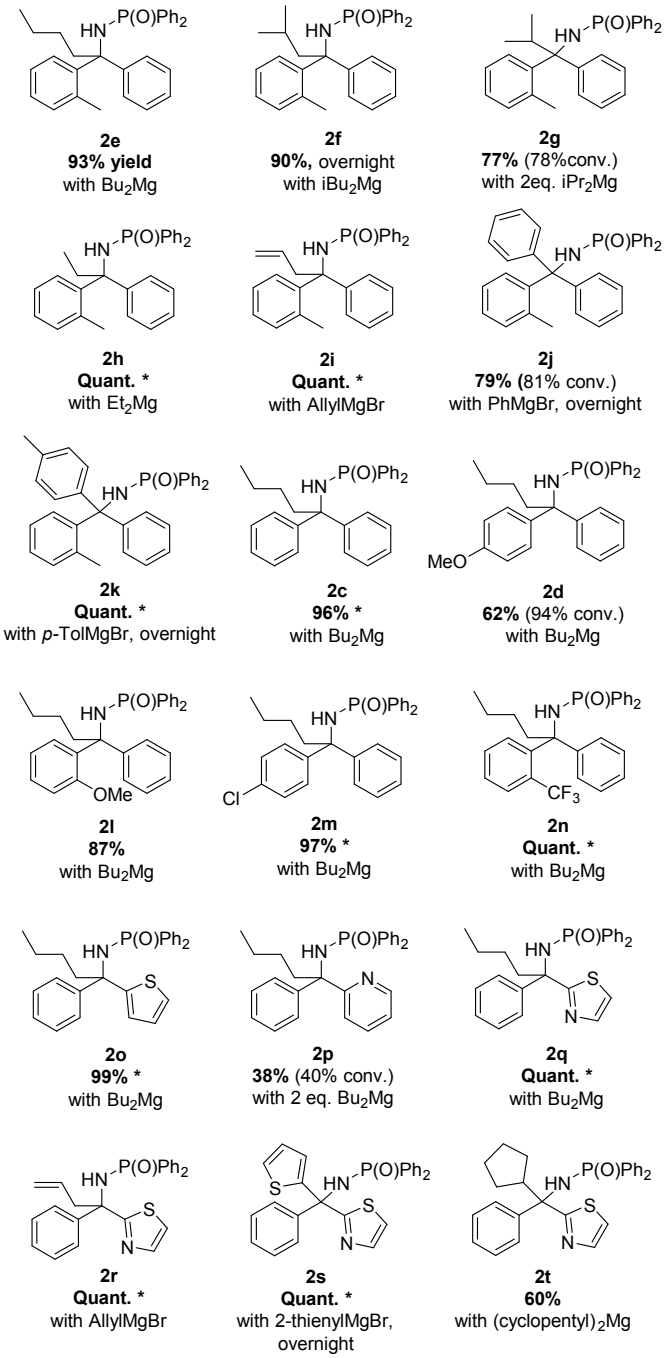
These optimized conditions were applied to a wider range of substrates and organomagnesium reagents (Scheme 3). Dialkylmagnesium reagents were readily prepared from the parent organomagnesium bromide by precipitation of $MgBr_2$ with dioxane and centrifugation (see ESI for details). Importantly, Grignard reagents that could not undergo β-hydride elimination (β-*C*-sp^2 reagents) were used directly as received.

Ortho-methyl substituted imine **1e** was chosen as the benchmark substrate for evaluation of organomagnesium reagents, as it undergoes extensive 1,2-reduction with conventional organomagnesium bromides, and is therefore sensitive to unsuitable conditions for the reaction (Scheme 2). Excellent results were obtained for *n*-Bu_2Mg (Scheme 3, **2e**), and remarkably *i*-Bu_2Mg gave full conversion to the desired product **2f** as well, despite the presence of a highly labile β-hydride. The more sterically hindered *i*-Pr_2Mg reagent required 2 eq. of reagent to yield amine **2g** with 78% conversion. Diethylmagnesium can also be used to provide the ethylated amine **2h** quantitatively, without the need for purification.

Unsaturated Grignard reagents that are not prone to β-hydride elimination provided the corresponding allylated product **2i** with full conversion, and even the relatively non-reactive PhMgBr lead to 81% conversion to **2j** after a prolonged reaction time of 16 h. Electron-rich *p*-tolyl magnesium bromide proved more reactive and lead to full conversion to amine **2k**.

A range of imines were also explored (Scheme 3). The imine derived from benzophenone gave the addition product **2c** in 96% yield. A methoxy group was tolerated both at the *para* and *ortho* positions (**2d** and **2l**, respectively), albeit compound **2d** proved unstable during purification. Substrates with

electron-withdrawing groups, such as *para*-chlorinated substrate **2m** and CF_3 substituted **2n**, also underwent alkylation smoothly.



Scheme 3: Scope of the reaction.

Conditions: imine **1** (0.1 mmol) in toluene (0.1 M) and R_2Mg (1.2 eq.) or RMgBr (2 eq.) were stirred at r.t. for 10-30 min, unless otherwise indicated (see ESI for further details).*products that did not require purification by column chromatography.

Heterocycle-functionalized imines were also amenable to the reactions conditions, *e.g.*, allowing access to thiophene-bearing amine **2o** with complete conversion and quantitative yield. A pyridine-derived substrate also underwent 1,2-addition, albeit in only 40% conversion and 38% isolated yield of **2p**, using a higher reagent loading. Finally, a thiazole derivative was subjected to our reaction conditions, and the use of both Bu_2Mg and AllylMgBr provided the desired amines (**2q** and **2r**, respectively) in quantitative yield. This substrate could also be functionalized with a thiophene moiety in quantitative yield (**2s**); and with a cyclopentyl substituent thanks to the corresponding dialkylmagnesium reagent, providing amine **2t** in 60% yield.

Overall, reaction times were generally short (10-30 min), and it is notable that more than half of these amines, denoted with an asterisk in Scheme 3, did not need purification by chromatographic methods, underlining the selectivity and efficacy of the methodology.

Conclusions

We have demonstrated that stable and readily accessible diarylmethylimines can undergo smooth 1,2-addition with Grignard reagents, and that undesired β-hydride elimination from alkylmagnesium bromides can be circumvented by using dialkylmagnesium reagents. High yields, low reagent loading, fast reactions and facile purifications, where necessary, complement the wide substrate and reagent scope. This new synthetic route thus provides a versatile tool to synthesize α-trisubstituted diarylmethylamines. We are currently exploring applications of this methodology, and its asymmetric versions, in our group.

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Notes and references

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† *Representative experimental procedure for the 1,2-addition of organomagnesium reagents to N-diphenylphosphoryldiarylketimines:*
To a solution of ketimine **1o** (0.1 mmol) in dry toluene (1 mL, 0.1M) at room temperature, under nitrogen atmosphere, is added a 1.0M solution of Bu_2Mg in Et_2O (0.12 mmol) in one portion. The reaction mixture immediately turns dark orange-brown, and then clears to a pale yellow colour within minutes. After stirring for 10 min at room temperature, the reaction is quenched with 1 mL of saturated aqueous NH_4Cl and extracted with EtOAc three times, then washed with brine, dried on $MgSO_4$, and filtered. Thorough drying under reduced pressure affords the desired amine **2o** as an off-white solid, as determined by ^1H, ^{31}P and ^{13}C NMR, in 100% conversion, and 99% yield (without chromatographic purification or recrystallization).

Electronic Supplementary Information (ESI) available: Experimental procedures, synthesis of substrates and reagents, and spectral data. See DOI: 10.1039/c000000x/

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