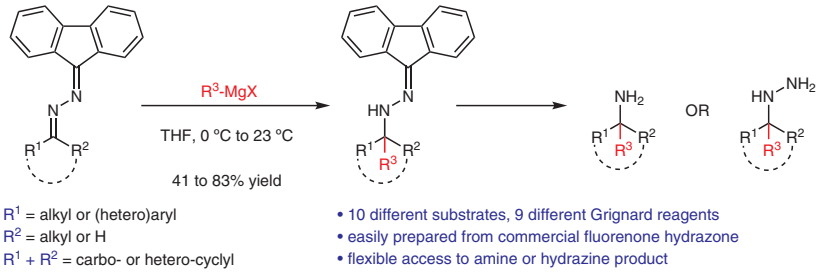
Synlett P. Mukashyaka, G. L. Hamilton Letter

A Fluorenyl Activating Group Enables Addition of Simple Grignard Reagents to C=N Electrophiles

Patience Mukashyaka
Gregory L. Hamilton*

Genentech Inc., 1 DNA Way, South San Francisco, CA 94080, USA
Hamilton.gregory@gene.com



Received: 17.05.2018
Accepted after revision: 10.06.2018
Published online: 10.07.2018
DOI: 10.1055/s-0037-1609551; Art ID: ss-2018-b0316-l

Abstract Nucleophilic addition of organometallic reagents to ketimines and hydrazones can be a challenging transformation. Here we report the use of fluorenone-derived mixed azines which promote facile addition of Grignard reagents. The fluorenylidene activating group is easily installed and removed, thereby offering practical access to highly substituted amines and hydrazines.

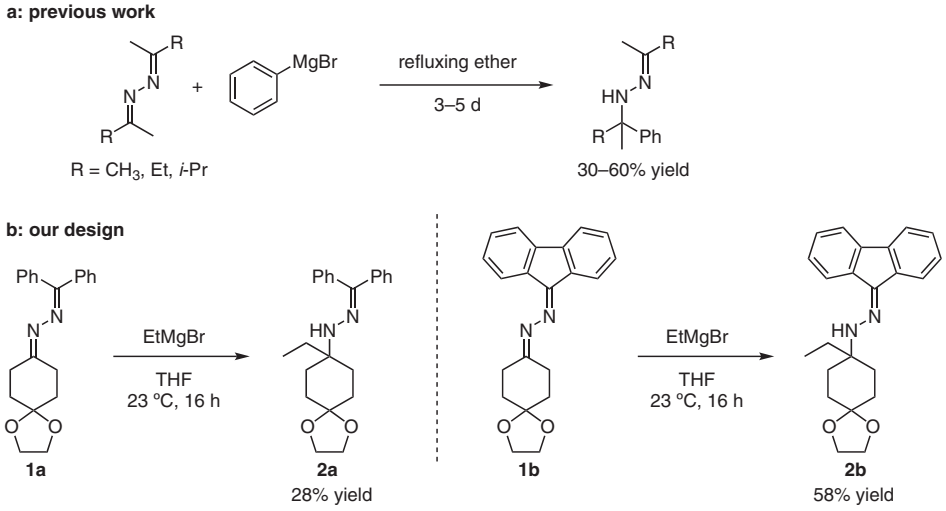
Key words amines, Grignard reaction, hydrazones, imines, nucleophilic addition, organometallic reagents

The reaction between an organometallic nucleophile and a carbonyl is one of the simplest and most versatile ways to forge a carbon–carbon bond.[1] Unfortunately, the coupling of unstabilized Grignard reagents and C=N electrophiles is much less general.[2] In the course of a medicinal chemistry campaign, we desired to make hydrazines substituted with an adjacent tertiary center of varying composition. It occurred to us that by far the most straightforward and diversifiable approach would be the addition of organometallic reagents to a ketone-derived hydrazone. However, the scope of published carbon nucleophiles for such an addition is limited to allyl,[3,4] cyano,[5] trifluoromethyl,[6] or silyl ketene acetal.[7,8] The main problem is that hydrazones, especially the ketimine variety, are poor electrophiles and are easily deprotonated. Furthermore, attempting to increase reactivity by adding electron-withdrawing groups can introduce undesired reaction pathways, such as Bamford–Stevens/Shapiro chemistry[9] or organometallic addition to the activating group itself.

This gap in available chemistry led us on a search for a masked hydrazine source that could be easily condensed with a carbonyl compound, resulting in a hydrazone that would react with a variety of Grignard reagents. Additionally, the activating group needed to be removable such that the products of organometallic addition could be deprotected to the free hydrazine. Naturally, reductive cleavage of the N–N bond to form useful substituted amine products would also be possible.

We were intrigued by selected reports from the mid-twentieth century of additions of Grignard reagents to symmetrical azines derived from double condensation of hydrazine with two equivalents of a ketone (Scheme 1, a).[10] This reaction works presumably because the second conjugated imine acts as a mild electron acceptor to facilitate the nucleophilic addition. Naturally, the azine must be symmetrical to avoid mixtures of products resulting from addition to both imines. The authors also showed that the hydrazone products obtained after Grignard addition could be hydrolyzed to the free hydrazines. However, this method did not meet our needs because one equivalent of ketone starting material is essentially sacrificed to serve as the protecting group. Accordingly, the published examples used inexpensive ketones like acetone or ethyl methyl ketone rather than more elaborated building blocks. Furthermore, yields were poor, and the reported reaction times were up to five days.

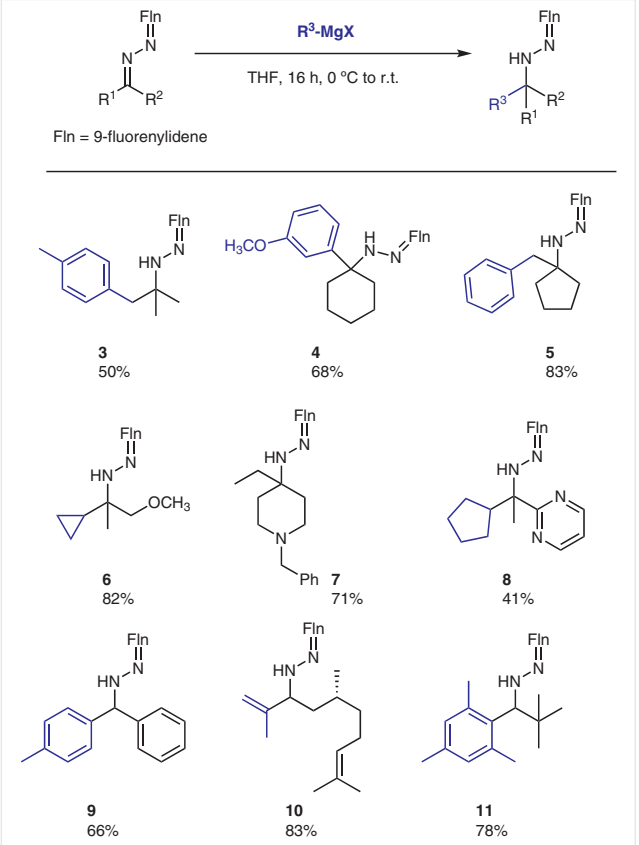
We imagined overcoming these shortcomings by using an unsymmetrical azine where nucleophilic addition would be biased toward one side (Scheme 1, b). Benzophenone seemed like a suitable group that could act as a better electron acceptor for organometallic addition to the opposite imine while disfavoring attack at its own carbon. Specifically, the conjugated rings of the benzophenone imine could stabilize by resonance the negative charge resulting from nucleophilic addition. At the same time, the aromatic rings would provide steric protection and electronic deactivation of the directly attached imine carbon. To test this idea, we prepared unsymmetrical azine **1a** from benzophenone hydrazone and 1,4-cyclohexanedione monoethylene acetal.



Scheme 1 Design of unsymmetrical azine activating group for Grignard additions

Treatment of **1a** with ethylmagnesium bromide in THF provided desired addition product **2a** in an encouraging 28% yield (Scheme 1, b). However, the conversion was rather sluggish and appeared to stall out after about 24 hours, with decomposition eventually taking over. To improve the reactivity, we considered a new activating group that could better stabilize a developing negative charge. Thus, we prepared fluorenone-derived azine **1b** to take advantage of the highly electron-withdrawing nature of the fluorenylidene group. Gratifyingly, the yield of the ethyl Grignard addition product **2b** was boosted to 58%.

Next, we tested the generality of the newly enabled transformation with various ketone starting materials and Grignard reagents (Scheme 2). Aliphatic ketones such as acetone, cyclohexanone, and cyclopentanone worked well to give the desired Grignard addition products **3**, **4**, and **5**, respectively. Functionalized partners *N*-benzylpiperidone and methoxyacetone also reacted smoothly to afford products **6** and **7** in high yields. Aromatic ketones including acetophenone and 4-(trifluoromethyl)acetophenone were not reactive, presumably due to electronic stabilization reducing the electrophilicity of the substrate. On the other hand, the electron-poor heterocyclic ketone 2-acetylpyrimidine proved to be a more viable building block, producing **8** in moderate yield. For the Grignard partner, we were quite pleased to find that essentially all reagents tested proved applicable, encompassing alkyl, cycloalkyl, benzyl, and aryl.



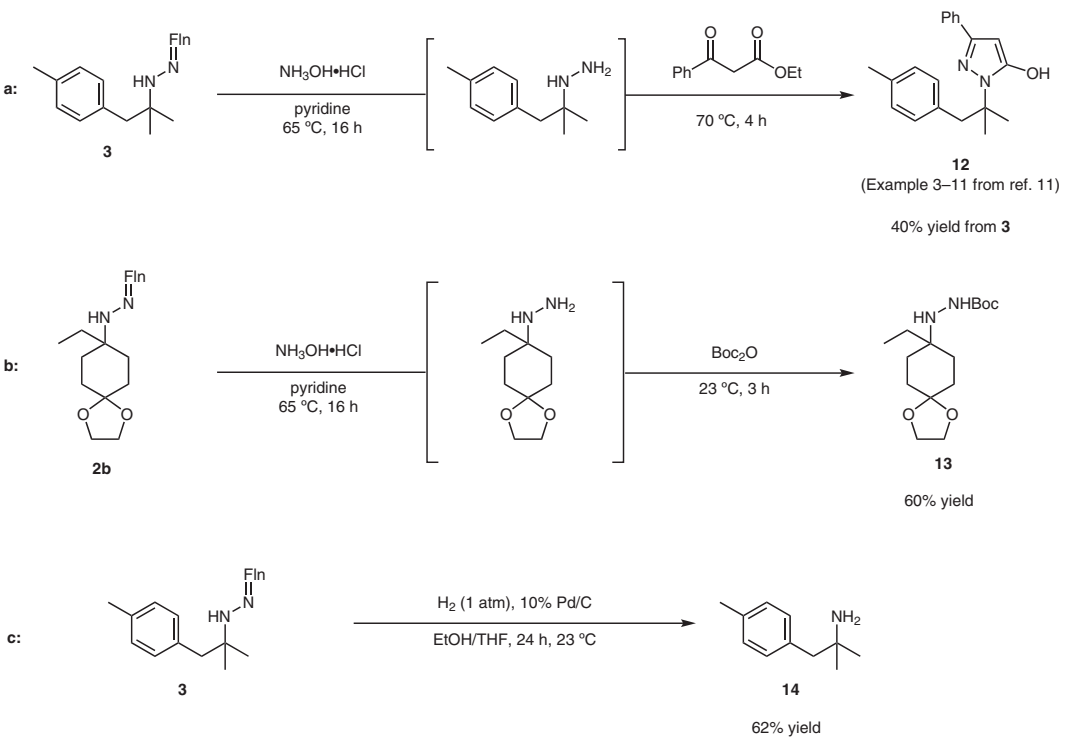
Scheme 2 Products Formed from a Variety of Examined Azines and Grignard Reagents. *Reaction conditions*: azine and Grignard reagent (1–5 equiv) in THF, 0 °C to room temperature, 16 h; fragments of products derived from the Grignard component are highlighted in blue; yields are isolated material.

We also evaluated several aldehyde-derived azines leading to products **9–11**. These substrates may be considered a lower priority, because additions to aldimines are easier and the resulting products can sometimes be obtained by reductive amination. Nevertheless, our method offers utility here as well as a complement to existing approaches. In this case, aromatic aldehydes gave satisfactory yields. Aliphatic aldehydes like citronellal and pivaldehyde also worked well as starting materials. Notably, even quite hindered products like **11** resulting from 2,4,6-mesityl addition to a pivaldehyde-derived azine can be obtained using this method.

Next, we explored a variety of conditions for removing the fluorenylidene group to expose the free hydrazine. The best protocol employed a transimination using hydroxylamine hydrochloride in pyridine, similar to deprotection of a benzophenone imine (Scheme 3). Because hydrazines are often unstable as the free base, we offer two options for utilizing the hydrazine following deprotection. First, the unmasking conditions are generally compatible with subsequent reactions one would want to perform on the hydrazine, such as alkylation, acylation, or condensation. As a demonstration, starting from product **3** we achieved a one-pot deprotection, condensation, and heterocyclization to form 5-hydroxypyrazole **12** that has published activity against multiple myeloma cell lines (Scheme 3, a).[11] Alternatively, if isolation of the hydrazine is preferred, a one-pot protecting-group-switch to Boc can be performed (Scheme 3, b). The Boc group can then of course be removed under acidic conditions to provide a stable hydrazine salt.

While our method is particularly advantageous for accessing substituted hydrazines, it also offers flexible entry into α-branched primary amines. The N–N bond of the hydrazones can be smoothly reduced under catalytic hydrogenation with Pd/C (Scheme 3, c), or alternatively using zinc as previously reported.[12] As noted above, additions of Grignard reagents to ketimines using other protecting groups is not always a workable transformation. Thus, we hope our fluorenone azine will find complementary use to existing imine activating groups like Boc, sulfinyl, sulfonyl, or aryl.

In conclusion, we developed a general and facile method to access functionalized hydrazines or amines by the addition of simple organometallic reagents to hydrazones or imines.[13–15] There is a number of practical advantages to our approach. First, the unsymmetrical azine substrates are easily accessed in high yield from condensation of ketones or aldehydes with the inexpensive commercial reagent 9-fluorenone hydrazone. The mildness of the condensation, which can be performed under neutral or slightly acidic conditions, is demonstrated by the selective preparation of substrate **1a**. By contrast, the synthesis of some other activated imine derivatives requires Lewis acids that would promote partial acetal deprotection and condensation at both ketones. Additionally, our approach works broadly with off-the-shelf Grignard solutions, with no need for acti-



Scheme 3 Conversion of addition products to hydrazines, heterocycles, or amines

vation with hygroscopic lanthanide salts. Finally, the fluorenylidene activating group can be removed under conditions compatible with many functional groups, leading to useful hydrazine or amine products. We hope that all of these features will make the method attractive to others, especially for medicinal chemistry.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609551.

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(13) **General Procedure for Reactions of Azine Substrates with Grignard Reagents**
To a solution of azine substrate in anhydrous THF (ca. 0.2 M) cooled to 0 °C was added slowly a solution of Grignard reagent (1–5 equiv). After addition, the reaction mixture was allowed to warm to room temperature and stir for 16 h. After this time, the reaction was quenched with 5% aqueous citric acid, and the mixture was extracted with isopropyl acetate (3×). The combined organics were washed with water and brine, dried over sodium sulfate, and concentrated. The resulting crude material was purified by column chromatography. NOTE: The azine substrates were generally found to be hygroscopic. Therefore, best yields were obtained when the azines were dried overnight in a vacuum dessicator over anhydrous calcium sulfate prior to use.

(14) **Analytical Data for Example Azine 1b**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 7.6 Hz, 1 H), 7.86 (d, J = 7.4 Hz, 1 H), 7.61 (dd, J = 11.1, 7.5 Hz, 2 H), 7.39 (tt, J = 7.5, 1.3 Hz, 2 H), 7.34–7.21 (m, 2 H), 4.05–3.93 (m, 4 H), 2.81–2.69 (m, 4 H), 2.04–1.95 (m, 2 H), 1.87–1.78 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.25, 155.11, 142.27, 141.01, 136.86, 131.54, 131.06, 130.55, 129.43, 128.01, 127.99, 122.48, 119.96, 119.75, 108.00, 64.56, 34.70, 33.73, 32.15, 25.06. LRMS: *m/z* [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_2^+$: 333; found: 333.

(15) **Analytical Data for Example Product 2b**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.73 (m, 3 H), 7.71–7.62 (m, 1 H), 7.40 (td, J = 7.5, 1.1 Hz, 1 H), 7.34 (td, J = 7.5, 1.3 Hz, 1 H), 7.33–7.23 (m, 2 H), 6.68 (s, 1 H), 3.96 (s, 3 H), 2.16–2.06 (m, 2 H), 1.96–1.85 (m, 2 H), 1.82–1.72 (m, 3 H), 1.72–1.62 (m, 4 H), 0.84 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$); δ = 140.63, 138.76, 138.47, 137.30, 130.35, 128.47, 127.46, 127.37, 127.10, 123.87, 120.48, 120.25, 119.35, 108.96, 64.28, 64.28, 57.78, 32.77, 31.55, 30.61, 7.55. LRMS: *m/z* [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_2^+$: 363; found: 363.