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Umpolung Synthesis of Diarylmethylamines via Palladium-Catalyzed Arylation of *N*-Benzyl Aldimines

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Abstract

An umpolung synthesis of diarylmethylamine derivatives is presented. This reaction entails a Pd catalyzed arylation of 1,3-diaryl-2-azaallyl anions, *in situ* generated from *N*-benzyl aldimines. A Pd(NIXANTPHOS)-based catalyst together with hindered silylamide bases enabled the coupling of aldimines with aryl bromides in good to excellent yields without product isomerization. Moreover, regioselectivity in the arylation of unsymmetrical 1,3-diaryl-2-azaallyl anions was studied. This method is suitable for a gram scale synthesis of diarylmethylamine derivatives at room temperature without use of a glovebox.

Graphical abstract

Keywords

diarylmethylamines; umpolung; 2-azaallyl anion; regioselectivity; NIXANTPHOS

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In the past decade, considerable effort has been devoted to the synthesis of diarylmethylamines due to their common occurrence in bioactive compounds.^[1] Among the methods for their synthesis,^[2] 2-azaallyl anions derived from either ketimines or aldimines have recently emerged as a valuable *umpolung* approach to prepare both diarylmethylamine and benzylic amine derivatives, as demonstrated by Oshima, Buchwald, Nolan and us (Scheme 1a–d).^[3] Recently, we reported the regioselective arylation of 1,1,3-triaryl-2-azaallyl anions generated from *N*-benzyl ketimines and aldimines (Scheme 1c). In the presence of a Pd(NIXANTPHOS)-based catalyst and hindered silylamide bases, 2-azaallyl anions are readily converted into diarylmethylamine derivatives.^[4] Recently, Nolan and coworkers showed that this chemistry can also be performed with Ni(NHC)-based catalysts (Scheme 1d).^[5]

Despite the broad scope and high yields of the arylated products, the arylation of ketimines and aldimines in Scheme 1c leaves room for improvement. First, formation of two byproducts detracts from the method's utility. As shown in Scheme 2, the starting ketimine undergoes deprotonation and isomerization to the aldimine, which requires more forcing conditions to deprotonate and regenerate the 2-azaallyl anion. Additionally, the 2-azaallyl anion forms a dimer, presumably through reaction with an equivalent of ketimine (Scheme 2). This process consumes two equivalents of the starting material. To circumvent these side reactions and maintain high yields, an excess of the 2-azaallyl anion precursor was necessary (usually 2 equiv.).^[6]

To improve our method to prepare diarylmethylamine derivatives, we envisioned an approach that could avoid the side reactions in Scheme 2 while also increasing the overall synthetic efficiency of the process. Herein, an effective *umpolung* synthesis of diarylmethylamines via palladium-catalyzed arylation of 1,3-diaryl-2-azaallyl anions is described. Under these reaction conditions, no dimerization or isomerization of the starting materials was observed. Additionally, good to excellent yields of the triaryl aldimine products were obtained without product isomerization or further arylation of the more acidic product.

To render the arylation of 2-azaallyl anions more efficient we focused on 1,3-diaryl-2-azaallyl anions **7** (Scheme 3). The challenge of this approach is that the product **8** also readily undergoes arylation (Schemes 1c and 3b). Therefore, it is important that the catalyst promote the selective formation of the monoarylation product. Moreover, the conditions must be sufficiently mild such that the product does not undergo deprotonation, as outlined noted above.

To identify conditions for the arylation in Scheme 3a, we studied the reaction of 1.0 equivalent of aldimine **6** with 1.5 equivalents of 1-bromo-4-*tert*-butylbenzene (**10a**). A Pd(NIXANTPHOS)-based catalyst, which exhibited high efficiency in our previous deprotonative cross-coupling processes (DCCP), including Scheme 1c, was examined.^{[4], [7]} We tested different silylamide bases, MN(SiMe₃)₂ (M = Li, Na and K) leading to up to 93% isolated yield of the desired product **8aa**. To prevent the bis-arylation and achieve this high yield, it was necessary to add the 1.5 equivalents of LiN(SiMe₃)₂ over 1 h in THF at room

temperature (Table 1). It is surprising that the reaction could be stopped at the monoarylation stage. Comparison of the reaction parameters between Table 1 and Scheme 1c highlights the importance of the base. In both reactions, the same catalyst system was used, but the more reactive $\text{NaN}(\text{SiMe}_3)_2$ is employed with the more sterically congested ketimine substrates, while the $\text{LiN}(\text{SiMe}_3)_2$ is used in Table 1.

The scope of the reaction was next briefly examined. The reactions of the parent aldimine **6a** with bromobenzene **10b** and 3-bromotoluene **10c** furnished the corresponding products **8ab** and **8ac** in 75 and 88% yield, respectively. Aryl bromides bearing electron-donating 4-methoxy (**10d**) and 4-bromo-*N,N*-dimethylaniline (**10e**) groups produced the desired imines **8ad** and **8ae** in excellent yields (85% and 93%, respectively). The reaction of imine **6a** with 1-bromo-4-fluorobenzene (**8af**) gave 52% yield of the mono-arylation product with 16% bisarylated product **9af**. Although the yield of **8af** was diminished due to bis-arylation, it is surprising that no isomerization or dimerization of **8af** was observed.

The scalability of this *umpolung* approach was next studied. We performed a 10.0 mmol scale reaction of imine **6a** with 15.0 mmol 4-bromo-*N,N*-dimethylaniline (**10e**) in the presence of 2.5 mol % $\text{Pd}(\text{OAc})_2$ and 5.0 mol % NIXANTPHOS at room temperature (Scheme 4). The reaction was conducted without use of a glovebox and employed a commercially available 1.0 M solution of $\text{LiN}(\text{SiMe}_3)_2$ (15.0 mmol) in THF. After 1.5 h slow addition of the base by syringe, the reaction was stirred for an additional 2 h. After workup, 85% yield (2.67 g) of product was obtained (see Supporting Information for details). The imine **8ae** was then hydrolyzed with 1N HCl in MeOH, free-based with NaOH, and the amine **11ae** was isolated in 98% yield.

Although the chemistry in Table 1 is useful, in some cases the synthesis of symmetric aldimines may be impractical due to availability or cost of the amine or aldehyde precursors. We therefore turned our attention to the arylation of unsymmetrical 1,3-diaryl-2-azaallyl anions. We wanted to explore the impact of electronic and steric effects on the distribution of product isomers (Scheme 5a). In order to develop the arylation of unsymmetrical 1,3-diaryl-2-azaallyl anions into a synthetically useful method, we hypothesize that increasing steric hinderance^[8] of one aryl would enhance the regioselectivity. Hence, we studied the arylation of *o*-anisyl substituted imine **6b** with 1-bromo-4-*tert*-butylbenzene (**10a**). Under the reaction conditions in Scheme 5b, arylation mainly occurred at the sterically less hindered position with a 4:1 ratio of isomers **8ba** and **8ba'** in 76% overall yield.

The moderate selectivity in the arylation of **6b** led us to examine the sterically more demanding mesityl substituted aldimine **6c**. Under the reaction conditions listed in Table 2, coupling of **6c** with 1-bromo-4-*tert*-butylbenzene (**10a**) afforded product **8ca** as a single isomer in 77% yield. We therefore examined the substrate scope based on mesityl substituted aldimine nucleophiles. Arylation of **6c** with aryl bromides containing alkyl (4- C_6H_4 -*t*Bu, Ph, 3- C_6H_4 -Me), electron donating (4- C_6H_4 -OMe, 4- C_6H_4 -NMe₂) and withdrawing (4- C_6H_4 -F) groups produced the desired products **8cb–8cf** in good yields (67–82%). The yield of coupling the mesityl-substituted aldimine **6c** and 1-bromo-4-fluorobenzene (**10f**) was 68%. This yield can be compared with coupling of the symmetrical

6a with 1-bromo-4-fluorobenzene, which provided only 52% yield of the mono-arylation product (Table 1).

Next, the substituents on the aldimine were varied. Coupling of 4-methoxy substituted aldimine **6d** with 1-bromo-4-*N,N*-dimethylaniline (**10e**) was accomplished by slow addition (1.5 h) of $\text{LiN}(\text{SiMe}_3)_2$ to the reaction mixture at room temperature followed by heating to 50 °C for 5 h. The arylation of fluoro substituted aldimines bearing either 4-fluoro (**6e**) or 2-fluoro (**6f**) substituents with 4-bromoanisole (**10d**) and 4-bromo-*N,N*-dimethylaniline (**10e**) required longer reaction times (6 h) at room temperature for complete consumption of aldimines and gave the products **8ed**, **8ee**, and **8fe** in 60–62% yield. To access heteroaryl substituted diarylmethylamines, we perform the reaction of 3-pyridyl substituted aldimine **6g** with 4-bromo-*N,N*-dimethylaniline **10e**. The product **8ge** was obtained in 80% yield with aryl bromide **10e** as limiting reagent.

Finally, given Eastgate and Blackmond's recent report of reactions catalyzed by mono-oxidized bidentate XANTPHOS and palladium,^[9] we wanted to determine if such species might be involved in the arylation reactions outlined herein. To address this issue, we employed the Buchwald precatalyst^[10] with NIXANTPHOS ligand, which generates Pd(0) by reductive elimination (Scheme 6). With 5 mol % of the precatalyst, coupling of **6a** with 4-*tert*-butyl bromobenzene resulted in 99% assay yield of the coupling product, suggesting that the reaction does not proceed via the oxidized phosphine ligand.

In summary, we present an *umpolung* approach to diarylmethylamine derivatives from both symmetrical and unsymmetrical 1,3-diaryl-2-azaallyl anions derived from *N*-benzyl aldimines under mild conditions. The reaction is promoted by a Pd(NIXANTPHOS)-based catalyst. Interestingly, this catalyst exhibits excellent selectivity in the mono-arylation of 1,3-diaryl-2-azaallyl anions, despite its known ability to promote the arylation of the product to generate tetraaryl ketimines. Selectivity in these reactions is controlled by careful choice of reaction conditions. It is also noteworthy that the arylation of 1,3-diaryl-2-azaallyl anions provides various diarylmethylamine derivatives without product isomerization or dimerization. This method is also amenable to gram scale synthesis in a time efficient manner.

Experimental Section

General Procedure and Characterization for Pd Catalyzed reactions of Aldimines

An oven-dried microwave vial equipped with a stir bar was charged with aldimine **6a** (39.0 mg, 0.20 mmol) and 1-bromo-4-*tert*-butylbenzene **10a** (51.9 μL , 0.30 mmol) under a nitrogen atmosphere in a glove box. A stock solution of $\text{Pd}(\text{OAc})_2$ (2.25 mg, 0.010 mmol, 5 mol %) and NIXANTPHOS (11.10 mg, 0.020 mmol, 10 mol %) in 0.5 mL of dry THF was taken up by syringe and added to the reaction vial under nitrogen. The vial was sealed with cap (with rubber septum) and removed from the glovebox. A solution of $\text{LiN}(\text{SiMe}_3)_2$ (50.2 mg, 0.30 mmol) in 1.5 mL THF was added portionwise by syringe at 23 °C over 1 h. The reaction mixture was stirred for 1 h after the addition (2 h in total) at 23 °C then opened to air, quenched with two drops of H_2O , diluted with 3 mL of ethyl acetate, and filtered over a pad (a 6mL Syringe) of MgSO_4 and silica. The pad was rinsed with ethyl acetate ($3 \times 2 \text{ mL}$),

and the combined solutions were concentrated *in vacuo*. The crude material was loaded onto a deactivated silica gel column and purified by flash chromatography using 20:1 hexanes/ethyl acetate as eluent to yield the product **8aa** (61 mg, 0.19 mmol, 93%) as a white solid.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.

Synthesis of diarylmethylamine and benzylic amine derivatives from arylation of 2-azaallyl anions.

Scheme 2. Side reactions in arylation of *N*-benzyl ketimines **1** and aldimines **3**.

(a) Arylation of 1,3-diaryl-2-azallyl anions

(b) Possible side reactions

Scheme 3.

Palladium catalyzed arylation of 1,3-diaryl-2-azaallyl anions **7**.

Scheme 4.

Large scale synthesis of imine **8ae** and its hydrolysis to produce diarylmethylamine **11ae**.

(a) Arylation of unsymmetrical 1,3-diaryl-2-azaallyl anions.

(b) Arylation of **6b**

Scheme 5.

Palladium catalyzed arylation of *o*-anisyl substituted imine **6b**.

Scheme 6.

Use of Buchwald's pre-catalyst in the arylation of azaallyl anions.

Table 1

Scope of aryl bromides in the arylation of aldimine **6a**^a

^[a] Reactions conducted on 0.2 mmol scale at 0.1 M and were stirred 1 h after slow addition (1 h) of LiN(SiMe₃)₂ into the reaction mixtures.

^[b] Under same reaction conditions, changing base to NaN(SiMe₃)₂ and KN(SiMe₃)₂ led to 53% and 6% assay yields.

Table 2

Scope of aryl bromides in the arylation of mesityl substituted aldimines.^a

[a] Reactions conducted on 0.2 mmol scale by using 1.0 equiv. aldimine, 1.5 equiv. aryl bromide and 1.5 equiv. LiN(SiMe₃)₂ at 0.1 M. Slow addition of LiN(SiMe₃)₂ over 1 h followed by 4 h stirring.

[b] 2.0 equiv. aryl bromide, 6 h, 50 °C.

[c] 2.0 equiv. aryl bromide, 6 h

[d] 2.0 equiv. aryl bromide, slow addition of LiN(SiMe₃)₂ in 1.5 h followed by 6 h reaction time.

[e] 2.0 equiv. aldimine, 1.0 equiv. aryl bromide and 2.0 equiv. LiN(SiMe₃)₂ at 0.05 M.