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Ruthenium(0)-Sequential Catalysis for the Synthesis of Sterically Hindered Amines by C–H Arylation/Hydrosilylation

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We report sequential ruthenium(0)-catalysis for the synthesis of sterically-hindered amines via direct C–H arylation of simple imines and imine hydrosilylation. The method involves direct C–H arylation under neutral conditions with organoboranes enabled by ruthenium(0) catalysis. The catalytic hydrosilylation was performed in a one-pot fashion using Et_3SiH. The reaction is compatible with a broad range of electronically- and sterically-varied imines, enabling rapid production of valuable biaryl amines in good to excellent yields. The method constitutes a two-step, one-pot procedure to synthesize sterically-hindered amines from aldehydes. The utility of this atom-economic strategy is demonstrated in one-pot, three-component coupling, direct in situ aldehyde arylation as well as the use of transfer hydrogenation.

The development of sequential catalytic processes represents an important goal in organic synthesis.[1,2] The emergence of ruthenium-catalyzed C–H activation[3–5] has provided a significant opportunity for direct functionalization of C–H bonds using versatile ruthenium catalysts in a cost-effective, operationally-simple, and environmentally benign manner with a broad functional group tolerance often not available to other metals.[6] A classical example of sequential catalysis using Ru(IV) alkylidenes as precatalysts was reported by Ackermann and co-workers, accomplishing direct alkene C–H arylation/ketone hydrosilylation (Fig. 1A).[7] In an elegant expansion of this methodology, Dixneuf and co-workers reported Ru(II)-catalyzed sequential C–H arylation of imines with aryl bromides and imine hydrosilylation (Fig. 1B).[8] The lack of compatibility of the hydrosilylation step with Ru(II)-acetate based C–H arylation catalytic system necessitates purification between the catalysis. Moreover, recent developments in the field of sequential Ru-catalysis involving metathesis, alkyne dimerization and hydroarylation have provided a plethora of effective catalytic methods,[9–12] demonstrating the utility of ruthenium catalysis in broadly useful synthetic transformations.[13–18]

Herein, we report sequential ruthenium(0)-catalysis for the synthesis of sterically-hindered amines via direct C–H arylation of simple imines and imine hydrosilylation (Fig. 1C). Most importantly, the method provides rapid access to valuable sterically-hindered biaryl amines that are of major importance in organic synthesis, pharmaceutical development, biology and medicinal chemistry (Fig. 2).[19,20] The key advantages of the method are mild, neutral conditions, the operationally-simple, one-pot procedure, Ru(0)-catalyzed hydrosilylation, and the use of low-valent Ru(0) for the synthesis of amines. As a key difference to Ru(II), the method involves direct C–H arylation under neutral conditions with organoboranes enabled by Ru(0)-catalysis.[21,22,13e,f] This leads to several major advantages including (i) environmentally-benign neutral conditions in the absence of inorganic additives, (ii) compatibility of the direct

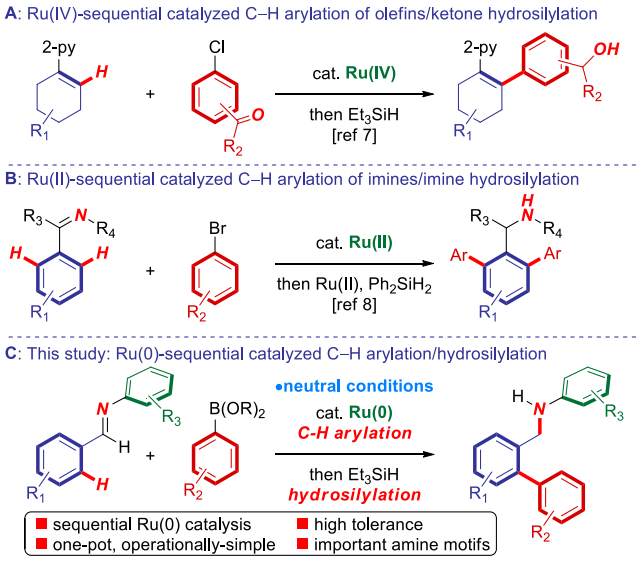

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Fig. 1 Ru-sequential catalysis. (A) Olefin C–H arylation/ketone hydrosilylation catalyzed by Ru(IV) precatalysts. (B) Imine C–H/hydrosilylation catalyzed by Ru(II). (C) This work: Ru(0)-catalyzed, one-pot sequential direct arylation/hydrosilylation.

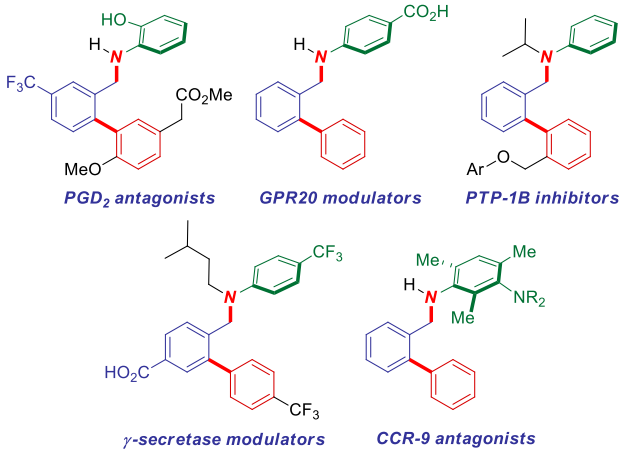
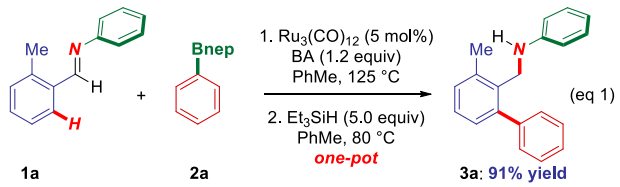


Fig. 2 Selected examples of biologically active benzyl amines.

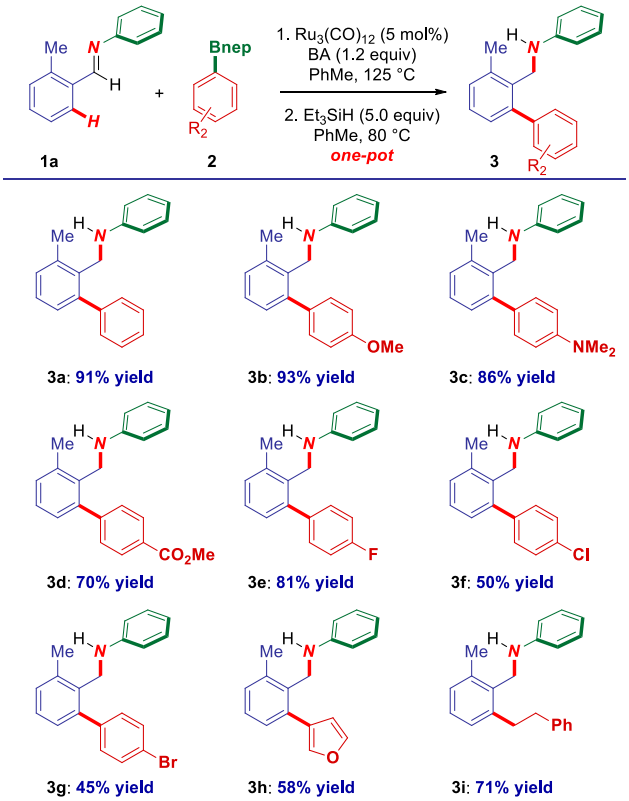
C–H arylation and hydrosilylation steps, (iii) the use of non-polar solvents enabling multicomponent sequences, (iv) complementary C–H arylation selectivity, (v) operational-simplicity. The reaction is compatible with a broad range of electronically- and sterically-varied imines, enabling rapid production of biaryl amines in good to excellent yields. The utility of this strategy is demonstrated in one-pot, three-component coupling, direct in situ aldehyde arylation as well as transfer hydrogenation. This versatile Ru(0) C–H arylation/hydrosilylation sequential catalysis provides a powerful alternative to the established methods for amine synthesis, such as Buchwald-Hartwig arylation, Ullman-type reactions or Pd-catalyzed amine-directed C–H arylation.[20a–c]

From the outset of our studies, we questioned whether Ru(0) that is utilized in the neutral C–H arylation of imines[13e] could be exploited in a productive hydrosilylation[23] of imines using the same catalyst in both steps. We were delighted to find that the proposed sequential C–H arylation/hydrosilylation proceeded in 91% yield in the presence of Et_3SiH (5 equiv) in toluene at 80 °C (eq 1) by simply adding the silane after completion of the C–H arylation step (BA = benzylideneacetone, Ru–H acceptor; Bnep = 5,5-dimethyl-1,3,2-dioxaborolane).[24]



The evaluation of stoichiometry revealed improvements in the reaction efficiency, however, as little as 2 equiv of Et_3SiH afforded the desired product in 63% yield. The temperature had a significant effect on the reduction with 80 °C being optimal (60 °C: 85% yield, 100 °C: 83% yield). Further increase of the silane loading or changes in the temperature did not improve the reaction efficiency. The one-pot protocol compares very favorably with the Ru(II)-catalyzed sequential C–H arylation of imines,[8] which requires separate purification, and highlights the potential of ruthenium(o) catalysis in organic synthesis.

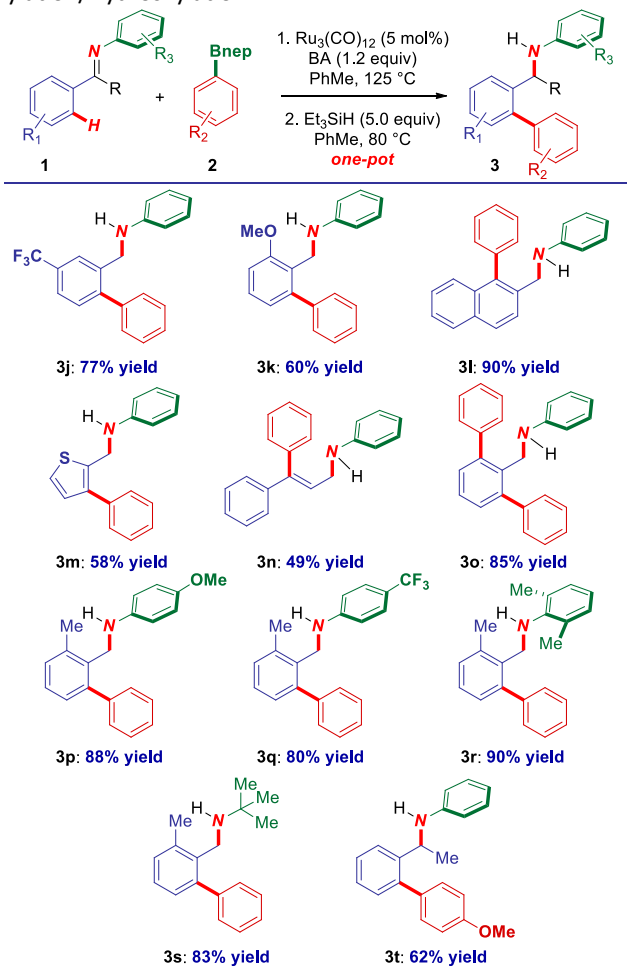
Scheme 1 Ruthenium(0) Sequential Catalysis: Direct C–H Arylation/Hydrosilylation[a,b]



[a]Conditions: imine (1.0 equiv), Ar-Bnep (1.2 equiv), BA (1.2 equiv), catalyst (5 mol%), PhMe, 125 °C, 1-8 h, then Et_3SiH (5 equiv), 80 °C, 3 h. [b]Isolated yields. See ESI for full details.

With an efficient catalyst system in hand, we next explored the substrate scope of this reaction. As shown in Schemes 1-2, the scope of this sequential Ru(0)-catalysis is very broad and enables the production of a wide range of electronically- and sterically-diverse biaryl benzyl amines from simple imines. Both electron-neutral (**3a**) and electron-donating methoxy (**3b**) and dimethylamino (**3c**) groups were well-tolerated on the boronate ester component as evidenced by excellent yields of the amine sequential catalysis products (Scheme 1). Likewise, electron-withdrawing ester (**3d**) and fluoro (**3e**) functionalities provided the benzylic amine products in high yields, and are accessible for further functionalization. Remarkably, halides such as chloro (**3f**) and even bromo (**3g**) are tolerated in this Ru(0) catalysis, providing handles for traditional cross-coupling strategies. While the reaction efficiency is slightly lower in these cases, the selectivity of aryl bromides and chlorides is particularly noteworthy providing complementary disconnection to Ru(II) catalysis. Furthermore, electron-rich heterocycles, such as furane (**3h**) are compatible with the reaction conditions. The reaction can be used to install phenethyl groups (**3i**) by sequential C–H vinylation/reduction.

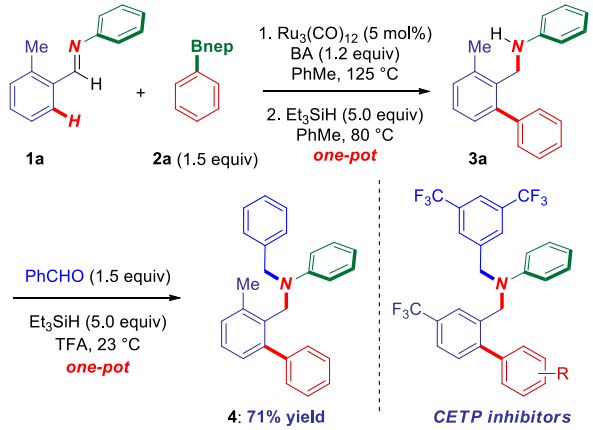
Scheme 2 Ruthenium(0) Sequential Catalysis: Direct C–H Arylation/Hydrosilylation[a,b]



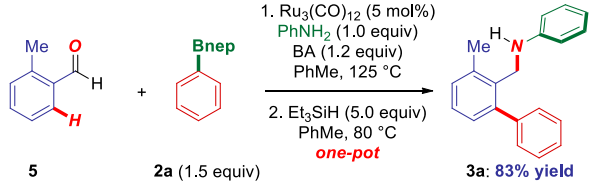
[a,b]See Scheme 1. See ESI for full details.

With respect to the imine scope, both electron-withdrawing (**3j**) and electron-donating groups (**3k**) on the aryl imine component are tolerated (Scheme 2). Polycyclic (**3l**) and electron-rich heterocyclic imines (**3m**) are excellent substrates, providing access to biaryl naphthylmethyl and thienylmethyl amines. With vinyl imines, C(sp^2)–H arylation is feasible, providing access to allyl amines after sequential hydrosilylation (**3n**). Notably, when the ortho-positions are unsubstituted, extremely sterically-hindered terphenyl amines are formed in high yield (**3o**). We were pleased to find that both electron-donating groups, such as methoxy (**3p**) and electron-withdrawing groups, such as trifluoromethyl (**3q**) on the amine component were well-tolerated. Furthermore, the very sterically-hindered 2,6-dimethylaniline (**3r**)and N-alkyl *t*-Bu amine (**3s**) generated the biaryl sequential catalysis products in high yields, attesting to the generality of this protocol. Note that sterically-hindered amines are often problematic substrates for Pd- or Cu-catalyzed amine synthesis. Finally, the sequential catalysis could be extended to ketimine substrates (**3t**) as demonstrated in the C–H arylation/hydrosilylation to afford the desired product with high mono-arylation selectivity (>20:1). This reactivity compares very favorably with the $RuH_2(CO)(PPh_3)_3$-catalyzed C–H arylation of ketones,[22] which is limited to pivaloylphenones and suggests that mono-arylation of simple ketimines by Ru(0) is possible. The method is compatible with ketimines; para or meta substituted imines follow the reactivity expected from the C–H arylation;[13e] the method is compatible with sensitive functional groups, however, reduction sensitive functional groups are not tolerated.[23a] The reaction mechanism involves Ru(0)-catalyzed C–H arylation, followed by Ru(0)-catalyzed hydrosilylation.[24]

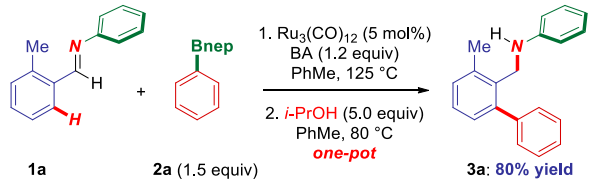
Scheme 3 Three-Component Sequential Ruthenium(0) C–H Activation/Reduction/Reductive Amination



Scheme 4 Three-Component Ru(0)-Catalyzed Arylation/ Reduction via In Situ Imine Synthesis



Scheme 5 Ruthenium(0) Sequential Catalysis: Direct C–H Arylation/Hydrosilylation using *i*-PrOH



To demonstrate the utility of this sequential Ru(0)-catalyzed protocol, we have showed that this reaction can be used in a three-component coupling to produce complex tertiary aromatic biaryl amines, which are valuable intermediates in medicinal chemistry campaigns, including the synthesis of analogues of cholesterylester transfer protein inhibitors (CEPT) for preventing atherosclerosis (Scheme 3).[19f]

To further underscore the advantage of this method, we performed a three-component coupling utilizing in situ imine assembly (Scheme 4).[13e] The neutral and waste-minimized conditions of Ru(0)-catalyzed sequential arylation/ hydrosilylation favor the rapid development of biaryl amine molecular complexity directly from aldehydes.

Finally, we also considered a possibility that Ru(0)-sequential catalysis could be used in a transfer hydrogenation protocol. In this regard, we found that using *i*-PrOH as the hydride source afforded the desired amine product in high

yield (Scheme 5).[25] This preliminary finding bodes well for the development of sequential catalysis methods using versatile Ru(0) catalysts and readily available alcohols. We are currently developing Ru(0)-catalyzed methods using H_2 as a reductant.

In summary, we have developed the sequential ruthenium(0)-catalysis for the synthesis of important sterically-hindered amines via direct C–H arylation of simple imines and imine hydrosilylation. This study shows the capacity of neutral, waste-minimized Ru(0)-catalyzed C–H arylation in sequential catalysis protocols, offering a major practical advantage and providing complementary selectivity to Ru(II)-catalysis.

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