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Communication

Multifunctionalization of Alkenyl Alcohols via a Sequential Relay Process

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ABSTRACT: Aryl-substituted aliphatic amines are widely recognized as immensely valuable molecules. Consequently, the development of practical strategies for the construction of these molecules becomes increasingly urgent and critical. Here, we have successfully achieved multifunctionalization reactions of alkenyl alcohols in a sequential relay process, which enables transformation patterns of arylamination, deuterated arylamination, and methylenated arylamination to the easy access of multifarious arylalkylamines. Notably, a novel functionalization mode for carbonyl groups has been developed to facilitate the processes of deuterium incorporation and methylene introduction, thereby providing new means for the diverse transformations of carbonyl groups. This methodology displays a wide tolerance toward functional groups, while also exhibiting good applicability across various skeletal structures of alkenols and amines.

Aryl-substituted aliphatic amines, serving as core structures in various important molecules, play a crucial role in the biological systems by acting as neurotransmitters, hormones, and pharmaceutical agents.[1] Their diversity and tunability make them ideal choices for synthesizing new materials or improving existing ones. Therefore, research and development of efficient approaches to the construction of arylalkylamines are of great importance.[2]

Multifunctionalization of alkenes is a highly valuable approach in organic synthesis, and it becomes even more impactful and powerful when the chain-walking strategy is incorporated.[3] In comparison with classical functionalization of alkenes at vicinal vinylic carbons to produce 1,2-functionalized products,[4] hydride shifts lead to alkene isomerization prior to the reaction in the chain-walking process, resulting in the generation of products with diversified frameworks.[5] Among various approaches, the prevalence of metal-catalyzed remote difunctionalization of alkenes is remarkable due to the ease of access to feedstock chemicals and the multitude of creative transformations (Scheme 1a). In recent years, most endeavors were concentrated on the difunctionalization of olefins with directing groups preserved (Scheme 1a, path a). On the other hand, achievements in the functionalization of alkenes accompanied by the directing group transformation are limited to oxidation of an alcohol to the carbonyl group[5j,6] or β-elimination of the directing group to an alkene unit[7] (Scheme 1a, path b). Thus far, research on subsequent post-transformation of a directing group in a relay manner following the functionalization of a double bond has remained a significant challenge[8] (Scheme 1a, path c).

In recent years, borrowing hydrogen catalysis has emerged as a powerful synthetic approach for derivatizing alcohols[9] (Scheme 1b). Using alcohols as starting materials, this reaction proceeds with metal-catalyzed dehydrogenation of alcohols, α- or *ipso*-functionalization of the resulting carbonyl intermediates, and subsequent reduction with an *in situ*-generated metal hydride. Inspired by these studies, it is envisioned that arylamination of alkenols is achievable by integrating remote arylation with the generation of a carbonyl group via chain-walking, followed by metal hydride-mediated reductive amination. Notably, α-functionalization of carbonyl intermediates would also become feasible in this case if reductive amination of the carbonyl functionality proves to be a slow process. This would address a significant challenge in current carbonyl compound transformations: prioritizing the functionalization of carbonyl intermediates over direct reductive amination (Scheme 1c).

Initial investigation was conducted with 4-iodoanisole (**1a**), (*Z*)-pent-2-en-1-ol (**2a**), and dipropylamine (**3a**), $Pd(OAc)_2$, tetrabutylammonium tetrafluoroborate (TBA·BF_4), and potassium formate (HCOOK) in toluene under N_2 atmosphere, furnishing the desired arylpropylamine product (**4a**) with a yield of 36% at 115 °C. It is worth noting that only trace amount of product was formed in the absence of a quaternary ammonium salt. Given the decisive role of these ammonium salts, we speculate that Pd nanoparticles (Pd NPs) are most likely formed and serve as the active catalyst, as it has been well documented that quaternary ammonium salts are capable of stabilizing palladium nanoparticles, preventing the aggregation and subsequent inactivation of the palladium catalyst, thereby enhancing the reactivity.[10] A subsequent survey of representative ammonium salts revealed that tetrabutylammonium triflate (TBA·OTf) was optimal (87% yield). Further screening on solvents and bases did not show any improvement (Table S1

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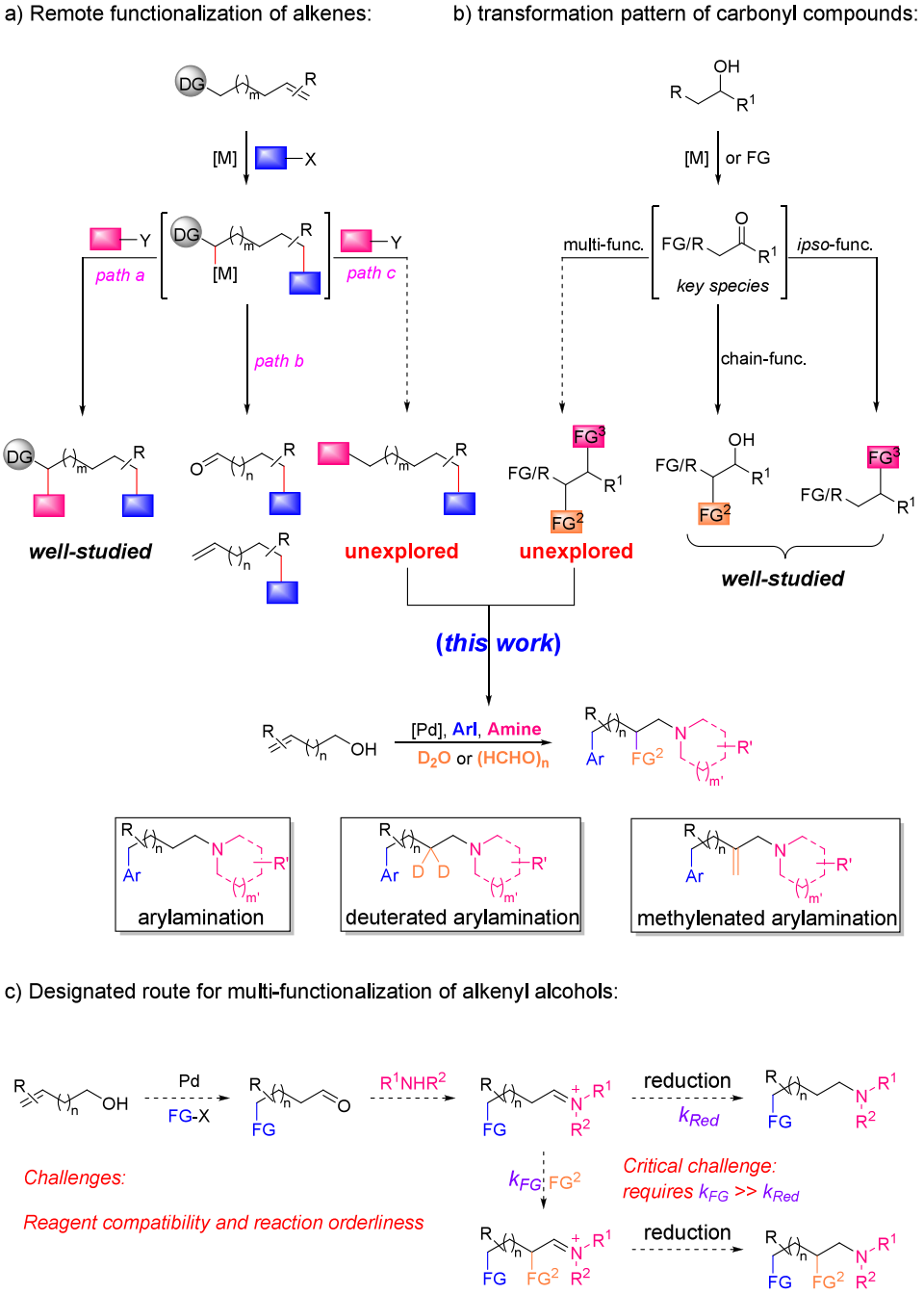
Scheme 1. Remote Functionalization of Olefins, Transformation Pattern of Carbonyl Compounds, and Our Design



in the SI). Notably, lowering the temperature to 105 °C dramatically reduced the reactivity, while almost no product was detected at 95 °C.

With an optimized protocol obtained, a wide range of aryl iodides were then evaluated (Scheme 2). Substrates bearing substituents at different positions underwent arylamination smoothly to provide the corresponding products in excellent yields, regardless of the presence of an electron-withdrawing or electron-donating substituent, or *mono*- or *di*-substituted groups on the aromatic ring. It is worth mentioning that a high yield was obtained with the very strong electron-withdrawing trifluoromethyl substituent (**4h**), while the nitro-substituted iodobenzene gave a moderate yield of the desired product (**4g**). Additionally, the coordination-capable substrates were effective (**4o**, **4p**). We also tested 3-iodopyridine and 4-iodopyridine, but unfortunately, neither of them gave the corresponding product while both substrates completely resulted in deiodination. Next, we surveyed the scope with respect to the alkenol substrates. It was found that alkenols with different frameworks consisting of a terminal or nonterminal double bond, as well as a varied chain length between the double bond and hydroxyl group were compatible, delivering corresponding products with good to excellent yields (**4q**−**4w**). Moreover, the challenging trisubstituted alkenol also provided the arylamine product bearing a quaternary center, albeit with a moderate yield (**4x**). Notably, alkenols bearing a styrene moiety have proven highly challenging substrates in chain-walking Heck-type processes

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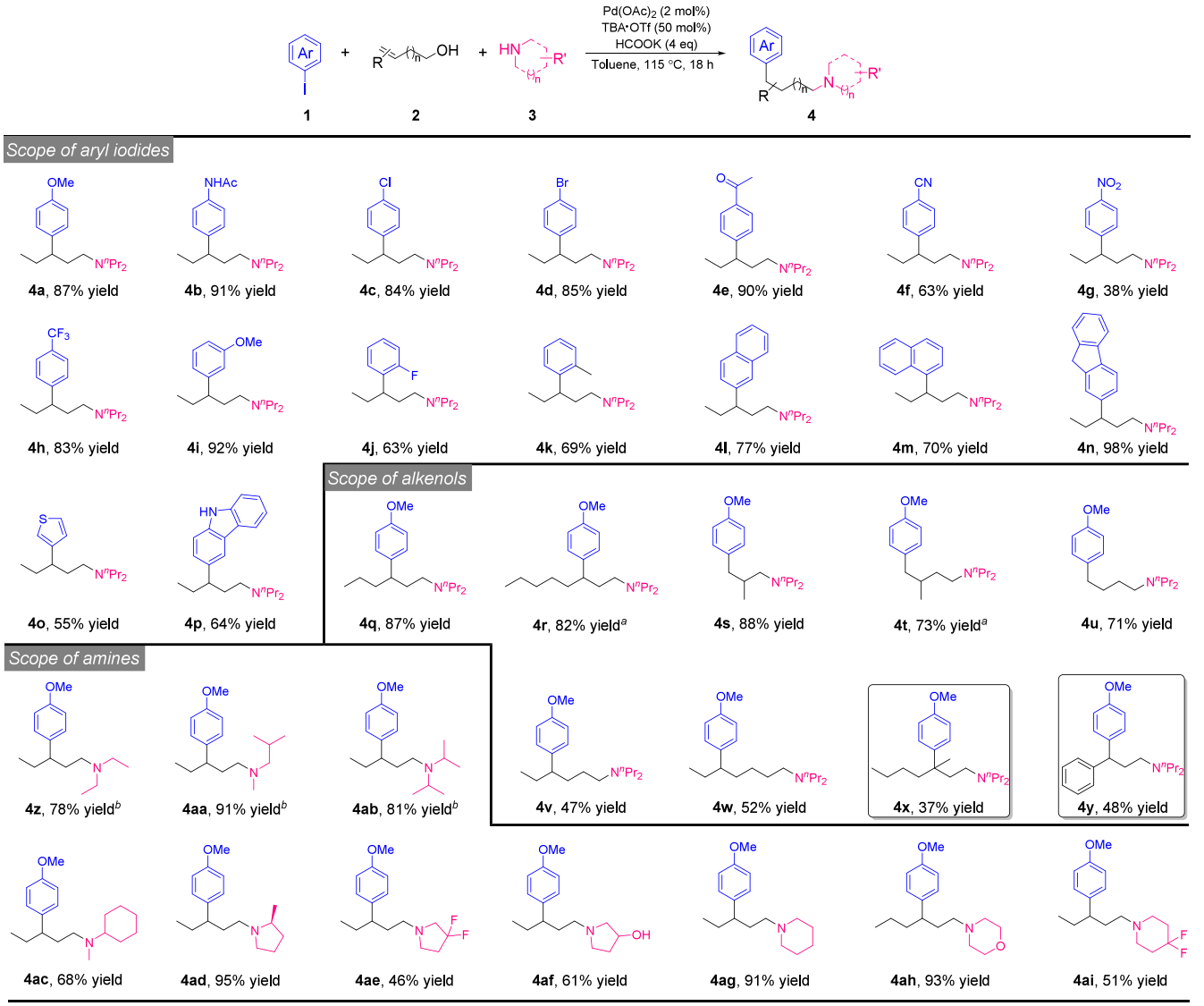
Scheme 2. Substrate Scope of the Arylamination Reaction[c]



[a]48 h. [b]Four equiv of amine were used. [c]Conditions: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.5 mmol), $Pd(OAc)_2$ (2 mol %), TBA·OTf (50 mol %), HCOOK (4 equiv), toluene (2 mL), 115 °C, 24 h, unless otherwise noted. Isolated yields.

due to notorious site-selectivity issues from competing insertion and β-H elimination. However, excellent site-selectivity was observed in our case (**4y**), further demonstrating the importance of this study. Overall, the compatibility of diverse alkenols under this catalytic system highlights the great potential of this methodology in the construction of arylalkylamines with versatile scaffolds. Finally, a wide range of amines were employed under the optimal conditions. Acyclic amines, as well as cyclic amines of varying sizes, all fitted well with this catalytic system and afforded the desired products in satisfactory yields (**4z**−**4ai**).

Deuterated compounds have been extensively researched in nonclinical settings and are widely used as metabolic or pharmacokinetic probes both *in vitro* and *in vivo*.[11] The incorporation of deuterium atoms into pharmacologically active agents offers potential benefits such as enhanced exposure profiles and decreased production of toxic metabolites,[12] which could provide improvements in efficacy, tolerability, or safety. Although there are many achievements on the deuteration of amine compounds, most of them focus on the α-position of the amino group,[13] while reports on selective β-deuteration are rare. Furthermore, current methods with high deuterium incorporation on the β-position of the amine moiety typically rely on the use of relatively expensive deuterated reagents, such as deuterated alcohols or carboxylic acids.[14] In contrast, those using D_2O as the deuterium source face significant challenges including the cumbersome procedures, low deuteration incorporation, or restricted substrate scope (Scheme 3).[15] Building on the aforementioned successes, we attempted to leverage the H/D exchange of *in situ*-generated imine intermediates (Scheme 1c) to achieve site-selective deuteration in the process. According to our hypothesis, the carbonyl intermediates formed in the system are present in extremely minute quantities relative to D_2O.[16] Thus, this "sustained-release" transformation mode could make this methodology a highly efficient means of conducting deuteration processes.

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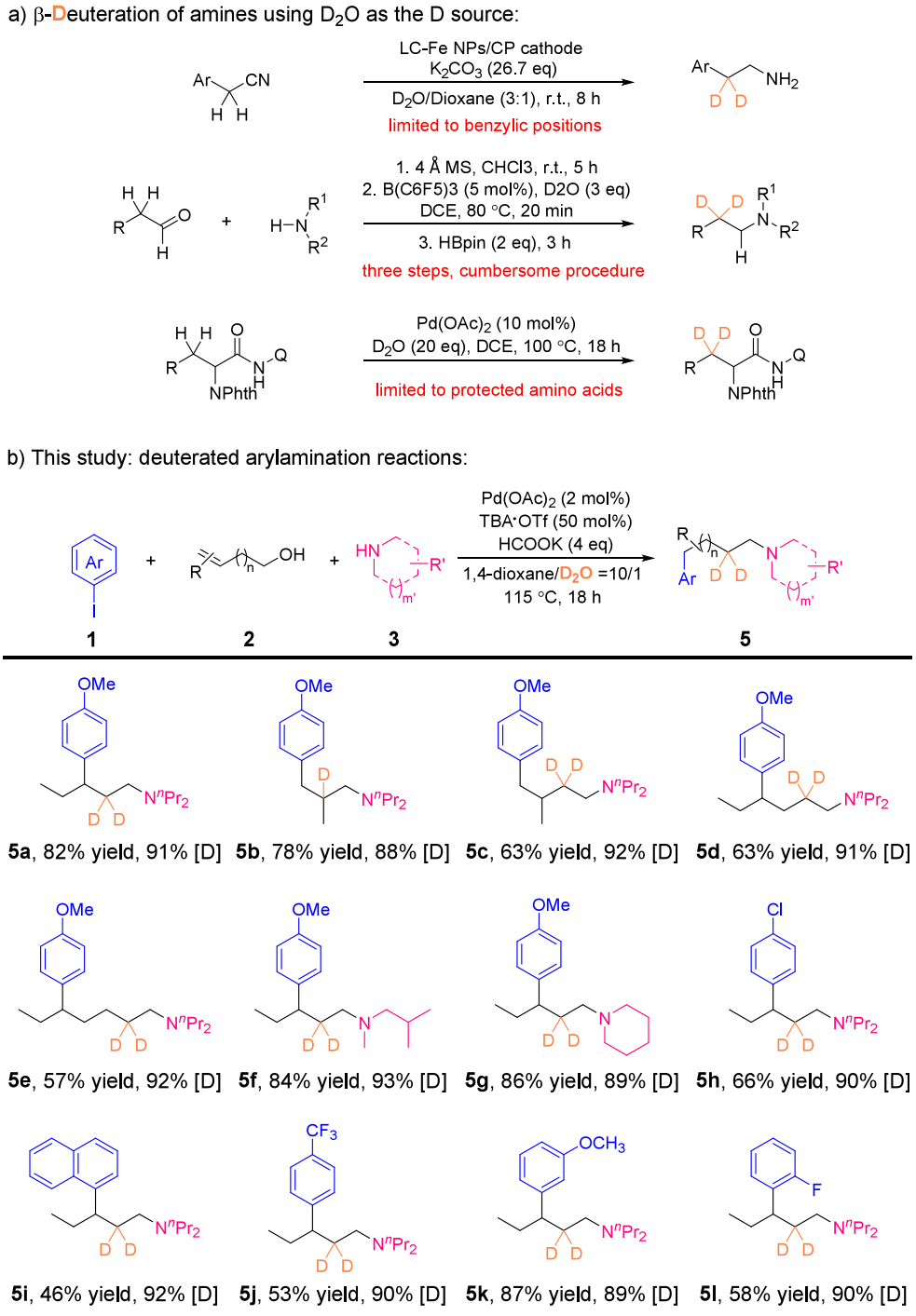
Scheme 3. Reported *β*-Deuteration of Amines Using D_2O and the Designed Deuterated Arylamination Reaction[a]



[a]Conditions: **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.5 mmol), $Pd(OAc)_2$ (2 mol %), TBA·OTf (50 mol %), HCOOK (4 equiv), 1,4-dioxane/D_2O (2 mL/0.2 mL), 115 °C, 24 h, unless otherwise noted. Isolated yields.

Gratifyingly, our initial attempt was successful in the presence of D_2O, the most economical deuterium atom source, and product (**5a**) was obtained in 45% yield with 73% deuterium incorporation under the established optimal conditions. After a detailed screening, the superior deuteration was achieved with 1,4-dioxane as solvent instead of toluene, furnishing the desired product in 81% yield with 83% deuterium incorporation (Table S2 in the SI). Further optimization resulted in the improvement of deuterium incorporation to 91%.

Next, we conducted an applicability study on the alkenol substrates and coupling partners. It was found that alkenols with different frameworks were compatible, resulting in the corresponding products with excellent deuterium incorporation (**5a**−**5e**). Additionally, both acyclic amines and cyclic amines were well-suited for this catalytic system, providing the desired products in satisfactory results (**5f** and **5g**).

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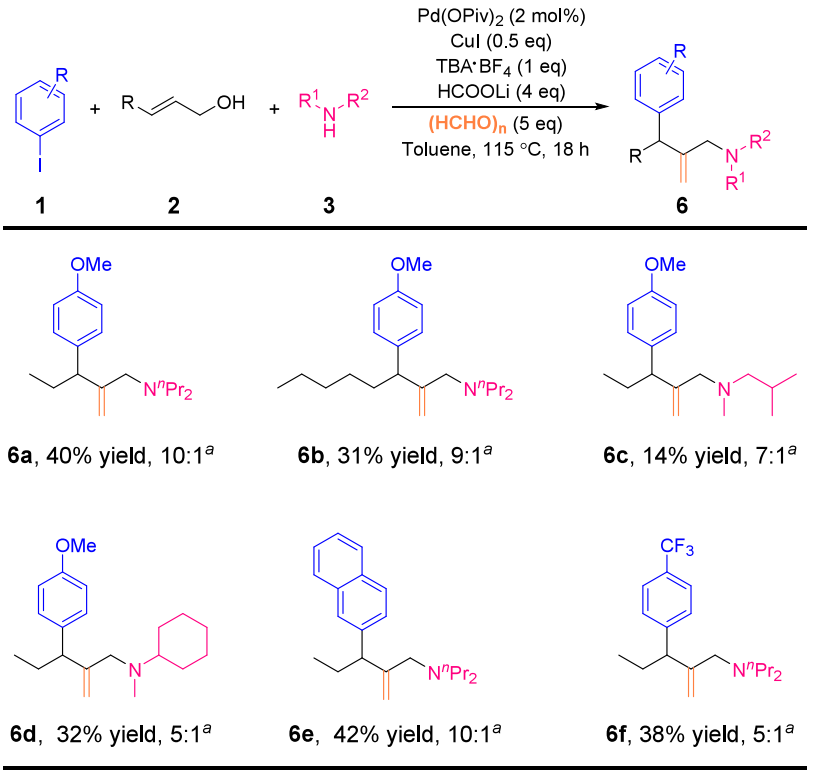
Scheme 4. Substrate Scope of the Methylenated Arylamination Reaction[b]



[a]The ratios of products to the direct reductive amination products. [b]Conditions: **1** (0.2 mmol), **2** (1.0 mmol), **3** (1.0 mmol), $Pd(OPiv)_2$ (2 mol %), CuI (0.1 mmol), $TBA{\cdot}BF_4$ (1 equiv), HCOOLi (4 equiv), $(HCHO)_n$ (5 equiv), toluene (2 mL), 115 °C, 24 h, unless otherwise noted. Isolated yields.

Furthermore, aryl iodides bearing substituents with different electronic properties or substituents at different positions also produced the target products with very satisfactory results (**5h**−**5l**).

To further broaden the multifunctionalization pattern, we attempted to test compatibility of this newly developed process with the aldol condensation reaction, aiming to generate valuable classes of allylamine compounds (Scheme 4). The key challenge lies in achieving the aldol condensation of carbonyl group prior to the direct reduction of the imine intermediate. Gratifyingly, when lithium formate and tetrabutylammonium tetrafluoroborate were used, the target product was successfully obtained, albeit in only 18% yield. Replacing $Pd(OAc)_2$ with $Pd(OPiv)_2$ significantly improved the ratio of the target product to the direct reductive amination product (6:1), resulting in an increased yield of 31%. Surprisingly, when CuI was added, the yield could be increased to 40%, along with an improvement in the selectivity of the allylamine over the direct reduction product to 10:1, further validating the feasibility of prioritizing α-functionalization. Although we were not able to achieve a highly satisfactory yield in the end, the approach to construct valuable allylamine products through a one-step, four-component cascade process is still very valuable. Further substrate examination showed that various types of substituted iodobenzenes, alkenols, and amines could achieve excellent chemoselectivity, yielding the corresponding target products in moderate yields.

To gain an insight into the reaction mechanism, a series of control and kinetic experiments have been carried out (Scheme 5). The results with *d*-potassium formate suggested that the hydride source is originated from the formate salt, excluding the borrowing hydrogen catalysis in reductive amination (Scheme 5a). Additionally, no desired product was detected when alcohol **9** was subjected into the reaction (Scheme 5b).[9] As such, a carbonyl intermediate is most likely formed via the relay Heck catalysis and serves as the precursor for reductive amination. To provide some evidence, aldehyde compound **10** was prepared and studied with amine under the optimized reaction conditions (Scheme 5c). Interestingly, while only a trace amount of the target product was obtained with 2 mol % Pd, the efficiency of this reaction was significantly improved by increasing the Pd loading to 30 mol %, implying that formate/Pd(II) could effectively promote reductive amination of the carbonyl compound.[17] We believe that this result is arisen from the deviation of reaction conditions from the standard process. In the standard reaction, the formation of aldehyde is accompanied with the formation of an equivalent amount of protons, which turns to be crucial for reductive amination. During the reductive amination with Pd(II)/HCOOK, the formation of the amine product is accompanied with the generation of an equivalent amount of hydroxide ions. While reductive amination could be well performed in the presence of protons, Pd(0) is ultimately formed in their absence and thus the reaction is stopped (Scheme 5d). In the control experiment, there are no protons to neutralize the hydroxide ions formed, thus resulting in the termination of the reaction. To verify this, 2 equiv of ammonium chloride were added to the control experiment, and the desired product was isolated in a 92% yield. Moreover, it is noteworthy that almost twice the amount product was isolated with 30 mol % Pd loading, reinforcing the essential role of protons in reductive amination. As Pd(II) is reduced to Pd(0), an equivalent amount of

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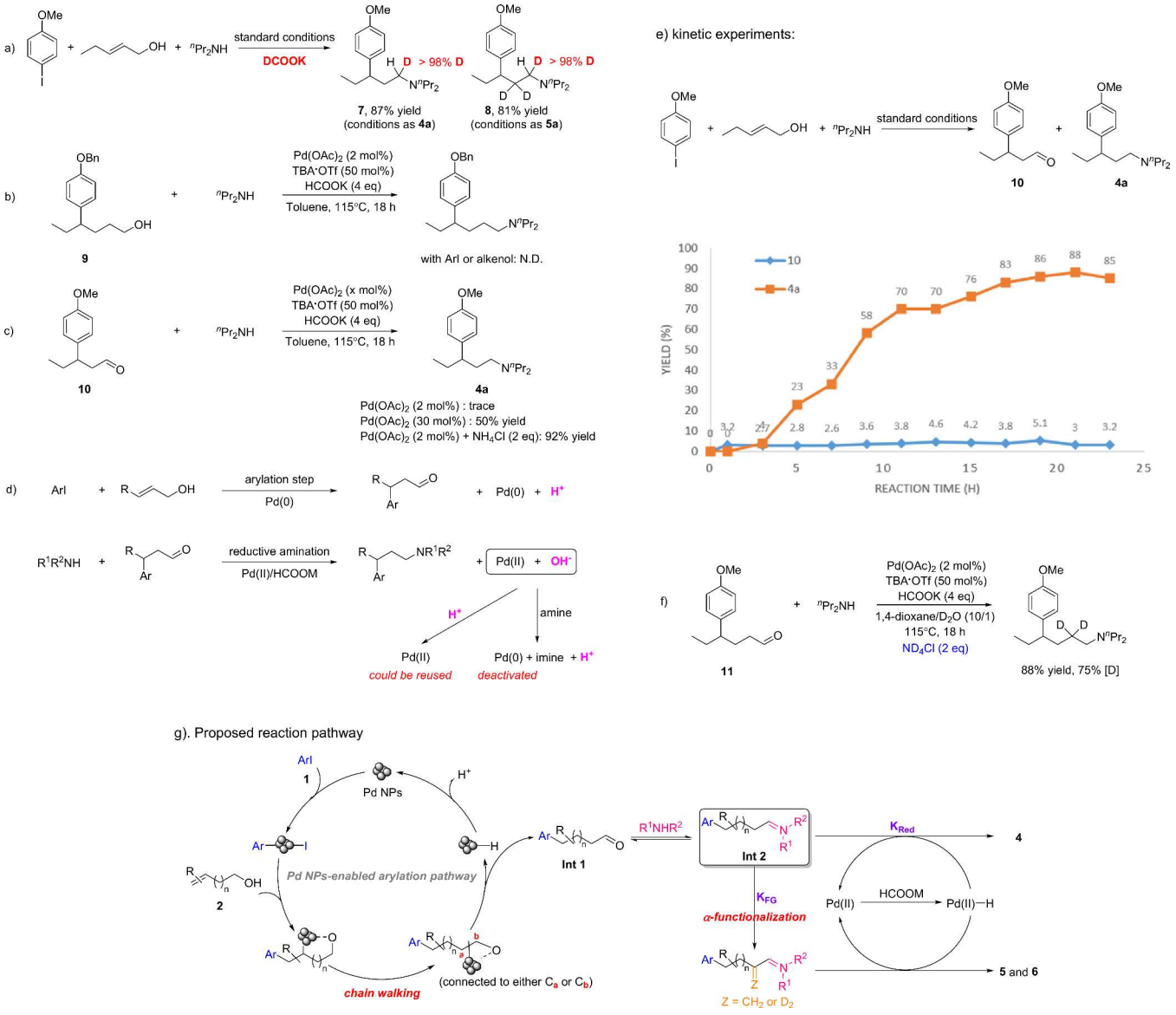
Scheme 5. Mechanistic Investigations



protons is also generated, and contributes to the formation of an additional, nearly an equivalent amount of the product.

To explore whether the aldehyde intermediate accumulates or undergoes rapid conversion during the reaction, a kinetic experiment was conducted (Scheme 5e). The results revealed that the aldehyde consistently remained at a very low concentration in the reaction, indicating that further conversion of aldehyde is very fast. Notably, this "slow-release-rapid-conversion" mode of the carbonyl intermediate allows for α-functionalization to be favored to direct reductive amination. It is also envisioned that at a high concentration, aldehyde may partially undergo direct reductive amination prior to α-functionalization. Unsurprisingly, when aldehyde **11** was used in the deuterated reductive amination reaction, the deuterium incorporation was significantly reduced (Scheme 5f).

Based on the above observations, a plausible reaction mechanism involving dual catalytic cycles is proposed (Scheme 5g).[18] This process begins with a quaternary ammonium salt-facilitated, Pd NPs-catalyzed arylation pathway, resulting in carbonyl intermediate **Int 1**, which encompasses hydroxyl group-directed functionalization of the double bond, Pd(II) migration via chain-walking, and oxidative conversion of the hydroxyl group. In the second stage, the reduction process is mediated by the *in situ*-generated "Pd−H" species from Pd(II) and formate salts, involving a competition between the direct reduction of **Int 2** to form product **4** and the functionalization-reduction to form product **5** or **6**. Mechanistic studies indicate that the aldehyde intermediate consistently remains at a very low concentration, which is favorable for α-functionalization to direct reductive amination. Ultimately, this "slow-release-rapid-conversion" transformation mode promotes the multifunctionalized products in a sequential relay process.

In conclusion, we have successfully achieved arylation of olefins accompanied by directing group transformations, yielding arylalkylamine derivatives with diverse scaffolds. Building upon this, through functionalization at the α-position of carbonyl groups and subsequent *ipso*-transformations, we have effectively realized the multifunctionalization of alkenyl alcohols, obtaining a variety of highly useful molecular structures. Additionally, the efficient implementation of H/D exchange facilitated the efficient construction of deuterated

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arylalkylamines. Moreover, highly chemoselective introduction of the aldol condensation reaction made the synthesis of aryl-substituted allylamine compounds a reality. The ability to access various arylalkylamines with a single catalytic system is likely to have a notable impact on the way in which many molecules of interest are prepared.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c09522.

Experimental procedures and relevant spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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