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Palladium-Catalyzed Secondary Benzylic Imidoylative Reactions

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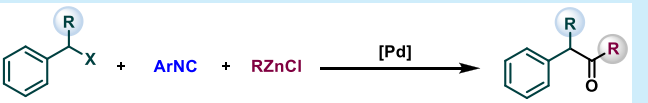
ABSTRACT: Reported herein is a palladium-catalyzed secondary benzylic imidoylative Negishi reaction leveraging the sterically bulky aromatic isocyanides as the imine source. This method allows the facile access of alkyl-, (hetero)aryl-, and alkynylzinc reagents to afford various α-substituted phenylacetone products under mild acidic hydrolysis, which are ubiquitous motifs in many pharmaceuticals and biologically active compounds. The diastereoselective reduction of imine can be accomplished to provide the expedient conversion of secondary benzylic halide into α-substituted phenethylamine derivatives with high atom economy.



α-Substituted phenylacetones are a versatile array of building blocks, ubiquitous in pharmaceutically active compounds, natural products, and agrochemicals.[1] The traditional synthetic route largely relies on the Buchwald−Hartwig α-arylation of ketone, which often suffers from selective enolate intermediate formation, especially for unsymmetric alkylated ketones substrates, thus requiring the additional preformation of silyl enol ether.[2] Recently, the cross-coupling of benzylic electrophiles via synergistic Pd/NHC-catalyzed umpolung of acyl anions[3] and Ni-catalyzed reductive cross-coupling of acyl chloride[4] have emerged as alternative synthetic approaches; however, both methods restrict incorporation of alkylated carbonyls. Meanwhile, phenethylamine derivatives represent one of the top five pharmaceutical scaffolds, present in a broad class of hormones, neurotransmitters, and psychoactive drugs.[5] Thus, their diastereoselective preparation has gained considerable attraction from organic chemists over several decades.[6] Therefore, a divergent synthesis of α-substituted phenylacetone and phenethylamine derivatives from easily accessible benzylic electrophiles with broad substrate scope would be of great research value.

Transition-metal-catalyzed carbonylative cross-coupling has been classified as a powerful and straightforward protocol for ketone synthesis with two carbon−carbon bond formations in a single transformation.[7] The majority of benzylic carbonylations are mainly centered on formation of primary benzyl ketones,[8] as substituted benzyl ketone are synthetically challenging due to the slow oxidative addition caused by steric obstruction of the secondary benzyl electrophiles, as well as inhibiting competitive reactions caused by the following β-H elimination.[9] More recently, Zhang and co-workers achieved the Ni-catalyzed secondary benzylic bromide with organoboron reagent under mild conditions; however, the nucleophiles largely relied on the aromatic boronic acid.[10]

Isocyanide, as an important C1 synthon,[11] has been implemented in transition-metal-catalyzed carbonylation for ketone synthesis, although the atom economy requires further improvement.[12] We recently reported a Ni-catalyzed formal aminocarbonylative reaction of secondary benzyl chloride using *tert*-butyl isocyanide, in which we identified inhibition of the rapid β-H elimination of imidoyl metal species as a significant challenge in developing an efficient secondary benzyl carbonylative cross-coupling reaction to forge C−C bond formation.[13] Instead, the rapid transmetalation of organometallic reagent with metal imidoyl intermediate should be a superior process which also avoids a direct coupling reaction with benzylic electrophiles. The broad functional group tolerating organozinc reagent would be an appropriate candidate.[14] In line with our research interest in practical carbonylation,[15] we describe a Pd-catalyzed imdoylative Negishi cross coupling of secondary benzyl halide with modified isocyanide to provide the α-substituted arylacetimines, which overcome competitive β-H elimination and direct Negishi cross-coupling side pathways. Moreover, a wide array of organozinc reagents containing sp, sp^2, sp^3, and heterocyclic organozinc reagents can be readily accessed. In addition, both α-substituted of phenylacetone and phenethylamine derivatives can be divergently obtained upon the different workup protocols: the mild acidic hydrolysis would provide the phenylacetones, and the phenethylamines are generated in high diastereoselective reduction with 100% atom economy (Scheme 1).[16]

We initiated our studies with commercially available 2-(1-chloroethyl) naphthalene **1a** as benzyl electrophile in Table 1, and the imidoylative reaction proceeded with treatment of *tert*-butyl isocyanide **2a** (1.5 equiv), *n*-butyl zinc chloride **3a** (1.5 equiv) as nucleophile, and Pd_2dba_3 (2 mol %) under 60 °C in

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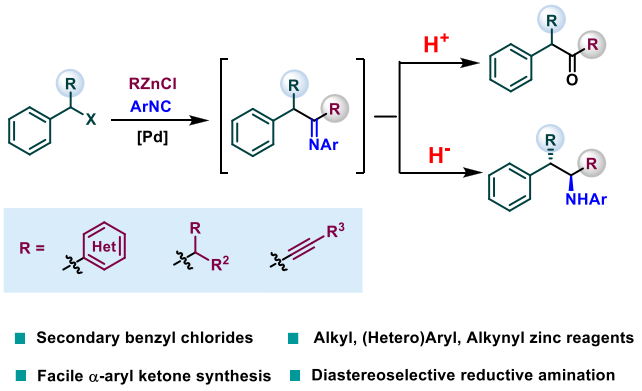
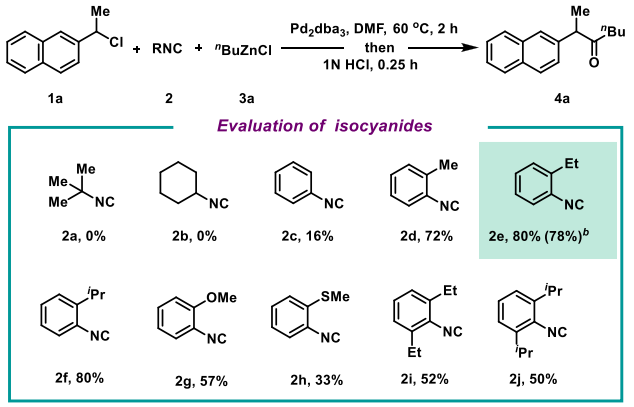
Scheme 1. General Strategy for Pd-Catalyzed Benzylic Imidoylative Coupling of Carbon Fragments



- Secondary benzyl chlorides
- Alkyl, (Hetero)Aryl, Alkynyl zinc reagents
- Facile α-aryl ketone synthesis
- Diastereoselective reductive amination

Table 1. Optimization of Reaction Conditions[a]

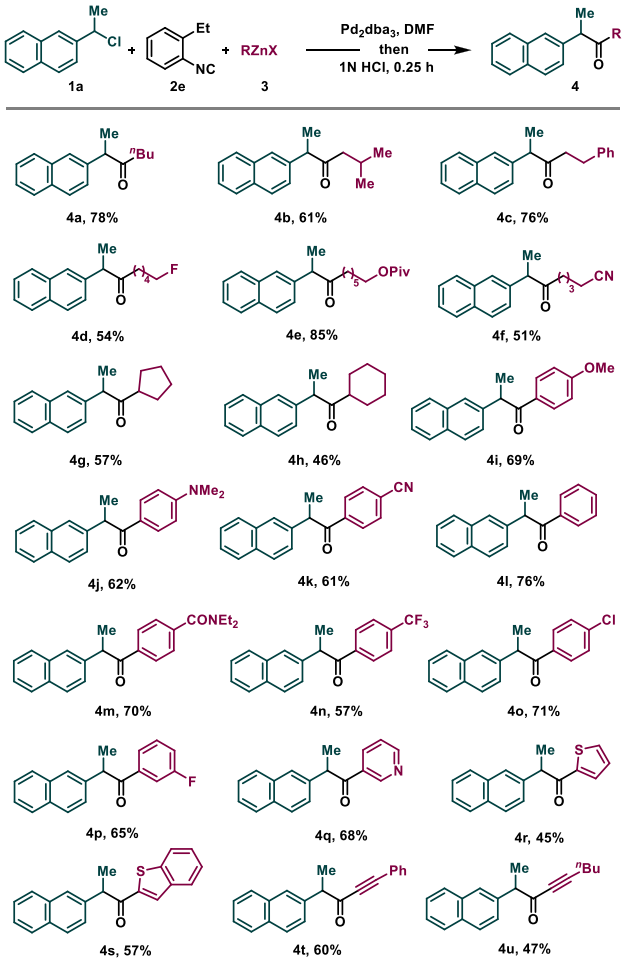


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol, 1.5 equiv), **3a** (0.3 mmol, 1.5 equiv), Pd_2dba_3 (0.004 mmol, 2 mol %), DMF (2 mL), 60 °C, 2 h. The reaction was quenched with 1 N HCl (2 mL) and stirred at 25 °C for 0.25 h. Corrected GC yield was reported. [b]Isolated yield shown in parentheses.

DMF. Nevertheless, no desired imidoylative Negishi coupling product was observed, while vinyl naphthalene was generated as the main side product due to undesired *β*-H elimination. The screening of another alkyl isocyanide (CyNC, **2b**) also failed to produce the desired product. Encouragingly, when phenyl isocyanide (**2c**) was employed as the imidoyl component, the desired product **4a** was observed after 1.0 N HCl workup, albeit with 16% GC yield. Varying the substitution of aromatic isocyanide dramatically influenced the efficiency of imidoylative Negishi coupling, and the introduction of an *o*-methyl group at the phenyl isocyanide (**2d**) greatly improved the yield to 72% presumably due to the slow addition of isocyanide, which restricts the highly coordinating nature of isocyanide.[17] 2-Ethylphenyl isocyanide (**2e**) was proven as the best imidoyl source in this reaction, resulting in a high GC yield of 80% with 78% isolated yield. Exchanging the ethyl with an isopropyl group (**2f**) exhibits similar reactivity. When the *ortho*-heteroatom substitution (methoxyl **2g**, methyl sufide **2h**) was employed at the phenyl group, the yield decreased to 57% and 33%, respectively. The introduction of both a 2,6-diethyl group (**2i**) and a 2,6-diisopropyl group (**2j**) on the phenyl ring resulted in a much lower yield.

With the optimized conditions in hand, we next examined the substrate scope and functional group tolerance of Pd-catalyzed benzylic imidolyative Negishi coupling reaction using secondary 2-(1-chloroethyl)naphthalene **1a** as a benzylic electrophile (Table 2). A wide array of organozinc reagents

Table 2. Substrate Scope of Zinc Reagents[a]



[a]Reaction conditions: **1a** (1.0 equiv), **2e** (1.5 equiv), **3** (1.5 equiv), Pd_2dba_3 (2 mol %), DMF, 60–80 °C, 1–24 h. The reaction was quenched with 1 N HCl and stirred at 25 °C for 0.25 h.

containing sp, sp^2, sp^3, and heteroaryl zinc reagents can be readily accessed. The scope of the sp^3 zinc reagents was first investigated. The isobutyl (**4b**) and 2-phenyl ethyl group (**4c**) could be accessed in 61% and 76% isolated yield, respectively, with acidic hydrolysis. Functional primary zinc reagents such as (5-fluoropentyl)zinc bromide, (4-cyanobutyl)zinc bromide, and (5-pivalatepentyl)zinc bromide can be successfully utilized as the alkylated reagents to afford the corresponding ketone products in moderate to good yield (**4d**–**4f**). It is worth noting that the cyclic Negishi reagents such as cyclopentyl- and cyclohexylzinc reagents worked well, furnishing **4g** and **4h** in moderate yield. Next, we started to explore the substrate scope of sp^2 organozinc reagents. Coupling of 2-(1-chloroethyl) naphthalene with phenylzinc reagents afforded the desired product in 76% isolated yield (**4l**). The aryl nucleophiles bearing electron-donating substituents such as methoxyl and *N*,*N*-dimethyl furnished the corresponding ketones in high yield (**4i**, **4j**). Arylzinc reagents bearing electron-withdrawing

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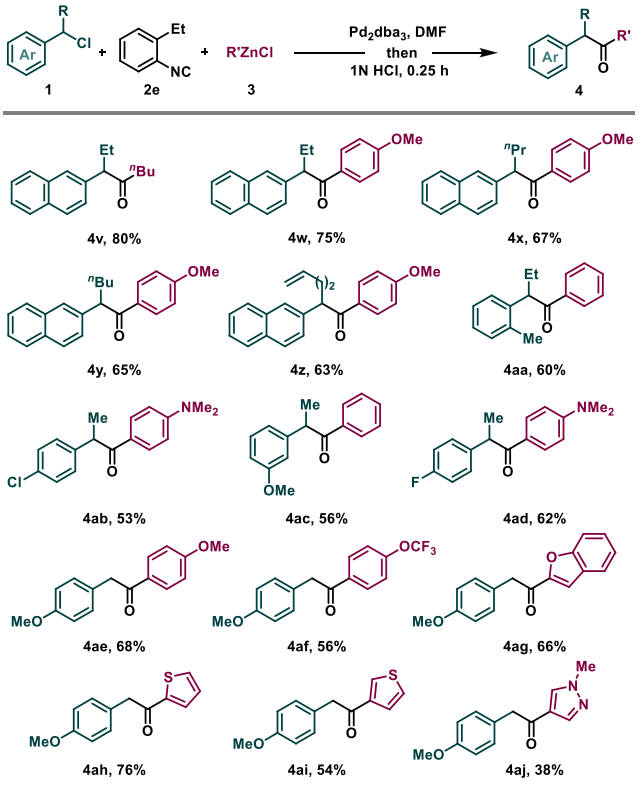
substituents also worked well, including amide (**4m**), trifluoromethyl group (**4n**), chloride (**4o**), fluoride (**4p**), and cyanide (**4k**). Heteroarenes are among the most significant structural backbones of pharmaceuticals. Pyridine (**4q**), thiophene (**4r**), and benzothiophene (**4s**) are tolerated in this imidoyl coupling chemistry. The protocol also extends to sp zinc reagents. Both phenyl-substituted alkynylzinc reagents and alkyl-substituted alkynylzinc reagents can be coupled and obtain the product (**4t**, **4u**). At the current stage, the unactivated alkyl halide electrophiles were not suitable for the Pd-catalyzed Negishi imidolylative reaction, and no product could be observed in the reaction mixture, presumably due to the challenge for oxidative addition for Pd(0) with alkyl halides.

Next, we explored the scope of secondary benzyl chloride (Table 3). Benzyl ketone products can also be obtained at a good yield when methyl groups are replaced with other alkyl groups including ethyl (**4v**, **4w**), *n*-propyl (**4x**), and *n*-butyl (**4y**). When a tether alkene group was incorporated in the starting material, the reaction did not proceed via the intramolecular migratory insertion yet provided the desired product **4z** in 63% isolated yield, demonstrating that the intermolecular 1,1-insertion of aryl isocyanide is a superior reaction pathway. The scope of benzylic electrophile was extended to phenyl-substituted benzyl chlorides, which exhibit slightly lower reactivity than the corresponding naphthalene benzyl chloride. Installations of various substituted phenyl benzyl chlorides containing both electron-donating and -withdrawing groups on the aryl rings could be tolerated (**4aa**–**4ad**). Notably, no significant steric hindrance was observed, as the methyl group in the *ortho* position had little effect on the yield of the reaction (**4aa**). Finally, the primary benzyl chloride was also investigated. We use 1-(chloromethyl)-4-methoxybenzene coupled with functional phenylzinc reagents and various heteroarylzinc reagents including thiophene, benzofuran, and pyrazole functionalities (**4ae**–**4aj**).

It was evident that this Pd-catalyzed benzylic imidoylative reaction proceeds via an imine intermediate, instead of the direct acidic hydrolysis, and we hypothesized that the corresponding phenylethylamine and phenylethanol could be obtained by diastereoselective reduction (Scheme 2). Fortunately, the benzyl ketone product and imine intermediate can smoothly convert to relevant phenyl ethanol (**5a**, **5b**, **5c**) and phenylethylamine (**6a**, **6b**, **6c**) in high diastereoselectivities with $LiAlH_4$ as reducing reagent. The relative stereoconfiguration of phenyl ethanol was *trans*, which was confirmed via the Ns protection of **5a**, and the structure of derivative **7a** was unambiguously assigned by single-crystal X-ray analysis.

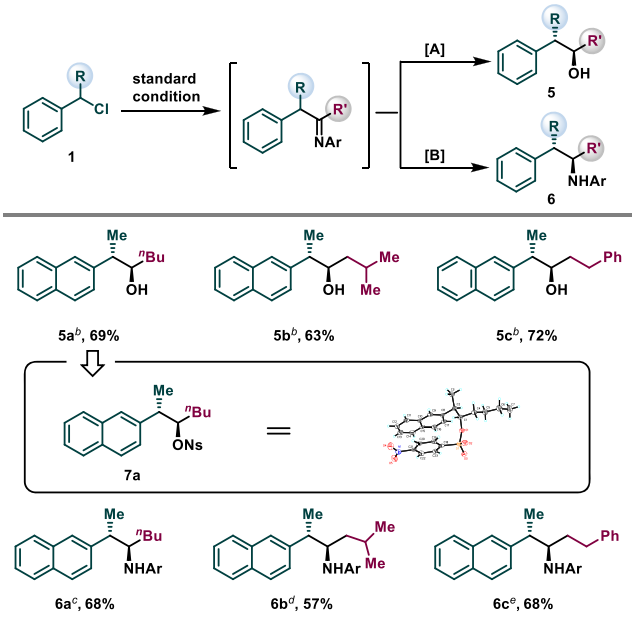
Considering the importance of phenethylamine derivatives in the field of pharmaceutical chemistry, we further examined the substrate scope of aromatic isocyanide (Table 4). It was found that when various alkyl groups such as methyl, isopropyl, *n*-butyl, and benzyl were introduced to the *ortho*-position of aromatic rings, the corresponding phenethylamine derivatives could be obtained with satisfactory yield and dr (**6aa**, **6ab**, **6ac**, **6ad**, **6ae**). Encouragingly, the chloride functionality on the isocyanide moiety could also be tolerated under this Pd-catalyzed imidoylative reaction, affording the amine **6af** with high diastereoselectivity. Notably, employing naphthyl isocyanide can also obtain imine intermediate and achieve

Table 3. Substrate Scope of Benzyl Chlorides[a]



[a]Reaction conditions: **1** (1.0 equiv), **2e** (1.5 equiv), **3** (1.5 equiv), Pd_2dba_3 (2 mol %), DMF, 60–100 °C, 6–12 h. The reaction was quenched with 1 N HCl and stirred at 25 °C for 0.25 h.

Scheme 2. Derivatization of Imidoylative Reaction[a]



[a]Reaction conditions: **1** (1.0 equiv), 2-ethylphenyl isocyanide (1.5 equiv), R′ZnCl (1.5 equiv), Pd_2dba_3 (0.02 equiv), DMF, 60 °C, 2 h. Conditions A: 1 N HCl, 0.25 h, then $LiAlH_4$ (2.0 equiv), THF, −78 to +25 °C, 4–12 h; Conditions B: aq NH_4Cl, then $LiAlH_4$ (5.0 equiv), THF, −78 to +25 °C, 12 h. [b]dr >20:1. [c]dr = 11:1. [d]dr = 5:1. [e]dr = 10:1.

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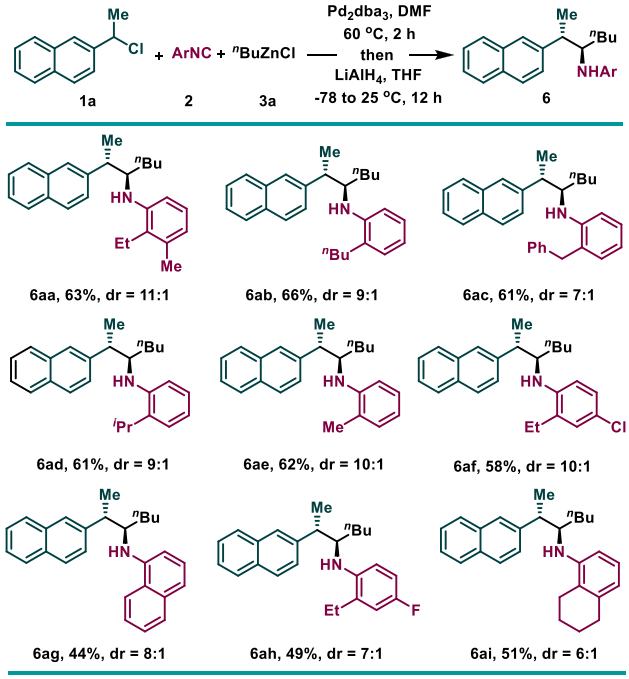
Table 4. Substrate Scope of Diastereoselective Amination[a]

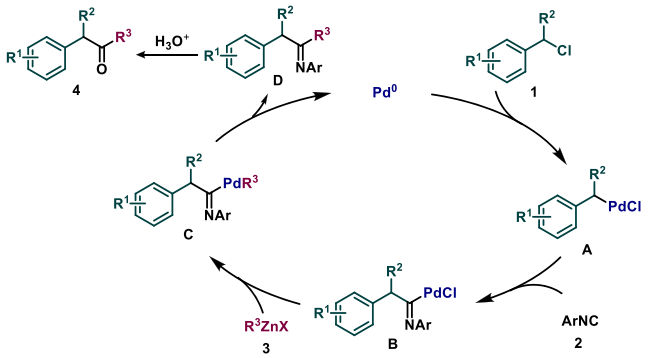


[a]Reaction conditions: **1a** (1.0 equiv), **2** (1.5 equiv), **3a** (1.5 equiv), Pd_2dba_3 (0.02 equiv), DMF, 60 °C, 2 h, aq NH_4Cl, then $LiAlH_4$ (5.0 equiv), THF, −78 to +25 °C, 12 h.

subsequent diastereoselective reduction but with lower yield (**6ag**). Utilizing phenyl isocyanide with electron-withdrawing substituents decreases both the yield and dr of the phenethylamine (**6ah**). The product can also be obtained in good yield by using tetrahydronaphthalene isocyanide (**6ai**).

A plausible reaction mechanism is proposed in Scheme 3: the reaction is initiated by oxidative addition of secondary benzyl chloride **1** with the palladium(0) to generate the benzylic palladium(II) intermediate **A**. The selective monomigratory insertion of sterically bulky aryl isocyanide provides benzyl imidoylpalladium intermediate **B**, which undergoes transmetalation with Negishi reagents and subsequent reductive elimination to produce the imine intermediate **D**. The desired phenylacetone **4** could be obtained via the acidic hydrolysis of the imine intermediate **D**.

Scheme 3. Proposed Reaction Mechanism



In summary, we have demonstrated a Pd-catalyzed imidoylative Negishi coupling with secondary benzyl chlorides. Harnessing of sterically bulky aryl isocyanides as the imine source allows the facile synthesis of α-substituted of phenylacetones under mild acidic hydrolysis. The protocol demonstrates a broad substrate scope and functional group tolerance and enables a variety of carbon nucleophiles including sp^3, sp^2, sp, and heteroaryl zinc reagents to be successfully incorporated. Moreover, the highly diastereoselective reductive amination of this imidoylative process enables the expedient construction of phenethylamine derivatives with high atom economy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02515.

Experimental procedures, X-ray crystallographic analysis, and NMR spectra (PDF)

Accession Codes

CCDC 1974859 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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