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Nickel-Catalyzed Formal Aminocarbonylation of Secondary Benzyl Chlorides with Isocyanides

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01284 Read Online

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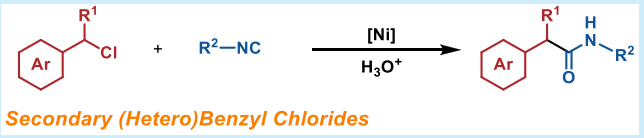
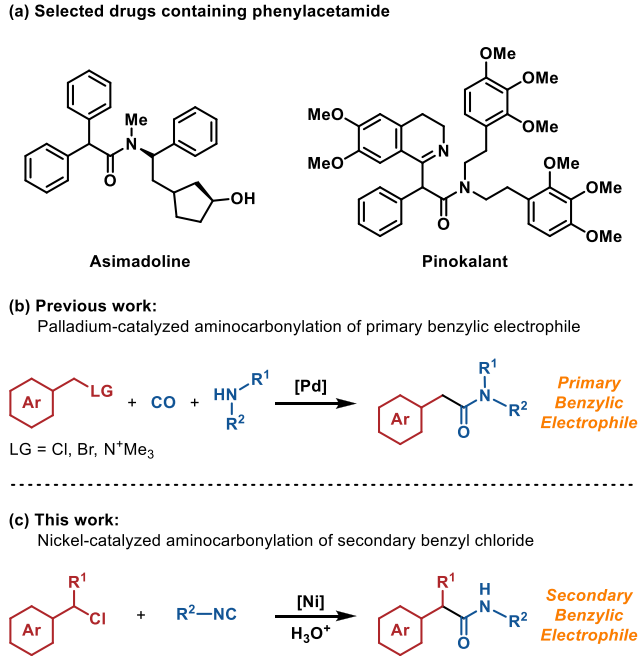
ABSTRACT: Phenylacetamides represent versatile feedstocks in synthetic chemistry, widely existing in drug molecules and natural products. Herein, we disclose a nickel-catalyzed formal aminocarbonylation of secondary benzyl chlorides with isocyanides yielding α-substituted phenylacetamide with steric hindrance, which is synthetically challenging via palladium-catalyzed aminocarbonylation. The reaction features wide functional group tolerance under mild conditions, highlighted by the tolerance of various aromatic halide (−Cl, −Br, −I) and heteroaromatic rings (pyridine and pyrazine).



Phenylacetamide is a quintessential functional group in organic chemistry and also plays a versatile role as scaffolds in drugs, natural products, and bulk chemicals (Scheme 1a).[1] Owing to their ubiquitous nature, chemists are still exploring novel strategies to synthesize phenylacetamides, especially the method for the α-position-substituted phenylacetamide with restricted steric hindrance. Among them, the transition-metal-catalyzed aminocarbonylation of easily accessible benzyl electrophiles represents a feasible and effective synthetic approach to synthesize the phenylacetamide derivatives. Since the pioneering work by Heck in 1974, palladium-catalyzed carbonylation with various electrophiles and CO gas as a C1 building block has become the standard procedure for syntheses of carbonyl compounds (ketone, ester, amide, etc.).[2] Not surprisingly, the access to phenylacetamide via palladium-catalyzed aminocarbonylation of benzylic electrophiles has also received much attention (Scheme 1b).[3] However, the scope of benzylic halides[3a−c] and benzylic ammonium salts[3d] of the reported three-component aminocarbonylation reaction limited on the use of the primary ones, most likely due to the undesired β-H elimination of benzyl palladium intermediate via oxidative addition. Recently, Pd-catalyzed oxidative aminocarbonylation with benzylic C−H activation under elevated CO atmosphere has emerged as an appealing strategy.[4] Nevertheless, the bulky toluene and ethylbenzene are the only two substrates which could capable of selective formation of benzylic palladium intermediate.

More recently, earth-abundant nickel-catalyzed cross-coupling of benzylic electrophiles, including secondary benzylic electrophile, has emerged as a robust platform for benzyl-substituted compounds synthesis.[5−7] Among these, nickel-catalyzed carbonylation of benzylic electrophiles is less developed with only a few research groups reporting the synthesis of benzylic ketones via the insertion of CO.[8] To the best of our knowledge, the facile synthesis of phenylacetamide via nickel-catalyzed aminocarbonylation of benzylic electrophiles remains elusive.

Scheme 1. Overview of Aminocarbonylation of Benzylic Electrophile



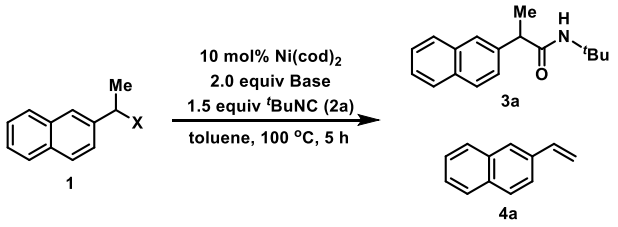
Received: April 12, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01284
Org. Lett. XXXX, XXX, XXX−XXX

Isocyanides as an efficient CO surrogate and C1 synthon are frequently employed as a carbonyl source in transition metal catalyzed carbonylations and heterocycle synthesis.[9] Pioneered by Saegusa and Zhu,[10] Yang and co-workers reported an elegant Pd-catalyzed migratory insertion of α-halo phosphonates with isocyanides to provide the *C*-phosphonoketenimines, which could undergo an additional hydrolysis to generate the corresponding amides, while all the secondary benzyl chlorides do not possess the β-hydrogen atom adjacent to the benzylic positions.[11] We have recently achieve the nickel-catalyzed regioselective allylic carbonylative Negishi reactions with isocyanides to afford the β,γ-unsaturated ketones,[12] and the aminocarbonylation to access alkyl amides leveraging isocyanide as both a carbonyl and amine source, whereas the secondary electrophiles limits on the relative and less stable alkyl iodides.[13] Thereby, we envisaged implementing isocyanide to achieve nickel-catalyzed aminocarbonylation of secondary benzylic electrophiles to tackle the challenge aforementioned for palladium catalysis. Herein, we report an efficient aminocarbonylation employing readily available secondary benzyl chloride as the feedstocks under nickel-catalyzed conditions to afford a series of hindered α-substituted phenylacetamides, exhibiting broad functional group tolerance under mild conditions (Scheme 1c).

We initiated the nickel-catalyzed aminocarbonylation using 2-(1-bromoethyl)naphthalene as the starting material and *tert*-butyl isocyanide as the carbonyl and amine source; the desired aminocarbonylative product *N*-(*tert*-butyl)-2-(naphthalen-2-yl)propenamide **3a** was obtained in 37% corrected GC yield, as no other detective side products was observed (Scheme 2, entry 1). The lack of mass balance revealed that the benzylic bromide electrophiles underwent the significant decomposition. Thus, we selected less reactive 2-(1-chloroethyl)-naphthalene **1a** as the benzylic electrophile, and the reaction efficiency greatly improved and the product **3a** was obtained in 73% GC yield (Scheme 2, entry 2). Investigation of the activate oxygen-containing leaving groups, including −OPiv, −OBoc, and −OTs, did not provide any desired amide **3a** (Scheme 2, entries 3−5). With the determination of the leaving group, we conducted the base screening, it was found that the type of base affected the formation of the elimination side products. When NaO^{t}Bu was employed as the base, the amide **3a** could be produced in 86% GC yield without formation of alkene **4a**, and the isolated yield was 77% (Scheme 2, entry 6). When stronger base KO^{t}Bu was utilized, the GC yield of amide **3a** dramatically dropped to 14% as well as 15% side product **4a** (Scheme 2, entry 7). Minimal product could be observed with treatment of LiO^{t}Bu as base (Scheme 2, entry 8). The examination of other common inorganic bases (Na_2CO_3, K_3PO_4, NaOEt) was also detrimental (Scheme 2, entries 9−11).

Scheme 2. Optimization of the Ni-Catalyzed Aminocarbonylation of 1a with ^{t}BuNC[a]



Entry	X	Base	3a [%][b]	4a [%][b]
1	Br	NaOMe	37	-
2	Cl	NaOMe	73	-
3	OPiv	NaOMe	-	-
4	OBoc	NaOMe	-	-
5	OTs	NaOMe	-	-
6	Cl	NaO^{t}Bu	86 (77)[c]	-
7	Cl	KO^{t}Bu	14	15
8	Cl	LiO^{t}Bu	4	32
9	Cl	Na_2CO_3	-	34
10	Cl	K_3PO_4	24	28
11	Cl	NaOEt	-	18

[a]Reaction conditions: **1** (0.1 mmol), *tert*-butyl isocyanide **2a** (0.15 mmol), Ni(cod)$_2$ (0.01 mmol), NaO^{t}Bu (0.2 mmol), toluene (1.0 mL), at 100 °C, 5 h. Then 1 M HCl (1.0 mL), rt, 5 min. [b]Corrected GC yield with dodecane as an internal standard. [c]Isolated yield.

With the optimized conditions in hand, the substrate scope of the nickel-catalyzed aminocarbonylation of secondary benzyl chlorides with isocyanides was examined (Scheme 3). It was found that various naphthyl chloroalkanes were well tolerated under the optimized conditions; when the ethyl group was incorporated, the corresponding amide **3b** was isolated in 84% yield. Gratefully, when the cyclohexyl group was introduced, the desired product **3c** could still be obtained as moderate yield. It was well known that the naphthalene functionality would significantly increase the aromaticity of the benzyl electrophiles. When the commercially available (1-chloroethyl)benzene **1d** was employed as the benzylic electrophile, the amide **3d** was still isolated with 80% yield, demonstrating that this protocol did not rely on the naphthalene substitution effect. The isopropyl-substituted benzyl chloride **1e** also worked under the standard conditions, although with moderate reaction efficiency (52%) likely due to the increased steric hindrance. This ligandless Ni-catalyzed amionacarbonylation protocol allowed the various aromatic halide substitutions (−Cl, −Br, −I) which were suitable and inert to the low-valent nickel species, especially for iodide substitution (**3h**) which would be extremely challenging for palladium catalysis, demonstrating the merits for this synthetic methodology, and the tolerance of activate aromatic halide allows for the various further functionalizations. The nitrogen-containing heteroarenes are among the most significant structural backbones of pharmaceuticals.[14] Furthermore, this catalytic system tolerated secondary heterobenzyl chloride, including several of the nitrogen-containing six-membered heteroarenes, such as pyridines (**3i**−**3k**) and pyrazines (**3l**), the corresponding secondary amide could be smoothly obtained in 58−71% isolated yield. Notably, the substitution on the pyridines has minimal effect on this carbonylative reaction, the *ortho*-, *meta*-, and *para*-substituted 1-chloroethylpyridines all worked. The tertiary amide could be traditionally synthesized via the Buchwald−Hartwig α-arylation of the enolized amides with the heteroarmoatic halide.[15] However, the secondary amide was extremely challenging for direct deprotonation for formation of enolate.[15b] Hence, the success of the heterobenzylic electrophile reveals its potential application in pharmaceuticals. In addition, analogues of (chloromethylene)-dibenzene could also be converted into amides (**3m**, **3n**, **3o**), respectively, albeit in moderate yield. By changing the isocyanide from ^{t}BuNC to AdNC, amide **3p** was available in 45% yield. When CyNC and 2-ethylphenyl isocyanide were

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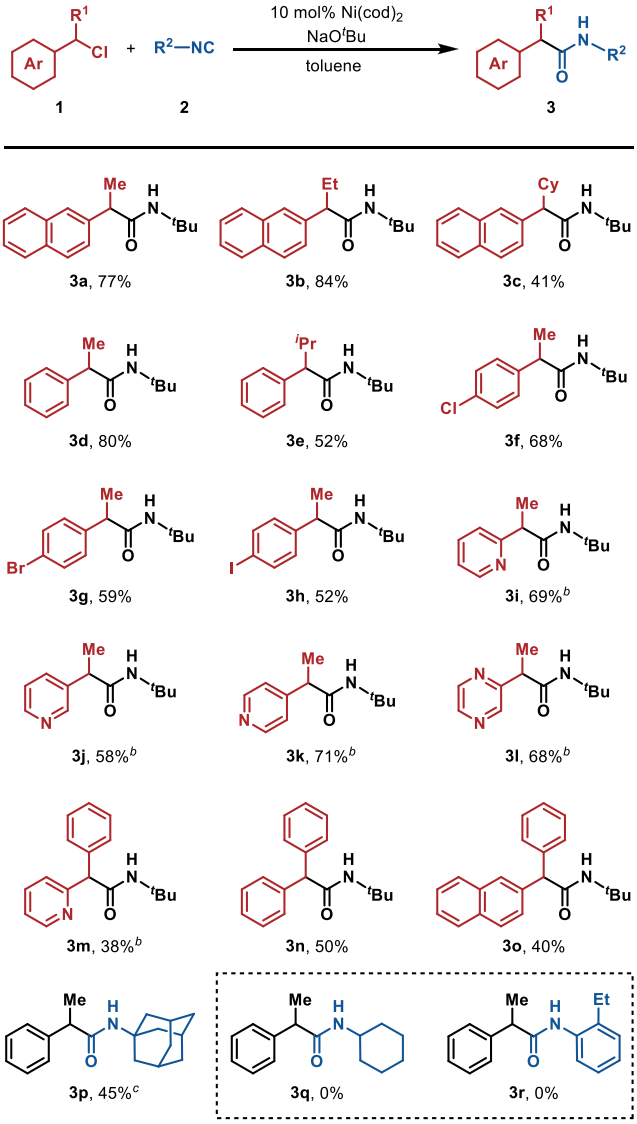
Scheme 3. Scope of Ni-Catalyzed Aminocarbonylation of Secondary Benzyl Chlorides with Isocyanides[a]

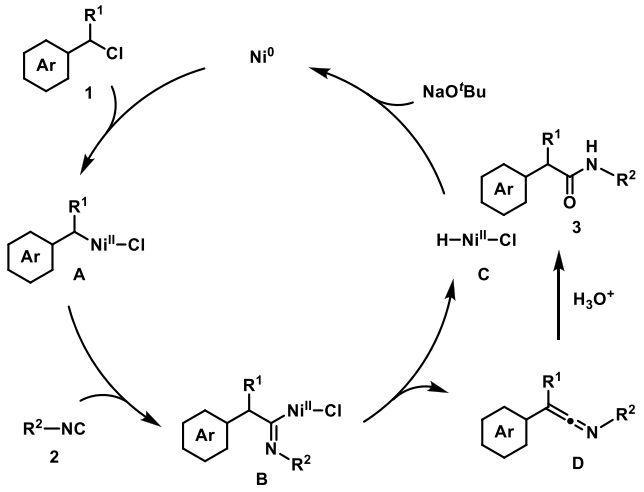


[a]Reaction conditions: secondary benzyl chloride **1** (1.0 equiv), isocyanide **2** (1.1−1.5 equiv), $Ni(cod)_2$ (10 mol %), NaO^tBu (1.0−2.0 equiv), toluene (0.1 M), 80−120 °C. Then 1 M HCl, rt, 5 min. [c]Saturated aq $NaHCO_3$ was added until pH > 7. [d]Three M HCl, rt, 1 h.

employed as the carbonyl and amine source, the desired product (**3q**, **3r**) could not be detected and the starting material largely remained, which revealed that the less bulky isocyanides might serve as ligand to deactivate the nickel catalyst.

On the basis of the Ni-catalyzed benzylation chemistry[6,7] and prior work on aminocarbonylation with isocyanides,[13] a plausible mechanism is proposed in Scheme 4. The Ni(0) species reacts with benzyl chloride **1** via oxidative addition to generate benzylic nickel intermediate **A**. After the selective 1,1-migratory insertion of isocyanide **2**, the imidoyl nickel species **B** is furnished, which further undergoes successive β-hydride elimination to offer the key ketenimine **D** intermediate.[16] Under the weak acidic condition, ketenimine **D** is hydrolyzed to produce the desired amide **3** product. Finally, the reductive elimination of **C** regenerates the Ni(0) species.

Scheme 4. Mechanistic Hypothesis



In conclusion, we have developed a nickel-catalyzed formal aminocarbonylation of secondary benzyl chlorides, capitalizing on the selective insertion of isocyanide. A range of potentially useful phenylacetamides are accessible under mild conditions, allowing the deployment in synthesis of medicinal chemistry and natural products. Further exploration on nickel-catalyzed carbonylation utilizing isocyanide as the carbonyl source is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01284.

Experimental details, NMR spectra (PDF)
FAIR data, including the primary NMR FID files, for compounds **1c**, **1l**, and **3a**−**3p** (ZIP)

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https://dx.doi.org/10.1021/acs.orglett.0c01284
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by NSFC/China (21421004, 21702060), Shanghai Municipal Science and Technology Major Project (Grant No.2018SHZDZX03), the Program of Introducing Talents of Discipline to Universities (B16017), and the Fundamental Research Funds for the Central Universities. The authors thank the Research Center of Analysis and Test of East China University of Science and Technology for the help with NMR analysis.

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(16) The ketenimine intermediate D could be observed with GC−MS; see the details in the Supporting Information.

https://dx.doi.org/10.1021/acs.orglett.0c01284
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