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Three-Component Visible-Light-Induced Palladium-Catalyzed 1,2-Alkyl Carbamoylation/Cyanation of Alkenes

Xiangqing Jia,

Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States

Ziyan Zhang,

Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States

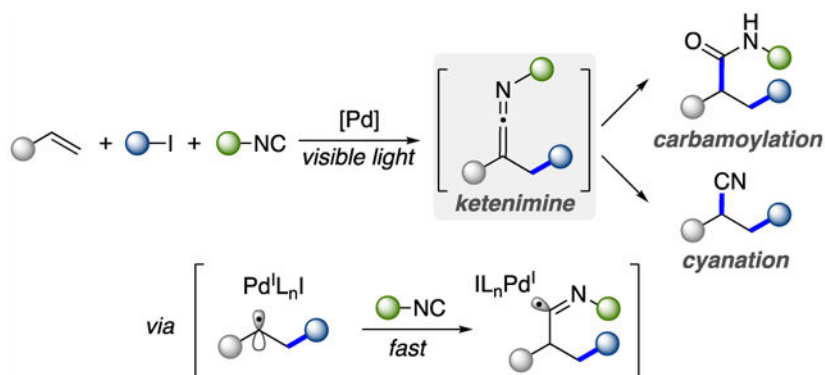
Vladimir Gevorgyan

Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States

Abstract

A mild visible-light-induced Pd-catalyzed one-pot three-component alkyl-carbamoylation and cyanation of alkenes was developed. This general transformation, which proceeds via the in situ formation of a reactive ketenimine intermediate, allows for a rapid construction of a broad range of valuable amides and nitriles from readily available alkenes, alkyl iodides, and isocyanides. An efficient synthesis of tetrazole and amidine via this approach was also demonstrated.

Graphical Abstract



Corresponding Author: Vladimir Gevorgyan – Department of Chemistry and Biochemistry, The University of Texas at Dallas, Richardson, Texas 75080-3021, United States; vlad@utdallas.edu.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.1c04183>.

Experimental procedures, analytical data for all new compounds (PDF)

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Keywords

difunctionalization; isocyanide; radical; palladium; light-induced

The multicomponent 1,2-difunctionalization of alkenes is a valuable synthetic strategy that allows for an efficient construction of complex molecules in a single step from easily accessible and commercially available starting materials (Scheme 1a).¹ Particularly attractive could be the 1,2-alkyl carbamoylation of alkenes, which would enable access to synthetically important amides, the prevalent structural motifs found in pharmaceuticals, biological molecules, and polymeric materials.² Along this line, the two-component intramolecular annulative approach of alkyl-carbamoylation has been reported,³ but the process is substantially limited to carbamoyl-tethered alkenes, furnishing cyclic amides (Scheme 1b). To the best of our knowledge, no general methodology for the overall three-component alkyl carbamoylation has been developed. Herein, we report a one-pot mild visible-light-induced Pd-catalyzed three-component 1,2-alkyl carbamoylation and cyanation of alkenes, which proceeds via the in situ generation of ketenimines **A** (Scheme 1c).

On the basis of the highly reactive nature of ketenimine functionality and its facile subsequent transformations,⁴ we envisioned a strategy for the in situ generation/hydrolysis of ketenimine intermediate to achieve the formal carbamoylation of alkenes. Traditionally, ketenimine can be prepared through cross coupling between isocyanides and carbenes or metal-locarbenes,⁵ α -halophosphonates,⁶ allyl carbonates,⁷ α -haloketones,⁸ and diazo compounds.⁹ Moreover, the synthesis of ketenimines via a radical addition to isocyanides was also demonstrated.¹⁰

Recently, visible-light-induced palladium catalysis has become an emerging field of study.¹¹ We and others demonstrated that hybrid palladium C(sp³)-centered radical species, generated through the cleavage of C–X (X = halide, CO₂NPhth) bonds in the presence of a photoexcited Pd(0) complex, enable desaturation,¹² alkyl Heck,¹³ and other transformations.¹⁴

Inspired by the synthesis of ketenimines via free radical additions to isocyanides¹⁰ and a new mild and general visible-light-induced method for generation of radical species,¹¹ we hypothesized an approach to ketenimines via an addition of hybrid palladium C(sp³)-centered radical species to isocyanides.

The initial two-component proof-of-concept experiments were performed between unactivated alkyl iodides and *tert*-butyl isocyanide (*t*-BuNC), under our standard palladium(II) acetate/Xantphos system.^{13a,c,d} The following acidic hydrolysis of the in situ generated ketenimines (Scheme 2) was expected to provide the alkyl carbamoylation product. To our delight, the intended amide products **4a–4c** were obtained in good yields, thus supporting the feasibility of the proposed strategy.

Encouraged by these promising results and the previously developed alkyl Heck-type reactions,^{13a,c,d,j} we turned our attention to more desirable three-component couplings of alkenes, alkyl iodides, and isocyanides. We hypothesized that the radical intermediate **B**

formed via an addition of hybrid alkyl Pd radical species across an alkene would undergo a fast trapping with isocyanide, thus outcompeting an undesired premature β -H elimination, to produce the imidoyl radical **C** (Scheme 1c). The anticipated ketenimine intermediate would be delivered upon a β -H elimination from the latter.

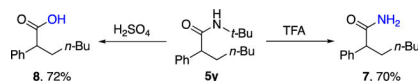
To this end, we examined a model reaction between styrene **1a**, (trimethylsilyl)methyl iodide **2a**, and *t*-BuNC **3a**, followed by a subsequent acidic hydrolysis of the in situ forming ketenimine (Table 1). We realized that the success of this three-component coupling reaction hinges on suppressing an undesired premature Heck reaction leading to product **6** and a direct trapping of an alkyl radical with isocyanide to give **4d**. After an extensive screening of reaction parameters,¹⁵ we found conditions that allowed for obtaining the desired alkyl-carbamoylation product **5a** in 65% yield, using Pd G3 as the precatalyst, Xantphos as the ligand, pivalic acid as an additive, and benzene/1,4-dioxane as the cosolvent (Table 1, entry 1). The reaction was less efficient when Pd(OAc)₂ was used (entry 2). Pivalic acid further promoted the reaction efficiency, which was consistent with the reported literature (entries 1 & 3).¹⁶ Control experiments proved the importance of Pd catalyst and Xantphos (entry 3) and light (entries 4 & 5) for this transformation.

With the optimized conditions in hand, the scope of alkenes was examined first (Table 2). A diverse array of styrenes, possessing electron-withdrawing and -donating groups at the *para*- or *meta*-positions, smoothly reacted with alkyl iodide and isocyanide to give the desired products **5a–5s** in moderate yields. Notably, 2-vinylnaphthalene and vinyl heteroarenes were fully compatible with this protocol, affording products **5t–5w**. We were pleased to find that this reaction can work in a more complex setting, producing estrone derivative **5x**, thus highlighting the broad applicability of this multicomponent coupling protocol.

Next, the scope of alkyl iodides was evaluated. In general, primary and secondary alkyl iodides proceeded smoothly to give products **5y–5z** and **5aa–5ah** in moderate to good yields. Importantly, primary alkyl iodides bearing α -germyl and γ -chloride functionalities were also amenable to this process. Moreover, saturated heterocyclic derivatives, such as tetrahydropyran (**5ai**) and piperidine (**5aj**) as well as (–)-menthol-derivative (**5ak**) can also be employed. Among isocyanides, all tested tertiary isocyanides, such as 1-adamantyl and 1,1,3,3-tetramethylbutyl isocyanides, readily participated in this reaction, furnishing diverse alkylated amides **5al** and **5am**. Finally, it was shown that the synthesized *N*-*tert*-butyl amide **5y** can routinely be transformed into unprotected amide¹⁷ **7** and carboxylic acid¹⁸ **8** in respectable yields (eq 1).

Motivated by the successfully developed alkyl-carbamoylation of alkenes, we sought to expand this protocol to an alkyl cyanation, which would provide one-pot access to organonitriles, versatile synthetic synthons,¹⁹ and common functional groups found in natural products and bioactive molecules.²⁰ Thus, we tested the cleavage of the N–C bond in the formed ketenimine by BF₃·Et₂O (Table 3).^{9b} It was found that this protocol allows for the synthesis of a range of benzyl nitriles that possess primary and secondary alkyl substituents at a side chain (**9a–9e**), differently substituted styrenes (**9f–9h**), and *m*-vinyl pyridine (**9i**).

It was also shown that other nitrogen-containing compounds, such as unprotected benzyl tetrazole **10** and amidine **11**, can easily be synthesized by combining this three-component coupling strategy coupled with a hydroazidation/[3 + 2] cycloaddition with tetramethylsuccinonitrile (TMSN₃) (Scheme 3, eq 1) or a nucleophilic addition of aniline (Scheme 3, eq 2).



(1)

Next, a series of mechanistic tests were performed. The radical nature of this transformation was unambiguously confirmed by radical clock and radical trap experiments (Scheme 4). Thus, the reaction of styrene **1a** and *t*-BuNC with alkyl iodide **2o**, possessing a cyclopropyl substituent,²¹ produced terminal alkene **12**, as a result of the ring opening of methylenecyclopropyl radical (Scheme 4a). Likewise, the latter, generated from a radical addition onto alkene **1y**, regioselectively rearranged into a benzylic radical, which was trapped by *t*-BuNC, producing a stereoisomeric mixture of trisubstituted alkene **13** in 43% yield. Moreover, the employment of alkenyl halide **2p** led to the product **5ab**, possessing a cyclic substituent, which resulted from an initial 5-*exo-trig* radical cyclization (Scheme 4b). Finally, the reaction in the presence of radical scavengers such as TEMPO, led to trapping product **15** in 61% yield (Scheme 4c).

On the basis of the above mechanistic studies and literature reports,^{13a,c,j} the following plausible mechanism was proposed (Scheme 5). First, the hybrid alkyl Pd(I)-radical species **D** is generated from the single electron transfer (SET) of photoexcited Pd(0) complex to alkyl iodide. Next, a radical addition to alkene takes place, leading to the hybrid benzylic radical **B**, which is rapidly trapped by isocyanide to give imidoyl radical **C**. A subsequent β -H elimination from the latter furnishes the reactive ketenimine intermediate **A** with the concomitant regeneration of Pd catalyst. With a quench, the ketenimine **A** under acidic conditions is hydrolyzed into amide **5** or, upon treatment with Lewis acid, is transformed into nitrile **9**.

In conclusion, we developed a visible-light-induced Pd-catalyzed protocol for three-component 1,2-alkyl functionalization of alkenes with alkyl iodides and isocyanides. It features the formation of a reactive ketenimine intermediate, which under one-pot conditions is transformed into various useful synthetic synthons, such as amides, nitriles, tetrazoles, and amidines. This mild multicomponent coupling reaction, which utilizes easily accessible reaction partners, exhibits a wide functional group tolerance. It is anticipated that this mild visible-light-induced approach will find applications in synthesis and will stimulate the development of new 1,2-difunctionalization methods.

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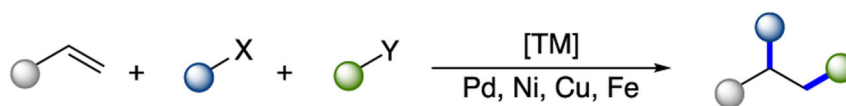
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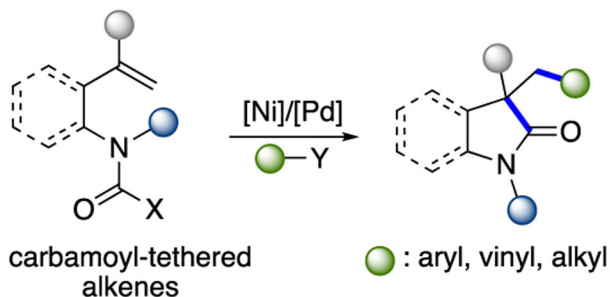
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a. Three-component 1,2-difunctionalization of alkenes

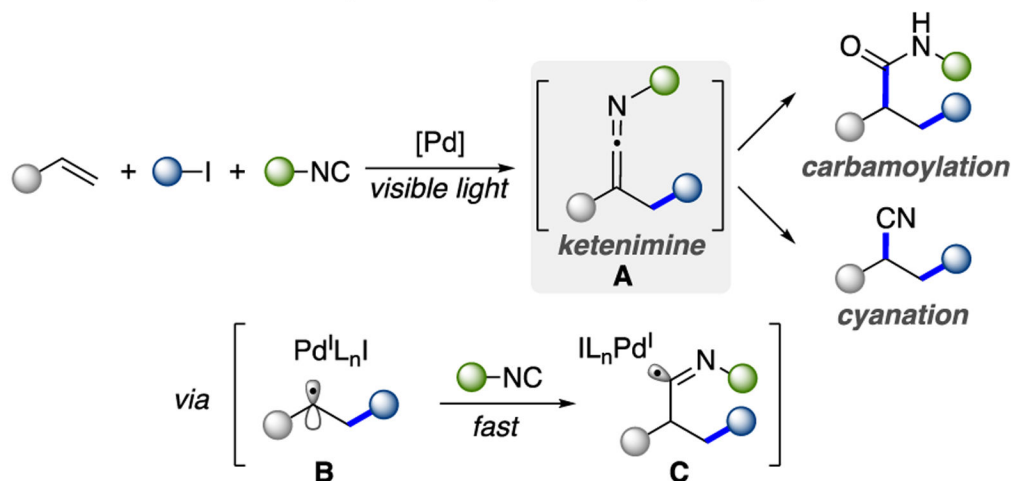


● or ● : (fluoro)alkyl, vinyl, alkynyl, aryl, acyl, cyano, amino

b. Intramolecular annulative carbocarbonylation of alkenes



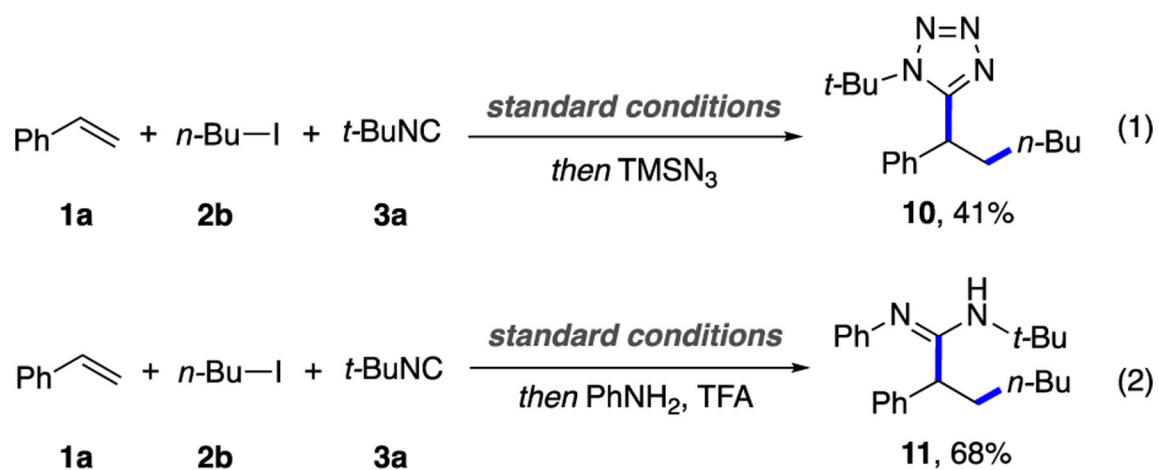
c. This work: three-component alkyl carbamoylation/cyanation of alkenes



Scheme 1.

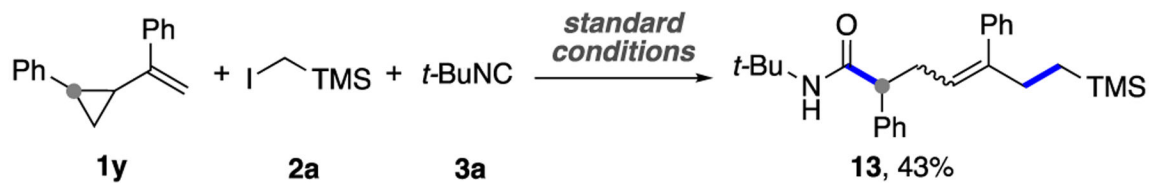
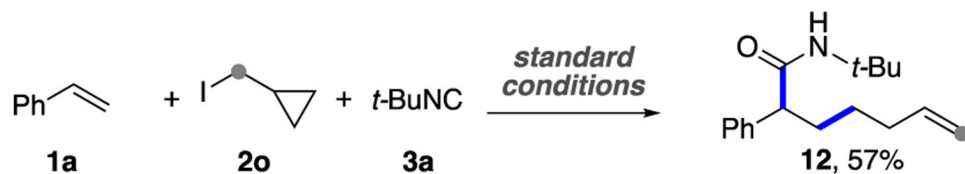
1,2-Difunctionalization of Alkenes^a

^a(a) Three-component 1,2-difunctionalization of alkenes. (b) Intramolecular annulative carbocarbonylation of alkenes. (c) This work: three-component alkyl carbamoylation/cyanation of alkenes.

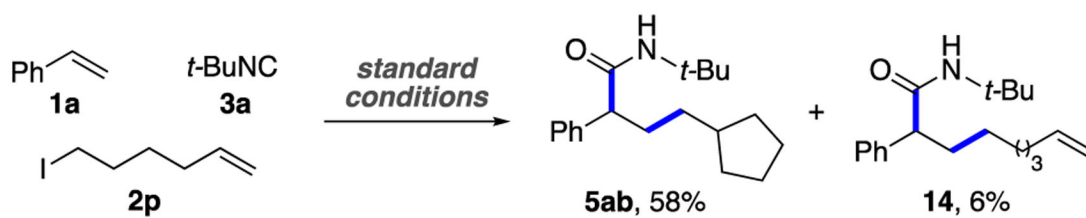


Scheme 3.
Synthesis of Tetrazole and Amidine

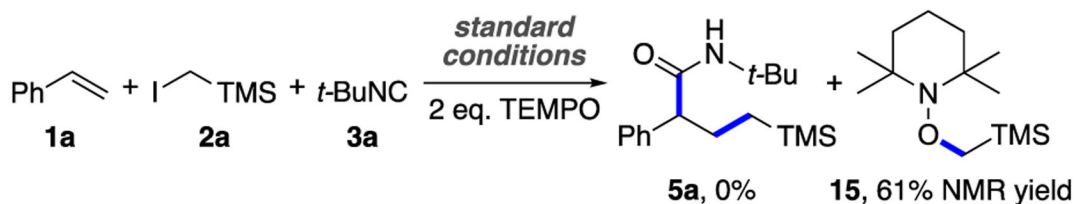
..... **a. Radical rearrangement experiments**



..... **b. Radical cyclization**

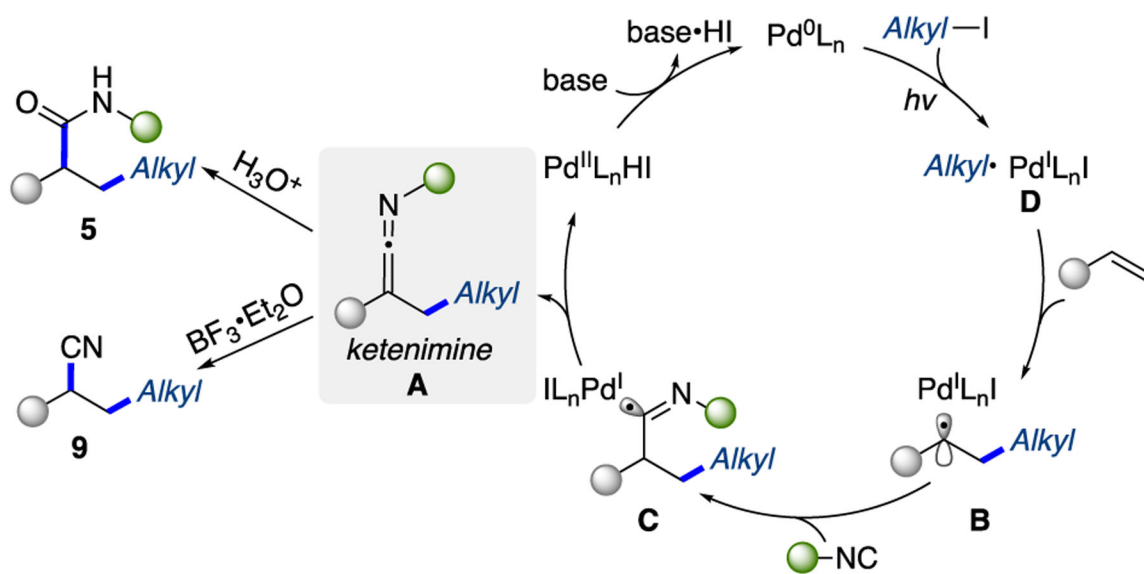


..... **c. Radical trapping experiment**



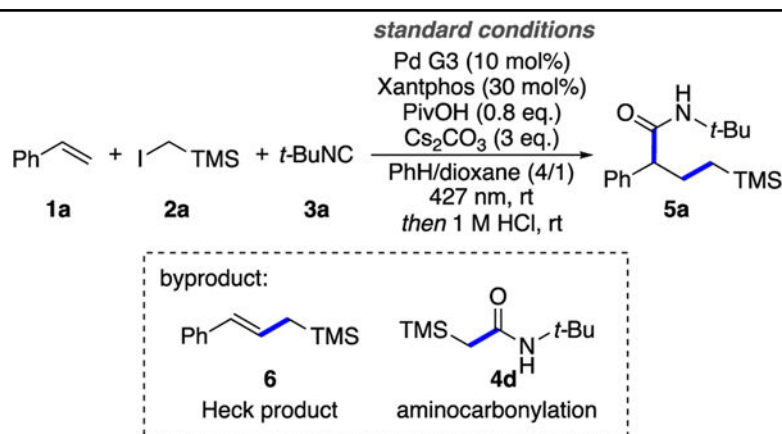
Scheme 4.
Mechanistic Studies^a

^a(a) Radical rearrangement experiments. (b) Radical cyclization. (c) Radical trapping experiment.



Scheme 5.
Proposed Mechanism

Table 1.

Reaction Optimization^a

entry	deviation from standard conditions	5a:6:4d ^b	yield of 5a, %
1	none	90:9:1	65(61 ^c)
2	Pd(OAc) ₂ instead of Pd G3	88:10:2	47
3	without PivOH	88:11:1	40
4	without Pd/Xantphos	0:0:0	0
5	rt, dark	0:0:0	0
6	80 °C, dark	0:0:100	0

^aYields of **1a** (0.1 mmol), **2a** (0.3 mmol), and **3a** (0.2 mmol) were determined by gas GC/MS using pentadecane as an internal standard. Pd G3: [(4,5-bis(diphenylphosphino)-9,9-dimethylxanthene)-2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate.

^bThe ratios were determined by GC/MS.

^c0.3 mmol scale, isolated yield.

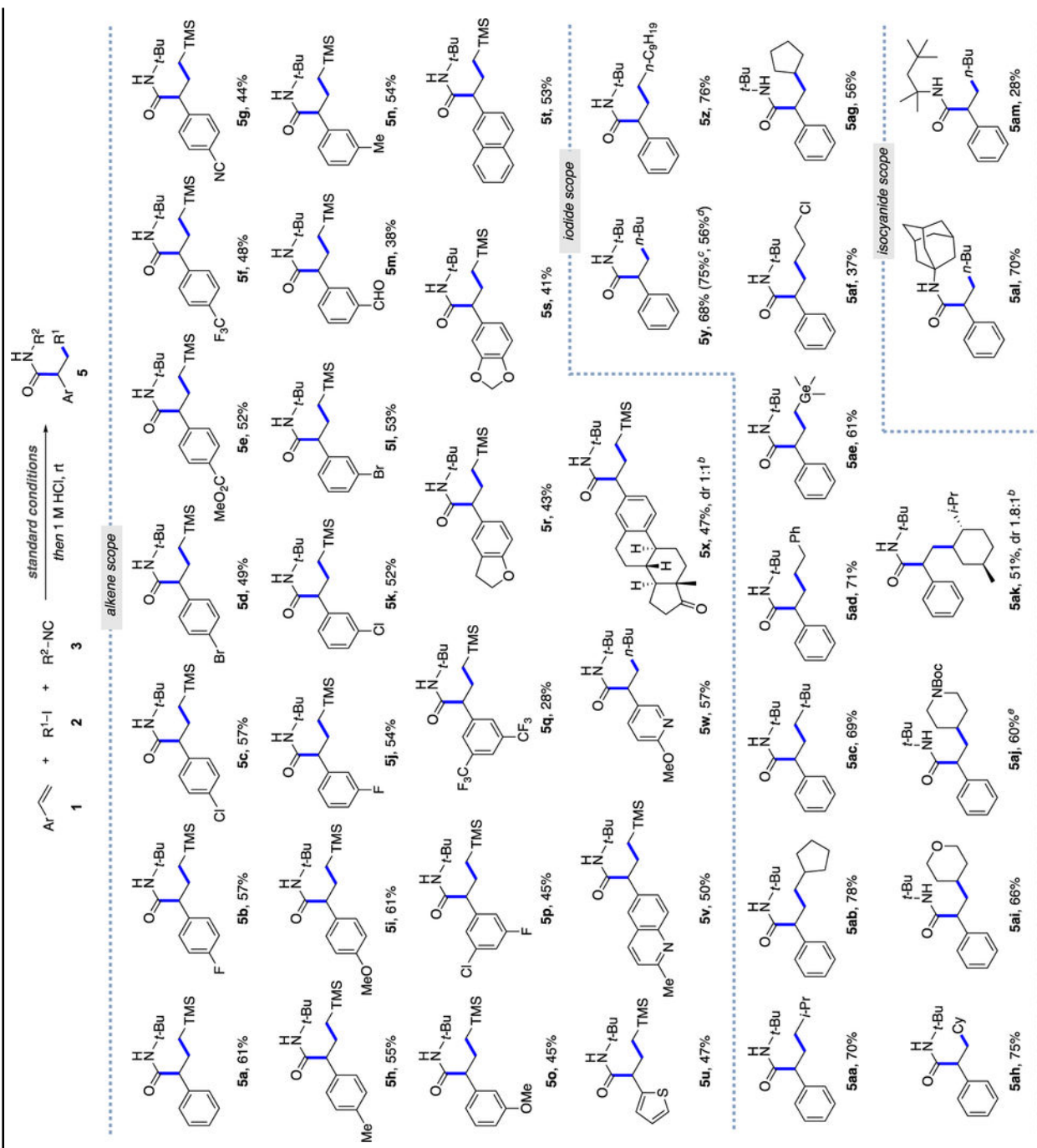
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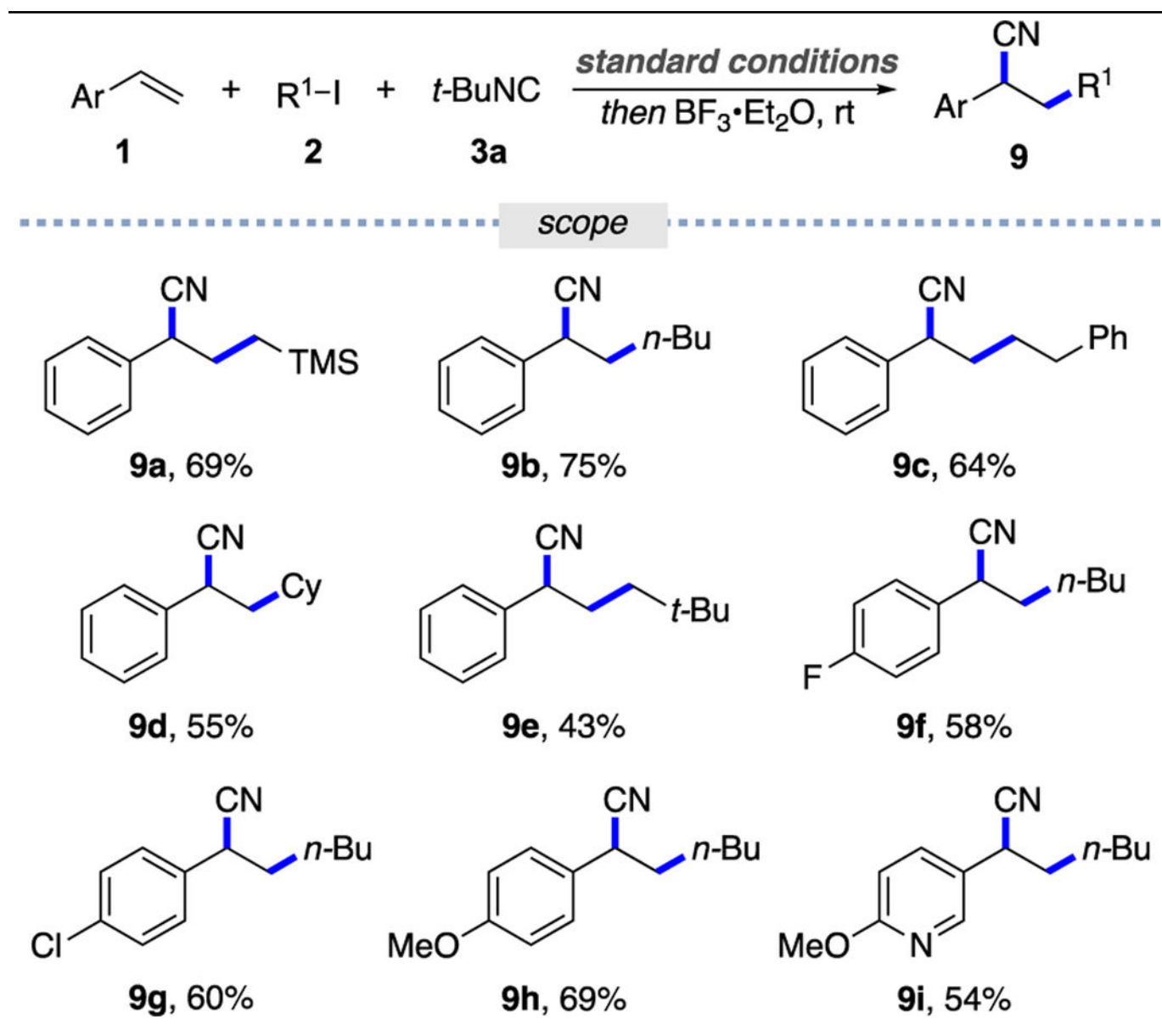
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Table 2.

Alkyl Carbamoylation of Alkenes²

^g0.3 mmol scale; isolated yields. ^hDiastereomeric ratio was determined by ¹H NMR of the crude reaction mixture. ^{c1} mmol scale using 10 mol % Pd G3 and 30 mol % Xantphos. ^{c1} mmol scale using 5 mol % Pd G3 and 15 mol % Xantphos. ^{c0.2} mmol scale.

Table 3.

Alkyl Cyanation of Alkenes^a^a0.3 mmol scale, isolated yields.