Double Ligand-Enabled Ni-Catalyzed C–H Alkenylation of Amines with Alkynes

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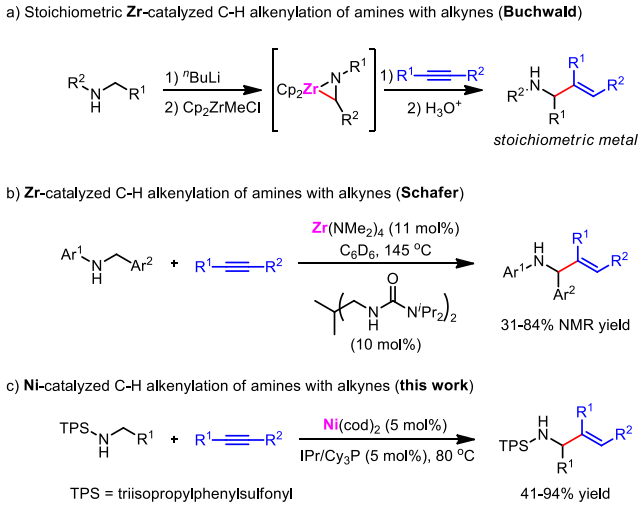
Supporting Information Placeholder

ABSTRACT: A nickel-catalyzed C−H alkenylation of amines with alkynes was developed, providing a series of allylic amines in up to 94% yield. The use of bulky amino protecting group (triisopropylphenylsulfonyl) and double ligands (IPr and PCy_3) proved critical to the reaction efficiency.

Transition metal-catalyzed direct α-C−H functionalization of amines provides rapid access to various functionalized amines that widely exist in bioactive compounds and materials.[1,2] Despite relatively difficult activation of sp^3 C−H bonds,[3] especially ubiquitous secondary sp^3 C−H bonds that are more resistant to transition metal insertion,[4] great progress has been achieved in alkylation,[5–7] arylation,[8] and other functionalization reactions[9] for a broad range of α-secondary sp^3 C−H bonds. Nevertheless, C−H alkenylation of amines with alkynes still remains as a formidable challenge,[10–14] probably owing to the instability of the produced allylic amines, as well as easy coordination of alkynes to metals. Although directing group-enabled Ir-catalyzed reactions allowed C−H alkenylations of amines with alkynes via oxidative addition pathway, these methods was quite sensitive to the steric hindrance of amines, rendering reported reactions compatible with in general less sterically hindered primary amines.[11,12] In order to accommodate a broader range of substrates, another distinctive pathway that underwent through η^2-imine complex was devised. In 1989, Buchwald and co-workers reported the first non-chelated alkenylation of secondary amines with alkynes. They found that zirconocene complex can effectively join two substrates into allylic amines (Scheme 1a),[13] while four steps and a stoichiometric amount of the Zr reagent were required. Since that, much effort has been devoted to improving this reaction,[14] while none of them could unify the four steps in one reaction and could reduce the loading of metals to a catalytic amount. During our submission, Schafer group reported a bis(ureate)-enabled Zr-catalyzed alkenylation reaction for the first time (Scheme 1b).[15] Despite this advance, the Zr-catalyzed system still suffered from harsh conditions (145 °C) and limited scope of amines and alkynes. Herein, we used inexpensive nickel as a catalyst to achieve direct C−H alkenylations of amines with alkynes, providing a series of allylic amines in up to 94% yield (Scheme 1c).[16] The use of bulky N-protecting group and the combination of N-heterocyclic carbene (NHC) and phosphine ligands proved critical to the reaction efficiency, not only leading to relatively mild conditions, but also significantly expanding substrate scope.

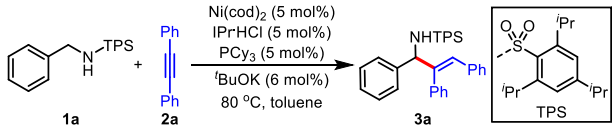
Scheme 1. Transition Metal-Catalyzed α-Alkenylation of Amines with Alkynes



Redox-neutral coupling of alcohols and alkynes elegantly developed by Matsubara[17] and Krische[18] groups provided an efficient pathway for direct α-functionalization of alcohols, while the similar coupling of amines and alkynes remains unsolved. We ascribed the difficulty to the following challenges: (1) strong basicity and nucleophilicity of amines could deactivate transition metals; (2) relatively difficult β-H cleavage of amines and instability of the in situ generated imine intermediates; (3) easy oligomerization of alkynes and facile addition of amines to alkynes. Therefore, we envisioned that the selection of a proper amino protecting group could reduce the basicity of amines, preventing catalyst deactivation and other side reactions. Following this hypothesis, we conducted extensive investigation of N-protecting groups, together with transition metals, ligands, and other reaction parameters. Ultimately, we found that triisopropylsulfonyl (TPS) was the superior protecting group, with which a redox-neutral and atom-economical coupling of secondary amide **1a** with alkyne **2a** was achieved for the first time, providing the corresponding allylic amide **3a** in nearly quantitative yield as determined by ^{1}H NMR (Scheme 2, entry 1). Control experiments showed that any alteration of TPS resulted into significantly diminished yields (entries 2−8). For example, the change of isopropyl groups (TPS) into methyl groups (TMS) gave only 9% yield (entry 2). Common *p*-tolylsulfonyl (Ts) further decreased the yield to only a trace amount (entry 3). The combination of NHC (IPr) and phosphine (PCy_3) ligands also proved critical to the reaction (entries 9−17). The absence of IPr·HCl completely inhibited the reaction (entry 9), whereas the reaction still gave **3a** in 14% yield without the addi-

tion of PCy_3 (entry 13), demonstrating the vital role of IPr and the promoting effect of PCy_3. In fact, a yield of 68% was detected with IPr alone at an elevated temperature (110 °C) but with poor reproducibility (see Supporting Information for details). Other carbenes and phosphines were less effective (entries 10−12 and 14−17). The absence of $Ni(cod)_2$ or replacement of $Ni(cod)_2$ by other nickel precatalysts gave almost no product (entries 18−20).

Scheme 2. Reaction Optimization[a]



1a 2a 3a

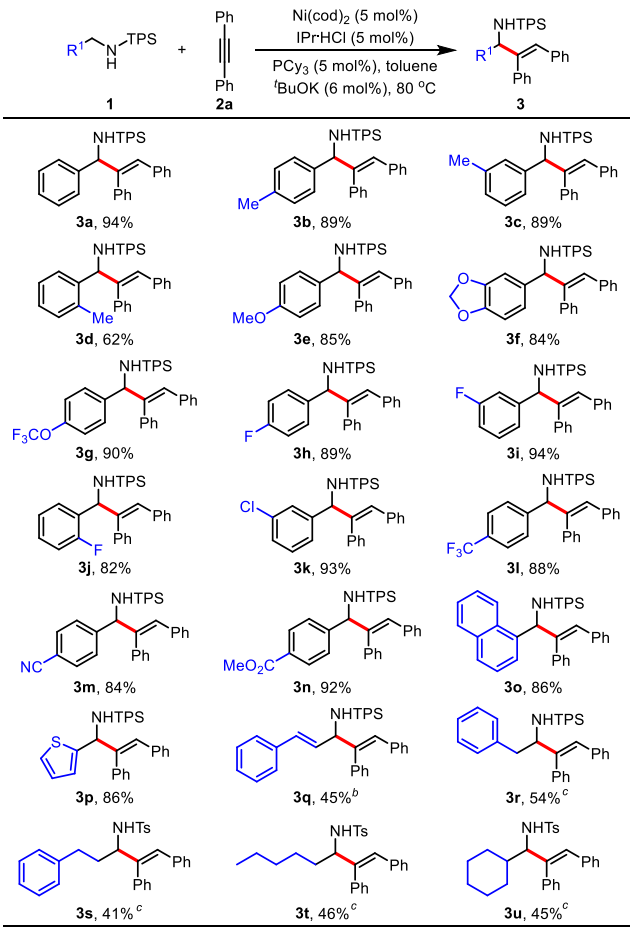
entry	deviation from the standard conditions		yield of **3a** (%)
1	***no deviation***		99
2	TPS replaced by	2,4,6-Me_3-$C_6H_2SO_2$ (TMS)	9
3		*p*-Me-$C_6H_4SO_2$ (Ts)	trace
4		*p*-CF_3-$C_6H_4SO_2$	7
5		*p*-MeO-$C_6H_4SO_2$	trace
6		CH_3-SO_2 (Ms)	7
7		CF_3-SO_2 (Tf)	0
8		^{t}Bu-SO_2 (Bs)	0
9	IPr·HCl replaced by	0	0
10		IPr^{Me}·HCl	76
11		SIPr·HCl	20
12		IMes·HCl	34
13	PCy_3 replaced by	0	14
14		Ph_3P	51
15		$^tBu_3P$	17
16		$^nBu_3P$	11
17		dppe	17
18	$Ni(cod)_2$ replaced by	0	0
19		$NiCl_2$·diglyme	0
20		$NiCl_2$·diglyme with Mn	0

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.22 mmol), toluene (2.0 mL) under N_2 for 1 h; yield was determined by ^{1}H NMR using $Cl_2CHCHCl_2$ as the internal standard.

Under the optimized conditions, various *N*-TPS amides were then examined (Scheme 3). Results showed that the reaction tolerated a broad range of functional groups on the phenyl ring of *N*-benzyl amides, including simple alkyl (Me, **3b**–**3d**), electron-donating groups (alkoxy, **3e**, and **3f**), and electron-withdrawing groups (OCF_3, F, Cl, CF_3, CN, and CO_2Me, **3g**–**3n**), providing the corresponding allylic amines in 62−94% yields. In addition, the position of substituents did not have a strong influence on the reaction yield (**3b**–**3d** and **3h**–**3j**). Notably, both 1-naphthyl (**3o**) and heteroaryl (**3p**) instead of the phenyl of **1a** also worked well, affording both 86% yields. When the phenyl was replaced by the alkenyl, a decreased yield was obtained (45%, **3q**) in the presence of 10 mol% of the catalyst at 110 °C. Notably, various *N*-alkylamides were still compatible with the reaction (**3r**–**3u**, 41−54% yields), but requiring harsher conditions (130 °C and 20 mol% catalyst) and a Ts protecting group.

Next, a broad range of alkynes were investigated under the standard conditions (Scheme 4). Various diaryl alkynes bearing alkyls (**4a**–**4d**) and electron-donating groups (**4e** and **4f**) on the phenyl rings were well compatible with the current reaction, providing the corresponding products in 79−92% yields. Notably, 2-tolylalkyne gave a 1:1 mixture of *E*:Z isomers (**4c**), probably because the significant steric hindrance on the aryl ring forced the alkene to isomerize. In contrast, electron-withdrawing groups such as OCF_3 (**4g**), F (**4h**), and CF_3 (**4i**) on the phenyl ring led to slightly lower yields even at a higher temperature. In addition, both dialkyl alkynes (**4j** and **4k**) and alkyl aryl alkynes (**4l**–**4p**) were well tolerated, providing both good yields and good to excellent regioselectivities. For example, 1-phenylpropyne gave 8.1:1 regioisomeric ratio (**4l**), and the change of methyl to ethyl significantly increased the ratio to 20:1 (**4m**). Bulkier alkyls (**4n**–**4p**) or silyl (**4q**) led to a single regioisomer. However, non-symmetrical dialkyl alkyne (**4r**) cannot afford good regioselectivity probably owing to low differentiation between isopropyl and methyl groups.

Scheme 3. Scope of Amides[a]



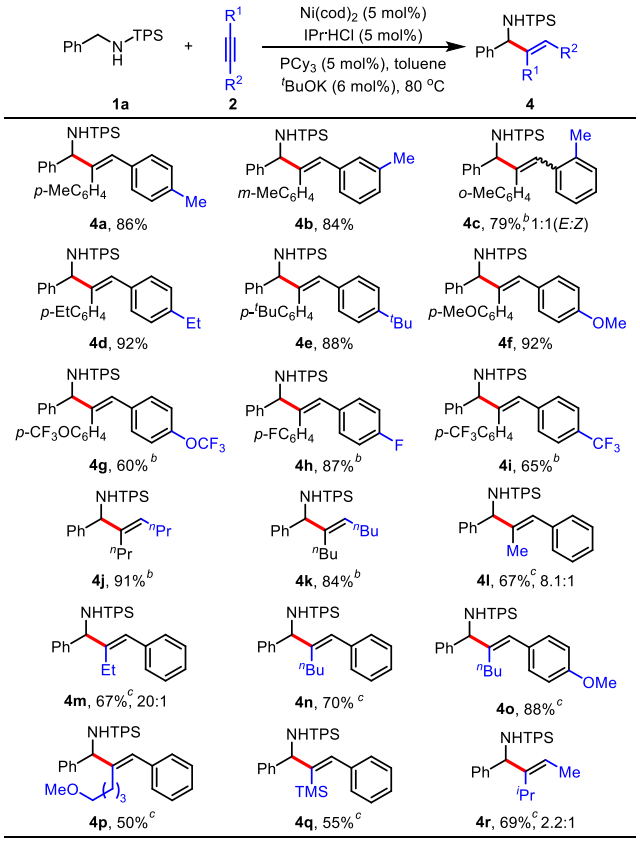
[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.22 mmol), toluene (2.0 mL) under N_2 for 1−12 h; yield of isolated products. [b]$Ni(cod)_2$ (10 mol%), IPr·HCl (10 mol%), PCy_3 (10 mol%), ^{t}BuOK (12 mol%) at 110 °C. [c]$Ni(cod)_2$ (20 mol%), IMes·HCl (20 mol%), PCy_3 (20 mol%), ^{t}BuOK (22 mol%) at 130 °C.

To demonstrate the utility of the reaction, a gram-scale reaction of the model substrates under the standard conditions was conducted, affording the desired product **3a** in 88% yield (Scheme 5a). In addition, the formed allylic amine **3a** can act as a versatile synthetic intermediate to participate into various transformations. For example, hydrogenation followed by deprotection and reprotection provided compound **5** in 68% yield. Simple oxidation of **3a** resulted into *α*-amino ketone **6** in 90% yield.

To gain insights into the reaction mechanism, some mechanistic experiments were carried out. Deuterium labeling experiments revealed that 100% allylic deuterium and 94% olefinic deuterium existed in product ***d*-3a**, suggesting that one benzylic hydrogen atom was transferred to the olefinic position (Scheme 5b, eq (1)). In addition, deuterated *Z*-stilbene was obtained, indicating that a part of alkynes were reduced during the reaction process. Crosso-

ver experiments between ***d*-1a** and **1e** suggested that the allylic and olefinic hydrogens may originate from different amide molecules (eq (2)), excluding the oxidative addition pathway as shown in Scheme 1a. The observed kinetic isotopic effect (k_H/k_D = 2.7 in the intermolecular competitive reaction and k_H/k_D = 2.2 in parallel reactions, eq (3)) implied that the cleavage of the benzylic C−H bond could be involved in the rate-determining step. Notably, when dimethylamino benzylic amide **1v** was used as the substrate, the corresponding imine **1v′** was detected (Scheme 5c). Moreover, the competitive reaction between amide **1a** and imine **1b′** showed that both of them gave the corresponding products in comparable yields (Scheme 5d). These results suggested that an imine intermediate could be involved in the catalytic cycle.[17] In addition, the stoichiometric reaction of a five-membered nickelacyle[19] and amide **1a** with or without IPr afforded the desired product **3b** in 68% and 9% yields, respectively, suggesting that both the nickelacycle and IPr were critical to the reaction (Scheme 5e).

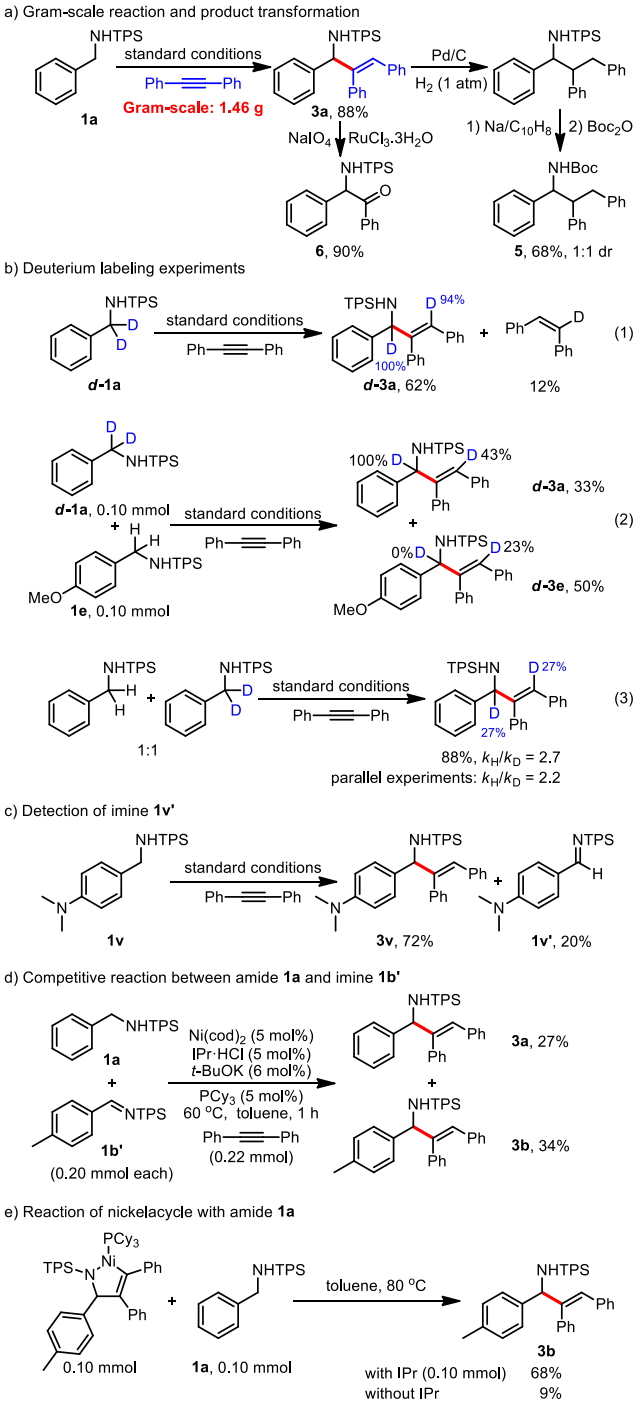
Scheme 4. Scope of Alkynes[a]



[a]Reaction conditions: **1a** (0.20 mmol), **2** (0.22 mmol), toluene (2.0 mL) under N_2 for 1−12 h; yield of isolated products. [b]110 °C. [c]Ni(cod)2 (10 mol%), IPr·HCl (10 mol%), PCy_3 (10 mol%), ^{t}BuOK (12 mol%) at 110 °C and regioselectivity for non-symmetrical alkynes.

Based on these mechanistic experiments and previous literature reports,[16,17,20] a possible mechanism was proposed (Scheme 6). At the induction stage, the nickel-catalyzed transfer hydrogenation of alkyne **2a** with sulfonamide **1a** furnishes *Z*-stilbene and imine **1a′**. Then, **1a′**, **2a**, and the nickel catalyst undergo an oxidative cyclometallation to generate nickelacycle **B**, which is subsequently protonated by **1a**. The resulting intermediate **C** then proceeds through a direct intramolecular hydrogen transfer (rather than a stepwise *β*-H elimination/reductive elimination pathway; vide post) to give Ni−product complex **D**.[20a] Finally, catalyst transfer between **D** and **2a** occurs, releasing product **3a** and completing the catalytic cycle.

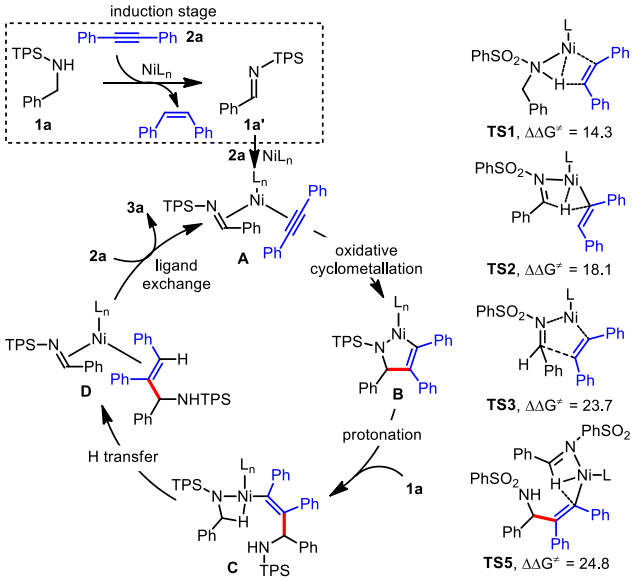
Scheme 5. Product Transformation and Mechanistic Experiments



To further shed light on each individual elementary step of the catalytic reaction, we performed DFT calculations on the model reaction of *N*-benzylbenzenesulfonamide and diphenylethyne in the presence of a simplified Ni/NHC catalyst (see Figure S1 for details). At the induction stage, two critical steps were a ligand-to-ligand hydrogen transfer (LLHT) via **TS1** with an activation Gibbs energy of 14.3 kcal/mol and an intramolecular hydrogen transfer via **TS2** with an overall activation Gibbs energy of 18.1 kcal/mol. At the product-formation stage, the turnover-limiting transition state is predicted to be the hydrogen transfer transition

state **TS5** with an overall activation Gibbs energy of 24.8 kcal/mol, which is accordance with the observed kinetic isotopic effect (eq (3)). Notably, an activation Gibbs energy for the transition state of the oxidative cyclometallation (**TS3**) is 23.7 kcal/mol, which is a little lower than that of **TS5**. DFT calculations with TPS-protected substrate **1a** and IPr ligand indicated that the overall activation Gibbs energy is 22.4 kcal/mol. Replacement of TPS by Ts leads to a higher overall activation Gibbs energy of 24.9 kcal/mol. These results suggested that, as compared with the Ts group, a ca. 30-fold acceleration effect of the TPS group would be expected at 80° C, which nicely reproduced the experimentally observed superior performance of the TPS protecting group (Scheme 2, entry 1 versus entry 3). In addition, DFT calculations also suggested that PCy_3 could not reduce the overall activation Gibbs energy of the [Ni(NHC)]-catalyzed reaction (see Figure S3), which suggests that PCy_3 might act as an auxiliary ligand to facilitate the generation of the catalytic species and/or to inhibit catalyst deactivation in the reaction.

Scheme 6. Proposed Mechanism and DFT Calculations



In summary, we have developed a nickel-catalyzed C−H alkenylation of amines with alkynes, providing a series of allylic amines with up to 94% yield in a redox-neutral and atom-economical fashion. Bulky N-protecting group (TPS) and the combination of IPr and PCy_3 ligands effectively promoted the reaction. Various benzylic amines were well tolerated, while other alkylamines displayed a little lower reactivity in the reaction. Besides symmetrical diaryl and dialkyl alkynes, non-symmetrical aryl alkyl alkynes also worked well, affording high regioselectivities (8.1:1 to sole regioisomer). Further exploring asymmetric version of the current method and other types of reactions of amines is underway in our lab.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI. Experimental procedures, characterization data, computational details, and spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interests.

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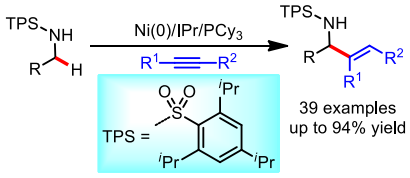
TPS
NH
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Ni(0)/IPr/PCy3
R1
R2
TPS =
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TPS
NH
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R2
R1
39 examples
up to 94% yield