Ni-Catalyzed Hydroaminoalkylation of Alkynes with Amines

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Abstract

Hydroaminoalkylations of alkenes with amines have been widely explored, while analogous reactions of alkynes have been a formidable challenge. Herein, a late transition metal nickel-catalyzed hydroaminoalkylation of alkynes with amines was developed, providing a series of allylic amines in up to 94% yield. The use of double ligands (IPr and PCy_3) and bulky amino protecting group proved critical to the reaction efficiency.

Introduction

Allyic amines not only widely exist in a broad range of natural products and bioactive compounds, but also serve as versatile building blocks in organic synthesis.[1–4] The development of efficient and general methods for their synthesis has received much attention during the past several decades.[5–23] Among various reported methods, transition metal-catalyzed hydroaminoalkylation of π-unsaturated compounds such as alkenes and alkynes represents one of the most straightforward and atom-economical synthetic routes.[24–32] With using either early[24–27] or late transition metals as catalysts,[28–32] a large number of hydroaminoalkylations of alkenes have been developed. However, in sharp contrast, analogous reactions of alkynes was faced with tremendous challenges, likely owing to difficult alkyne insertion and challenging protonolysis.[33–40] A pioneering investigation was conducted in 1989 by Buchwald and co-workers, who successfully obtained the allylic amine product by aqueous work-up. Despite an efficient protonolysis, the regeneration of Zr catalyst cannot be realized in this protocol, leading to stoichiometric Zr-complex needed.[33] Since then, much effort has been devoted to improving the reaction,[34–40] while the development of a catalytic method has been an elusive challenge. Most recently, during our submission,[41] Schafer group used a tetradentate bis(ureate) ligand and metal Zr to in situ form a bulky Zr catalyst, achieving a catalytic hydroaminoalkylation of alkynes for the first time (Fig. 1b).[42] The bulky ligand proved critical to the reactivity, not only facilitating alkyne insertion, but also allowing the coordination of neutral amines to the metal center for subsequent easier protonolysis. Despite this big advance, the early transition metal Zr-catalyzed method still suffered from some undesired limitations such as unavoidable hydroamination side reaction in many cases, difficult-to-remove N-aryl protecting groups, and tricky regioselectivity under relatively harsh conditions. Therefore, the development of other efficient catalytic systems for hydroaminoalkylation of alkynes is still highly desirable. Herein, we used an inexpensive nickel as a catalyst to achieve the first example on late transition metal-catalyzed hydroaminoalkylation of alkynes with N-sulfonyl amines, providing a series of allylic amines in up to 94% yield (Fig. 1c). The reaction features relatively mild conditions (80 ^{o}C), general substrate scope of both amines and alkyens and high regioselectivity.

Results

Reaction optimization. In comparison with various hydroaminoalkylations of alkenes, the difficulty of hydroaminoalkylation of alkynes was ascribed to the following possible reasons: (1) strong basicity and

nucleophilicity of alkyl or aryl amines could coordinate to metal centers, resulting ni either deactivation of transition metals or undesired side reactions such as hydroaminations; (2) weak acidity of N–H bonds cannot effectively undergo protonolysis of metallacycle intermediates. Thereby, the selection of proper N-protecting groups to increase the acidity of amines could be critical to the reaction efficiency, because more acidic amine would significantly reduce its coordination with metal centers and other side reactions such as hydroamination. However, to accommodate acidic N–H bonds, sensitive early transition metal complexes should be replace by late transition metals such as Pd, Ru and Ni, because they could have better compatibility with protonic substrates and solvents.

Following this hypothesis, we conducted an extensive survey on N-protecting groups, transition metals, ligands and other reaction parameters. Ultimately, triisopropylsulfonyl (TPS) was identified as the superior N-protecting group and Ni/IPr/PCy_3 was identified as the optimal catalyst. With their combination, hydroaminoalkylation of alkyne **2a** with N-TPS amine **1a** smoothly proceeded under mild conditions (80 °C), providing the corresponding allylic amines **3a** in nearly quantitative yield (Fig. 2, entry 1).

Control experiments showed that the alteration of TPS resulted into significantly diminished yields (entries 2 – 8). For example, the replacement of isopropyl groups (TPS) by methyl groups (TMS) gave only 9% yield (entry 2). Common *p*-tolylsulfonyl (Ts) further decreased the yield to 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 addition 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 the Supporting Information for details). Other carbenes and phosphines were less effective (entries 10 – 12 and 14 – 17). Without $Ni(cod)_2$ or with other nickel species, the reaction did not work (entries 18 – 20).

Scope of amines and alkynes. Under the optimized conditions, various N-TPS amines were then examined (Fig. 3). Results showed that the reaction tolerated a broad range of functional groups on the phenyl ring of N-benzyl amines, 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, **3 g** – **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 **3 h** – **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 ^{o}C. Notably, various N-alkyl amines were still compatible with the reaction (**3r** – **3u**, 41 – 54% yields), but requiring harsher conditions (130 ^{o}C and 20 mol% catalyst) and a Ts protecting group.

Next, a broad range of alkynes were investigated under the standard conditions (Fig. 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-deficient groups such as OCF_3 (**4 g**), F (**4 h**), 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 **4 k**) and alkyl aryl alkynes (**4 l** – **4p**) were well tolerated, providing both good yields and good to excellent regioselectivities. For example, 1-phenylpropyne gave 8.1:1 regioisomeric ratio (**4 l**), and the change of methyl to ethyl significantly increased the ratio to 20:1 (**4 m**). 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.

Reaction Utility and mechanistic discussion. To demonstrate the utility of the reaction, a gram-scale reaction of the model substrates was conducted under the standard conditions, affording the desired product **3a** in 88% yield, without significant loss of the yield (Fig. 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 typical deprotection protocol of the sulfonyl group provided compound **5** in 68% yield. And direct oxidation of **3a** resulted into a synthetically useful *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 (Fig. 5b). In addition, deuterated *Z*-stilbene was obtained, indicating that a part of alkynes were reduced during the reaction process. Crossover experiments between d-**1a** and **1e** suggested that the allylic and olefinic hydrogens may originate from different amide molecules (Fig. 5c), excluding an oxidative addition pathway. 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, Fig. 5d) implied that the cleavage of the benzylic C – H bond could be involved in the rate-determining step. Notably, in case of dimethylamino benzylic amide **1v** as the substrate, the imine **1v'** was detected (Fig. 5e). Moreover, the competitive reaction between amide and the imine showed that both of them gave the corresponding products in comparable yields (see Scheme S7). These results suggested that an imine intermediate could be involved in the catalytic cycle.

In addition, the stoichiometric reaction of a five-membered nickelacylce[43–45] 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 S10). Based on these mechanistic experiments and previous literature reports,[46–50] a possible reaction mechanism was proposed (Fig. 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 to give Ni – product complex **D**. Finally, catalyst transfer between **D** and **2a** occurs, releasing product **3a** and completing the catalytic cycle.

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 (Fig. 5d). 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 (Fig. 2, entry 1 *vs* entry 3). In addition, DFT calculations also suggested that the presence of PCy_3 could not reduce the overall activation Gibbs energy of the [Ni(NHC)]-catalyzed reaction (see Fig S3), and instead, PCy_3 may act as an auxiliary ligand to facilitate the generation of the catalytic species and/or to inhibit catalyst deactivation.

Conclusions

In summary, we have developed the first late transition metal-catalyzed hydroaminoalkylation of alkynes with amines, providing a series of allylic amines with up to 94% yield. Double ligands of IPr and PCy_3 along with bulky sulfonyl group (TPS) effectively promoted the reaction. A broad range of symmetrical or non-symmetrical alkynes with various benzyl and alkyl amines were well compatible with the reaction, providing allylic amines in good to high yields and with high regioselectivity (8.1:1 to a sole regioisomer). Further exploration on asymmetric version of the current method is underway in our lab.

Methods

General Procedure for Redox-Neutral Coupling Reaction. To a 15 mL pressure tube were added $Ni(cod)_2$ (2.75 mg, 0.01 mmol), IPr·HCl (4.25 mg, 0.01 mmol), PCy_3 (2.8 mg, 0.01 mmol), KO^tBu (1.34 mg, 0.012 mmol), toluene (2.0 mL), alkynes (0.22 mmol) and amines (0.20 mmol) in a glove box. The tube was sealed with a Teflon cap and the mixture was stirred at 80 °C or 110 °C for 1–12 h. After cooled to room temperature, the crude product was filtered through a short pad of Celite, and the filtrate was concentrated under vacuum. The resulting residue was obtained by chromatography on silica gel column with petroleum ether/ethyl acetate as the eluent. The analytic data for the products are listed below.

Declarations

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Author contributions

W.-W.Y. discovered and developed the reactions. R.L., H.C, M.-K.C. performed part of synthetic experiments. Y.W., Z.-X.Y., Y.-X.L. performed the DFT calculations, Y.-X.L., M.Y. conceived, designed the investigations and wrote the manuscript. W.-W.Y. wrote the Supplementary Information.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.Y.

Competing financial interests

The authors declare no competing financial interests.

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Figures

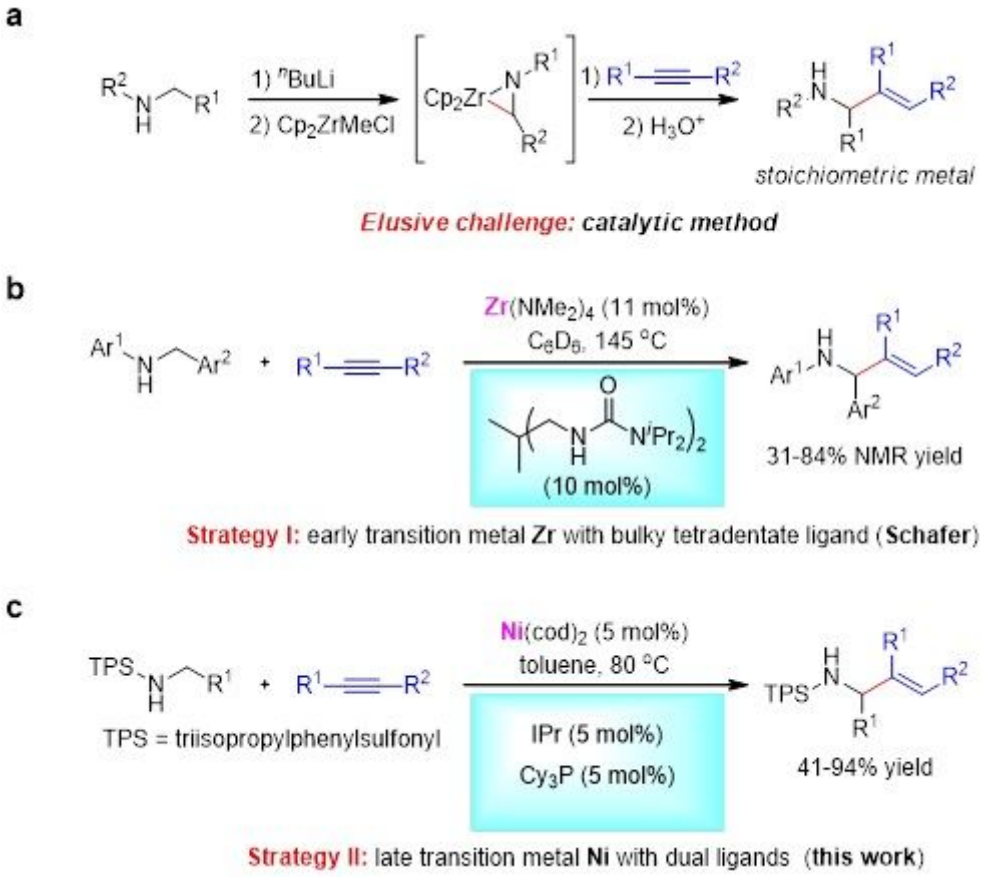
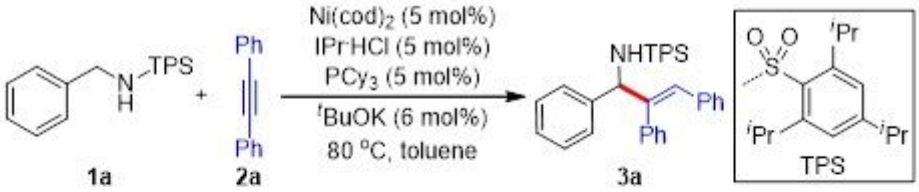


Figure 1

Transition metal-catalyzed hydroaminoalkylation of alkynes. a, Pioneering investigation with using stoichiometric Zr-complex (Buchwald). b, Strategy I with using early transition metal Zr and bulky tetradentate ligand (Schafer). c, Strategy II with using late transition metal Ni with dual ligands (this work).



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

Figure 2

Reaction optimization. Reaction conditions: 1a (0.20 mmol), 2a (0.22 mmol), toluene (2.0 mL) under N2 for 1 h; yield was determined by 1H NMR using Cl2CHCHCl2 as the internal standard.

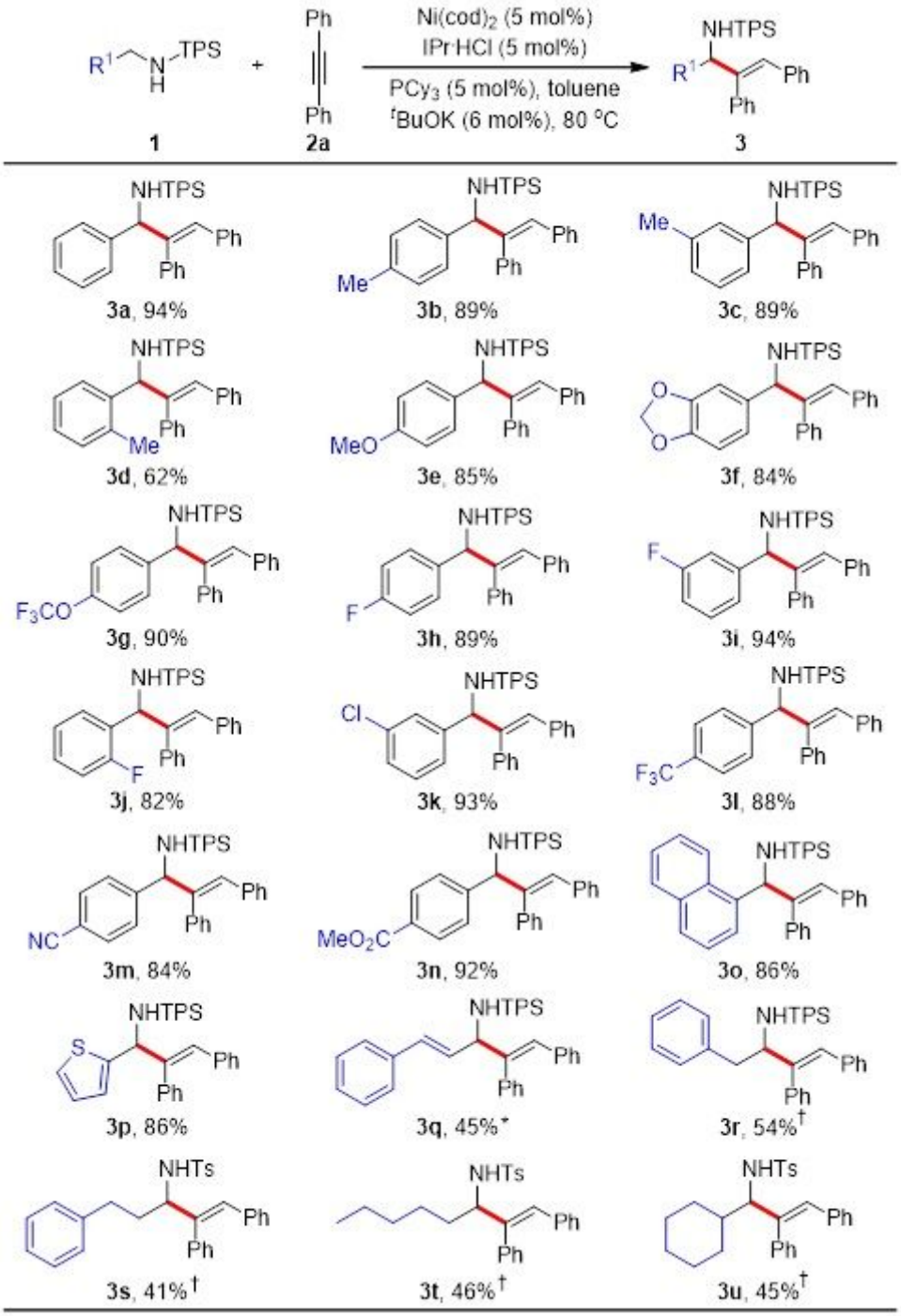


Figure 3

Scope of amines. Reaction conditions: 1 (0.20 mmol), 2a (0.22 mmol), toluene (2.0 mL) under N2 for 1–12 h; yield of isolated products. *Ni(cod)2 (10 mol%), IPr.HCl (10 mol%), PCy3 (10 mol%), tBuOK (12 mol%) at 110 oC. †Ni(cod)2 (20 mol%), IMes.HCl (20 mol%), PCy3 (20 mol%), tBuOK (22 mol%) at 130 oC.

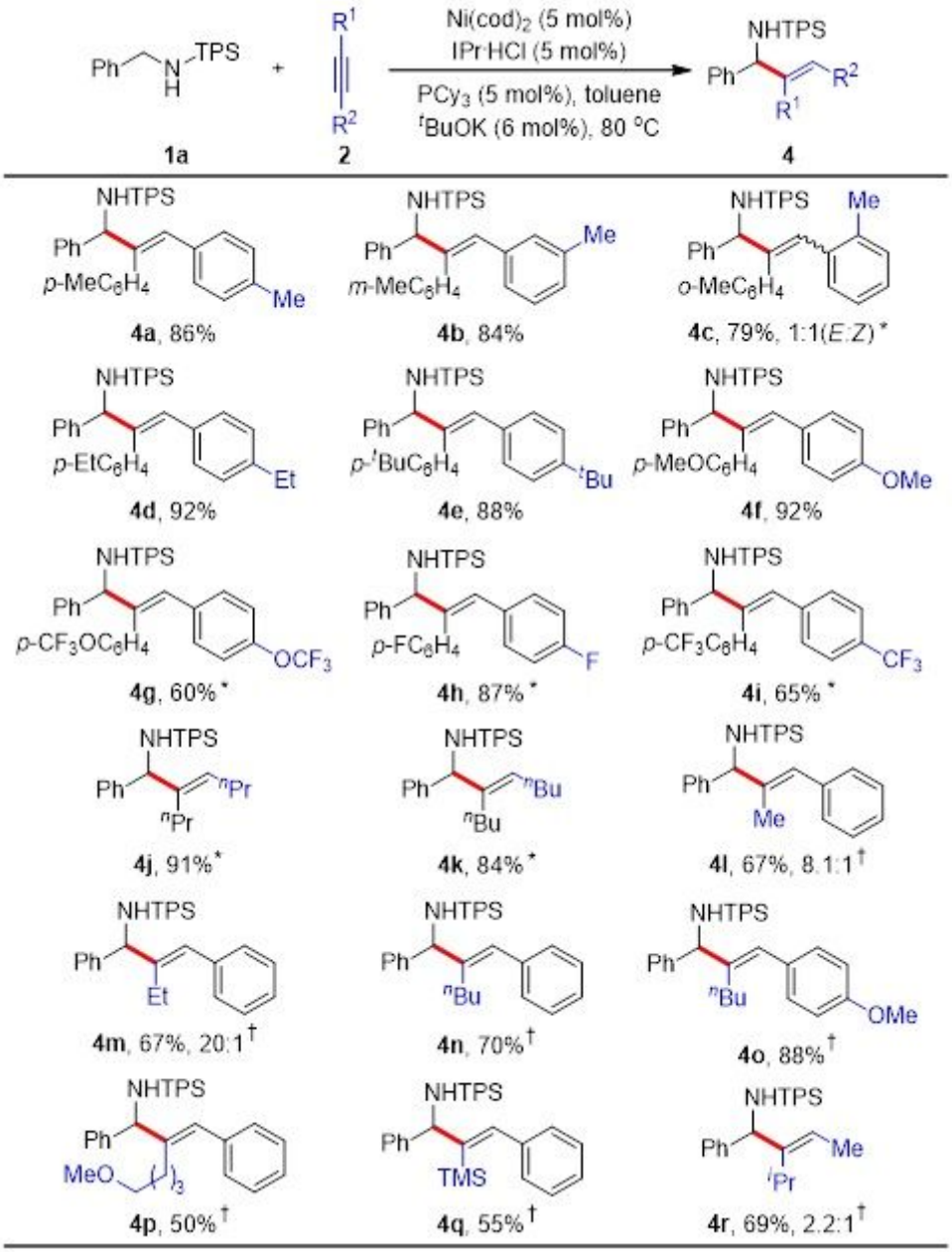


Figure 4

Scope of alkynes. Reaction conditions: 1a (0.20 mmol), 2 (0.22 mmol), toluene (2.0 mL) under N2 for 1−12 h; yield of isolated products. *110 oC. †Ni(cod)2 (10 mol%), IPr.HCl (10 mol%), PCy3 (10 mol%), tBuOK (12 mol%) at 110 oC and regioselectivity for non-symmetrical alkynes.

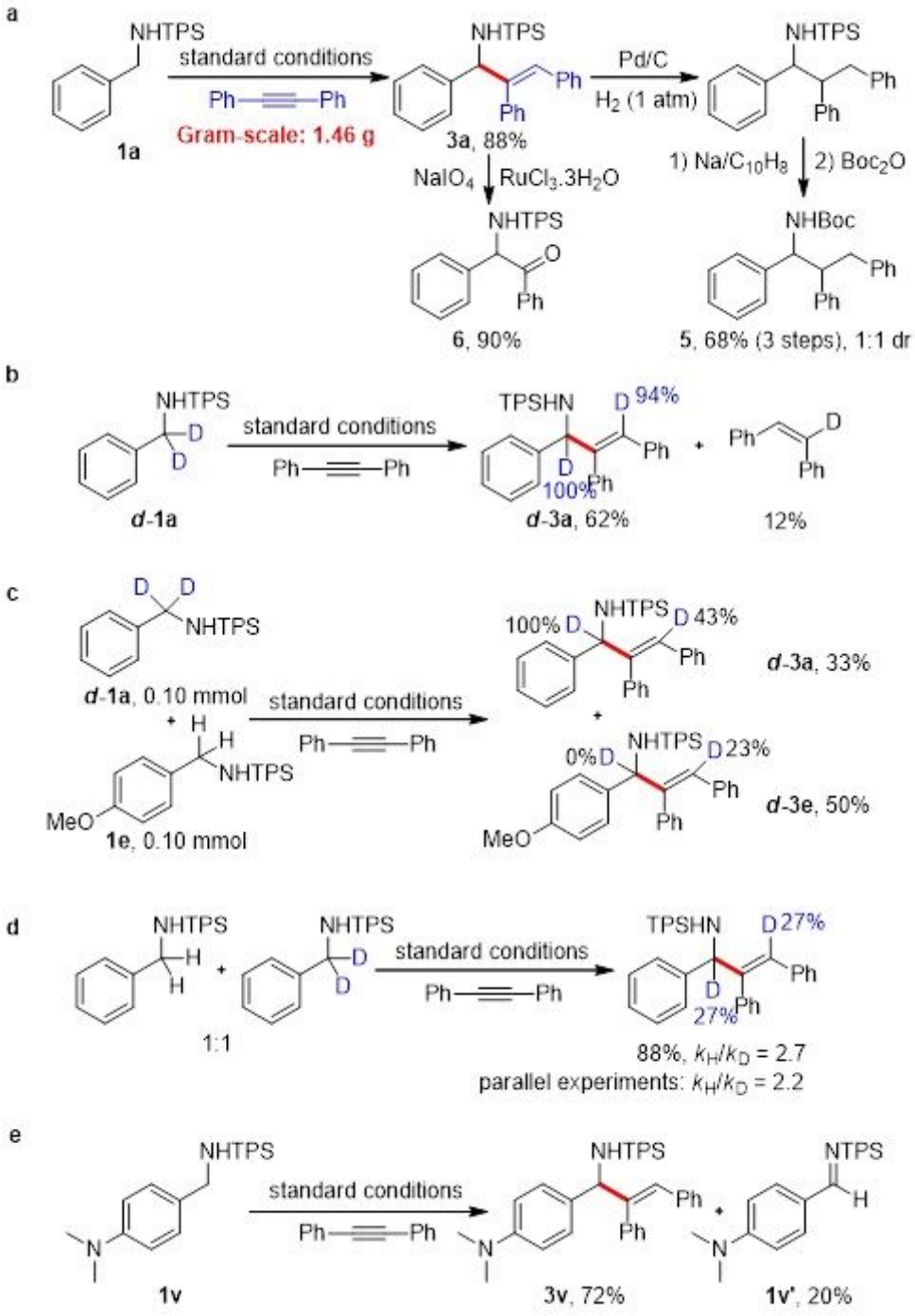


Figure 5

Synthetic utility and mechanistic experiments. a, Gram-scale reaction and product transformation. b, Deuterium labeling experiments, c, Intermolecular competition. d, Determination of kinetic isotope effect. e, Detection of imine.

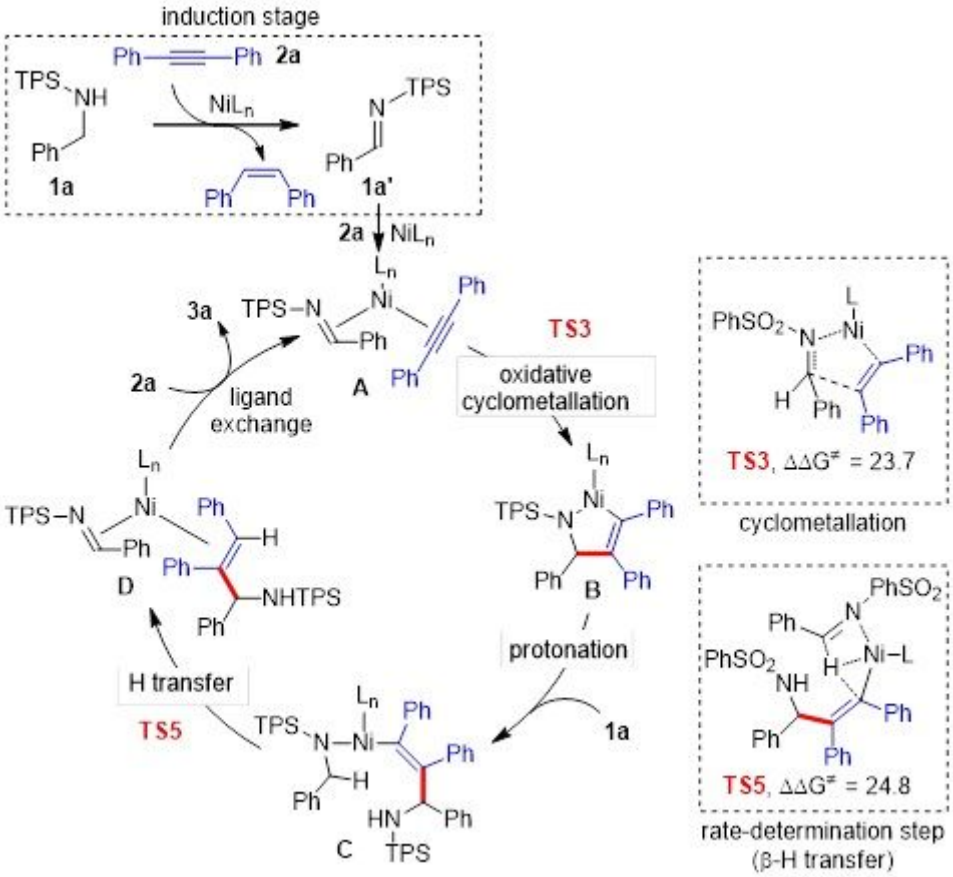


Figure 6

Proposed mechanism and DFT calculations.

Supplementary Files

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- SINialkenylation2020112.pdf
- GraphicalAbstract.jpg