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Authors: Lin Yu, Leiyang Lv, Zihang Qiu, Zhangpei Chen, Ze Tan, Yu-Feng Liang, and Chao-Jun Li

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Pd-Catalyzed Formal Hydroalkylation of Aryl-Substituted Alkynes with Hydrazones

Lin Yu,[a],[b],‡ Leiyang Lv,[a],‡ Zihang Qiu,[a] Zhangpei Chen,[a] Ze Tan,[b] Yu-Feng Liang,[a] Chao-Jun Li*[a]

Dedication ((optional))

[a] L. Yu, Dr. L. Lv, Dr. Z. Qiu, Dr. Z. Chen, Dr. Y.-F. Liang, Prof. Dr. C.-J. Li
Department of Chemistry and FRQNT Center for Green Chemistry and Catalysis
McGill University
801 Sherbrooke Street West, Montreal, Quebec H3A 0B8, Canada
E-mail: cj.li@mcgill.ca
[b] L. Yu, Prof. Dr. Z. Tan
State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering
Hunan University
Changsha 410082, P. R. China
‡ These authors contributed equally to this work

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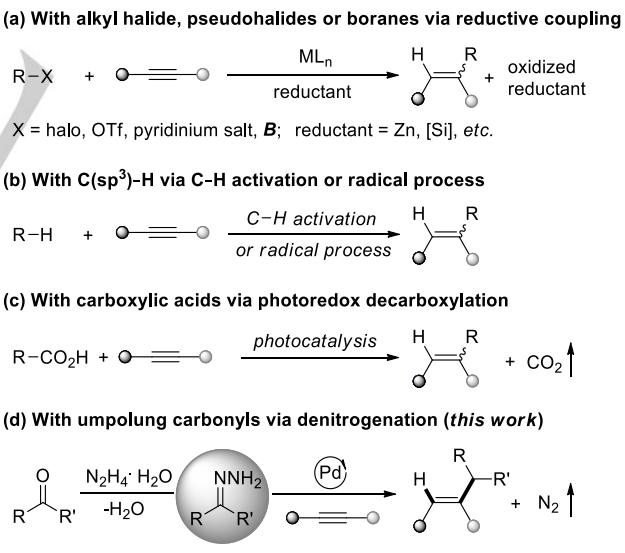
Abstract: We have developed an unprecedented Pd-catalyzed formal hydroalkylation of alkynes with hydrazones, which are generated in situ from naturally abundant aldehydes, as both alkylation reagents and hydrogen donors. The hydroalkylation proceeds with high regio- and stereoselectivity to form *(Z)*-alkenes, which are more difficult to generate, instead of *(E)*-alkenes. The reaction is compatible with a wide range of functional groups, including hydroxyl, ester, ketone, nitrile, boronic ester, amine and halide. Furthermore, late-stage modifications of natural products and pharmaceutical derivatives exemplify its unique chemoselectivity, regioselectivity and synthetic applicability. The mechanistic studies indicate the possible involvement of palladium-hydride intermediates.

Alkenes are basic functionalities and highly desirable building blocks. They are not only frequently used as versatile synthetic intermediates but are also prevalent among organic molecules with a wide range of applications.[1] Therefore, the exploration of efficient methods for their synthesis has been a continuous pursuit throughout the history of organic chemistry.[2] Among the many efforts for alkene syntheses, the transition-metal-catalyzed "formal" hydrofunctionalization of simple and readily available alkynes is considered as one of the most straightforward and versatile stereo-controlled approaches to access various alkenes.[3-4]

Despite requiring a stoichiometric amount of reductant or organometallic reagent, transition-metal-catalyzed "formal" hydroalkylation reaction between alkynes and alkyl halides, pseudohalides or boranes has been considered as an attractive strategy in this field and has attracted great interests (Scheme 1a).[5-8] Without using halides and other functional groups, the C(sp^3)–H bond alkenylation represented another promising method for conversion of alkynes to alkenes, and some elegant examples have been disclosed involving the direct C-H activation[9] and radical processes (Scheme 1b).[10] Very recently, MacMillan and Rueping independently developed the iridium and nickel dual-catalytic photoredox decarboxylative hydroalkylation reactions with carboxylic acids as the alkyl donors (Scheme 1c).[11] Despite much progress having been made, a number of challenges still remain unsettled in this field. For example, most methods require the stoichiometric reductant/organometallic reagents, oxidants or directing groups, and the alkyl donors are limited to alkyl halides, pseudohalides, boranes, carboxylic acids and compounds with activated C(sp^3)–H bonds. As the synthetic community is placing increasing emphasis on more sustainable, versatile and operationally simple chemical syntheses, the development of new alkylation reagents that readily derived from naturally abundant chemical feedstocks with harmless byproducts would be highly desirable.



Scheme 1. Catalytic (formal) hydroalkylation of alkynes.

Recently, our group developed the easily available umpolung carbonyls as nucleophiles in a series of transformations with unsaturated compounds, including carbonyls,[12] imines,[13] carbon dioxide[14] and activated alkenes,[15] as well as 1,3-dienes.[16] Furthermore, the reactions between umpolung carbonyls and several relatively polar compounds involving carbon-heteroatom bonds cleavage were also achieved by us[17] and others.[18] Although the reaction of carbonyl compounds with alkynes have

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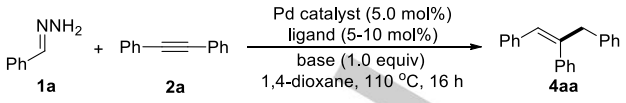
well developed,[19] the reaction of umpolung nucleophiles with unactivated alkyne remains an un-resolved challenge. The main obstacles may be ascribed to the following aspects: a) easy oligomerization or polymerization of alkyne, b) the difficult direct-addition of the nucleophile to unactivated alkyne, c) issues associated with the regio- and stereoselectivity of the addition. Considering the synthetic importance of hydroalkylation of alkynes together with our continuous investigation on hydrazone chemistry, herein, we wish to report a novel Pd-catalyzed formal syn-hydroalkylation of alkynes using umpolung carbonyls as both the alkylation reagents and hydrogen donors, with nitrogen gas as "traceless" byproduct (Scheme 1d).

We selected the simple hydrazone **1a** and easily available alkyne **2a** as model substrates. Bis(1,5-cyclooctadiene)nickel(0), which demonstrated high catalytic efficiency in the reaction of alkenes,[15-16] was evaluated in this hydroalkylation; however, the desired product was not observed (Table 1, entry 1). Systematic studies have shown that other nickel catalytic systems were also inefficient, generating a complex mixture and low stereoselectivity (Table1, entries 1-4, please see Table S1, in Supporting Information for details). Therefore, it is necessary to develop a new catalytic system to realize the hydroalkylation of alkynes. In view of the inherent difference of alkyne and alkene in binding affinity and reactivity,[20] we investigated other transition-metals, including Cu, Ni and Pd (entries 5-7). Much to our delight, we found that the desired product **4aa** was formed in 44% yield with 77:23 of *Z:E* ratio with $Pd(OAc)_2$/ (^{t}Bu)$_2$PMe as catalyst and DBU as base in 1,4-dioxane at 110 °C for 16 h under nitrogen atmosphere (entry 7). Notably, the major product was switched from (*E*)-alkene to (*Z*)-alkene. Encouraged by this result, various mono- and bidentate-phosphine ligands such as trimethylphosphine (PMe_3), 1,2-bis(dicyclohexylphosphino) ethane (dcype), tricyclohexylphosphine (PCy_3) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) were examined, and we found that the sterically hindered, strong σ-donor mono alkylphosphine ligand, PCy_3 was the best ligand for this transformation, and the desired product **4aa** could be isolated in 55% yield with 86:14 of *Z:E* ratio (entry 10). We subsequently explored other palladium catalysts and found that allylpalladium chloride dimer not only gave the best yield of **4aa** (86%) but also showed high stereoselectivity (*Z:E* = 90:10, entry 14). Control experiments showed that no product was produced in absence of palladium catalyst or base (entries 15-16). Replacing the base DBU with TEA, K_3PO_4 or ^{t}BuOLi, the reactions were found to be unreactive (entries 17-19).

With the optimized conditions identified (Table 1, entry 14), we investigated the scope of hydrazone **1**. As shown in Table 2, hydrazone **1** bearing a variety of functional groups including both electron-donating and electron-withdrawing groups reacted smoothly with diphenylacetylene **2a** to provide the hydroalkylation of alkynes products in moderate to good yields with high ratios of *Z:E* (generally > 90:10) (Table 2). The functional groups, regardless of the *ortho*-, *meta*-, *para*-, or multiple substitutions, were all tolerated to generate the corresponding products **4aa**-**4av** in modest to excellent yields under the standard conditions. It is worthwhile to mention that even the reaction of a 3-nicotinaldehyde and 3-thiophenecarboxaldehyde derived hydrazones were smoothly tansformed into the corresponding desired products **4an** in 82% and **4at** in 80% yields, respectively. Gratifyingly, the boronic ester

Table 1. Optimization of the reaction conditions.[a,b]



entry	catalyst	ligand	base	yield(%)/(*Z:E*)
1	$Ni(cod)_2$	ICy·HCl	^{t}BuOLi	0
2	$Ni(cod)_2$	dmpe	^{t}BuOLi	0
3	$Ni(cod)_2$	PMe_3	DBU	trace
4	$Ni(cod)_2$	(^{t}Bu)$_2$PMe	DBU	25 (32:68)[c]
5	$Cu(OAc)_2$	(^{t}Bu)$_2$PMe	DBU	0
6	$CoCl_2$	(^{t}Bu)$_2$PMe	DBU	0
7	$Pd(OAc)_2$	(^{t}Bu)$_2$PMe	DBU	44 (77:23)
8	$Pd(OAc)_2$	PMe_3	DBU	<10
9	$Pd(OAc)_2$	dcype	DBU	<10
10	$Pd(OAc)_2$	PCy_3	DBU	55 (86:14)
11	$Pd(OAc)_2$	IPr·HCl	DBU	0
12	$Pd(PPh_3)_4$	PCy_3	DBU	23 (84:16)
13	$Pd_2(dba)_3$	PCy_3	DBU	32 (80:20)
14	$[Pd(allyl)Cl]_2$	PCy_3	DBU	86 (90:10)
15	-	PCy_3	DBU	0
16	$[Pd(allyl)Cl]_2$	PCy_3	-	0
17	$[Pd(allyl)Cl]_2$	PCy_3	TEA	0
18	$[Pd(allyl)Cl]_2$	PCy_3	K_3PO_4	0
19	$[Pd(allyl)Cl]_2$	PCy_3	^{t}BuOLi	trace

[a] Reaction conditions: phenyl hydrazone **1a** (0.5 mmol, 1.0 M generated in situ from benzaldehyde and hydrazine), diphenylacetylene **2a** (0.2 mmol), catalyst (0.01 mmol), ligand (10 mol% for monodentate, 5 mol% for bidentate and carbene ligand) and base (0.2 mmol) in 1,4-dioxane (0.5 mL) at 110 °C for 16 hr under N_2; [b] NMR yields were determined by ^{1}H NMR; [c] Along with further hydroalkylation products of obtained alkenes, namely the alkane products.

substituent on the phenyl ring of hydrazone is well compatible, which can be utilized for further transformations (**4ap**). Notably, aliphatic hydrazones such as 3-phenylpropionaldehyde and phenylacetaldehyde derived hydrazones were also found to be applicable substrates, albeit furnishing the desired products in lower yields (**4ax**, **4ay**). It is noteworthy that the target product **4aw** was obtained in 50% yield when a hydrazone derived from acetophenone was subjected to our standard conditions. However, for other types of ketones, such as cyclohexanone and acetone, only trace amounts of desired products were detected.

Subsequently, the scope of alkynes was examined, as summarized in Table 3. Notably, the reactivity was higher when trifluoromethyl benzaldehyde was used as the substrate, which allows the reaction to proceed at 100 °C with a better Z/E selectivity (Table 2 vs Table 3). In general, moderate to good yields with high stereoselectivities and regioselectivities (generally >95:5) were obtained with a wide

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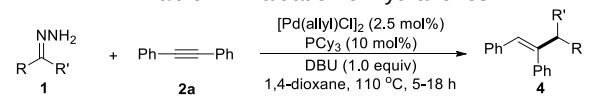
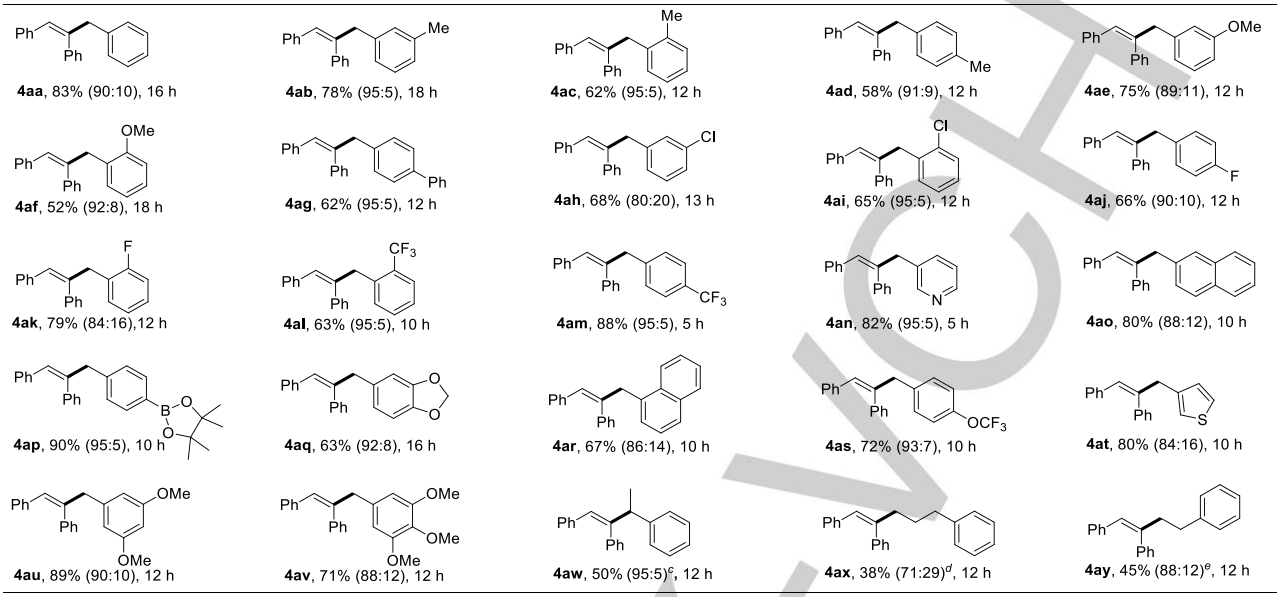
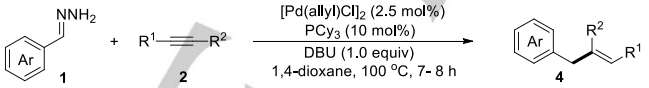
Table 2. Evaluation of hydrazones.[a,b]

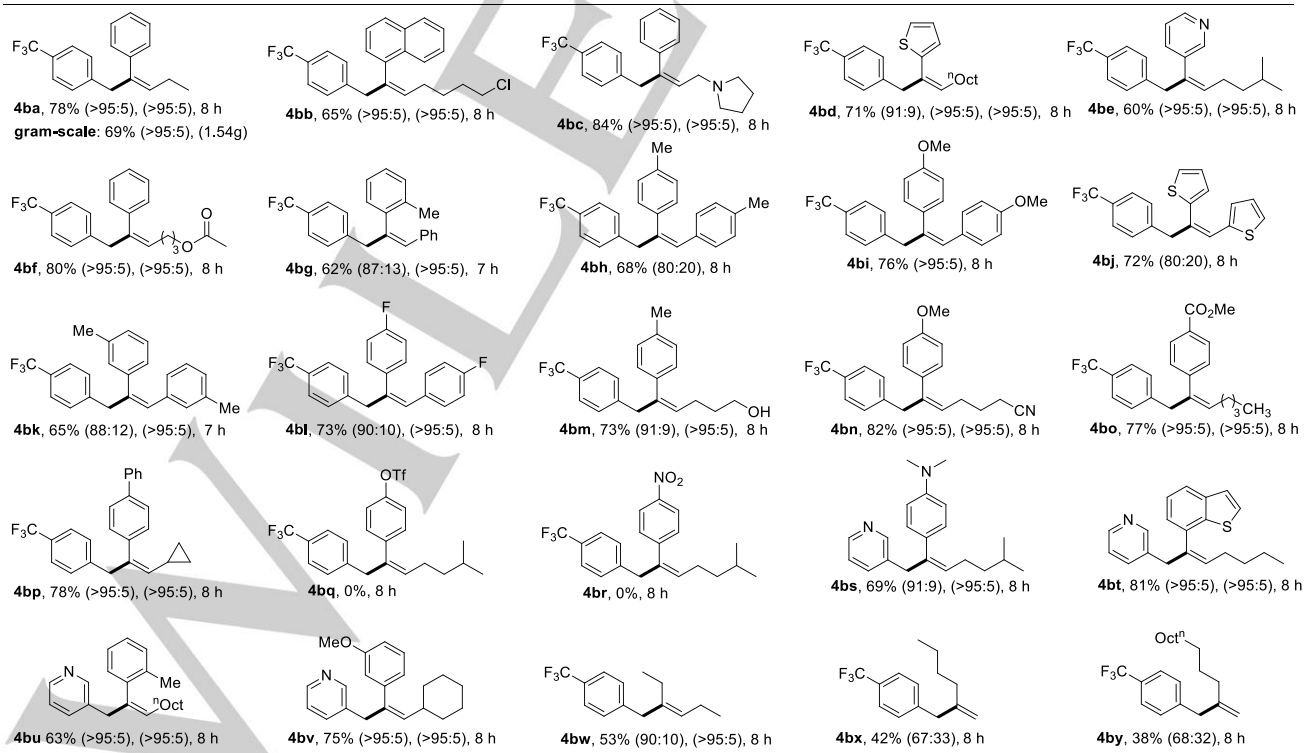




[a] Reaction conditions: hydrazone **1** (0.5 mmol, 1.0 M generated in situ from aldehyde and hydrazine), diphenylacetylene **2a** (0.2 mmol), $[Pd(allyl)Cl]_2$ (0.005 mmol), PCy_3 (0.02 mmol) and DBU (0.2 mmol) in 1,4-dioxane (0.5 mL) at 110 °C for 5-18 hr under N_2; [b] isolated yields; [c] yield was based on recovered alkyne (35%); [d] yield was based on recovered alkyne (35%); [e] yield was based on recovered alkyne (32%).

Table 3. Evaluation of alkynes.[a,b]





[a] Reaction conditions: hydrazone **1** (0.25 mmol, 1.0 M generated in situ from aldehyde and hydrazine), alkyne **2** (0.1 mmol),), $[Pd(allyl)Cl]_2$ (0.0025 mmol), PCy_3 (0.01 mmol) and DBU (0.1 mmol) in 1,4-dioxane (0.25 mL) at 100 °C for 7-8 hr under N_2; [b] isolated yields; Z/E ratios and regioselectivity were determined by ^1H NMR.

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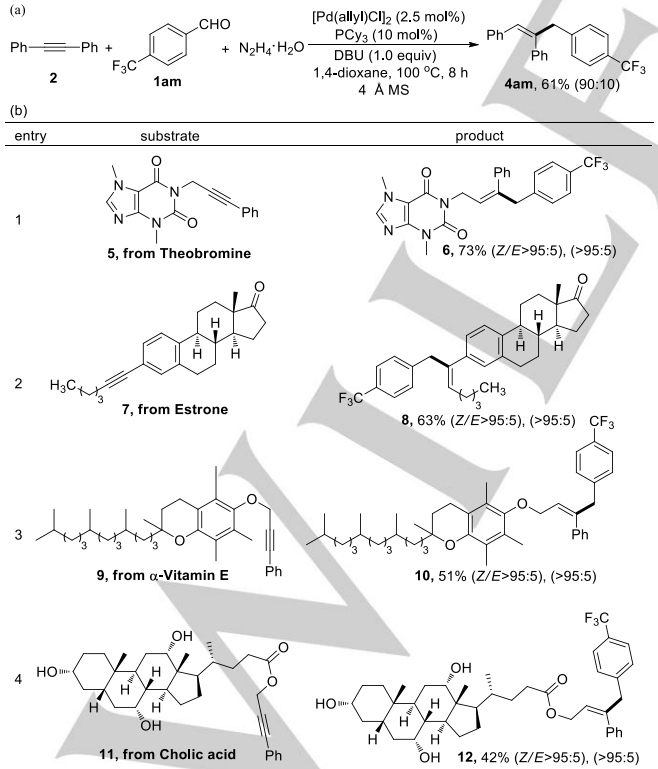
range of symmetrical and non-symmetrical alkynes (Table 3). A number of functional groups, including chloro (**4bb**), fluoro (**4bl**), methoxyl (**4bi**, **4bn**, **4bv**), nitrile (**4bn**), alkylester (**4bf**), arylester (**4bo**), hydroxyl (**4bm**) and protected amino groups (**4bc**, **4bs**) were all viable in this transformation. Heteroaromatic alkynes containing pyridine (**4be**), thiophenes (**4bd**, **4bj**), and benzothiophene (**4bt**) were also effective as coupling partners. Notably, a gram-scale hydroalkylation of alkyne gave the product **4ba** in 69 % yield (1.54 g). Moreover, aliphatic alkynes are also suitable substrates for this transformation (**4bw, 4bx, 4by**). However, the alkynes with triflate or nitro substitutions at the *para*-position of phenyl ring were unreactive (**4bq**, **4br**).

To further exploit the practicability of this method, we performed this hydroalkylation reaction in one-pot. Gratifyingly, the desired product could be obtained in 61% yield with the ratio of *Z:E* = 90:10 (Scheme 2a). The high efficiency and good functional-group tolerance of this method enabled its application to the late-stage modification of natural products and pharmaceutical derivatives. Theobromine, an alkaloid, derivative **5** was investigated under the current catalytic system, and the expected hydroalkylation product **6** was obtained in good yield with high regio- and stereoselectivity (*Z:E* > 95:5) (Scheme 2b, entry 1). The estrone derivative **7** proceeded smoothly under the optimized conditions, with the ketone moiety untouched (entry 2). In addition, α-Vitamin *E* derivative **9** was also tested, delivering the target product **10** (entry 3). Furthermore, cholic acid derivative **11** with multiple hydroxyl groups was found to be a viable partner, affording **12** in moderate yield with high ratio of *Z:E* (95:5) (entry 4). Notably, the *Z*-configuration of major products (**6**, **8**, **10**, **12**) were confirmed by NOESY experiments (Please see SI in details). To gain preliminary insights into the hydroalkylation reaction



Scheme 2. One-pot reaction and application to the late-stage modification of natural products and pharmaceutical derivatives.

mechanism, several control experiments were subsequently carried out. Please see SI for details of the following mechanistic studies. Firstly, *N*-tosylhydrazones are often used as the carbene precursors.[21] In order to verify whether our reaction went through the carbene process, we used *N*-tosylhydrazones as substrates to react with alkynes under standard conditions; and no desired product was detected, suggesting the unlikely involvement of a carbene process in the reaction. When the reaction was ran for 1 hr under the standard conditions, the high ratio of *Z:E* (99:1) was obtained, which suggests the generation of *E*-configuration from *Z*-configuration. Moreover, it was found that the reaction time has a significant effect on the ratio of *Z:E*, with the shorter reaction time affording a higher ratio of *Z:E*. Finally, in deuterium-labelling experiments, 0.95 deuterium was incorporated into the benzyl position, and 0.45 deuterium into the alkene position of product, which implies the hydrogen of hydrazone serving as hydrogen donors of product. It should be noted that the hydride species was observed with the *in situ* ^{1}H NMR, when the reaction was performed under the standard conditions. However, the hydride species was not observed in absence of palladium catalyst or hydrazone (Please see SI for a possible reaction mechanism).

In summary, we have demonstrated an unprecedented Pd-catalyzed formal hydroalkylation of alkynes with hydrazones, which were generated *in situ* from naturally abundant aldehydes and ketones, as both alkylation reagents and hydrogen donors. The formal hydroalkylation proceeds with high regio- and stereoselectivity to form the more difficult (*Z*)-alkenes instead of (*E*)-alkenes. The reaction is compatible with a wide range of functional groups, including hydroxyl, ester, ketone, nitrile, boronic ester, amine and halide. Furthermore, late-stage modifications of natural products and pharmaceutical derivatives exemplify its synthetic potentials. The preliminary mechanistic studies indicate that the reaction may proceed via an oxidative addition of N-H bond, carbopalladation of an alkyne and denitrogenative alkylation of an alkenyl-palladium intermediate.

Acknowledgements

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Keywords: Palladium • Hydroalkylation • Alkynes • Aldehydes • Alkenes

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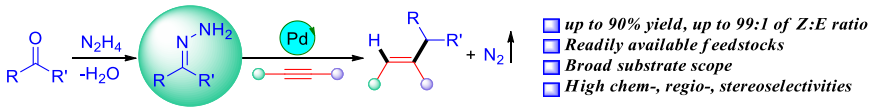

A Pd-catalyzed formal hydroalkylation of alkynes with hydrazones has been realized. The reaction proceeded with high regio- and stereoselectivity to form (*Z*)-alkene through a Pd-H species.