Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201901394

Link to VoR: http://dx.doi.org/10.1002/adsc.201901394

10.1002/adsc.201901394

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Synthesis of Isoquinoline Derivatives via Palladium-Catalyzed C-H/C-N Bond Activation of *N*-Acyl Hydrazones with *α*-Substituted Vinyl Azides

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A palladium-catalyzed cyclization of *N*-acetyl hydrazones with vinyl azides has been developed. Various substituted isoquinolines, including diverse fused isoquinolines can be prepared via this protocol in moderate to good yields. Mechanistic studies suggest that *α*-substituted vinyl azide serves as an internal nitrogen source. Also, C-H bond activation and C-N bond cleavage have been realized using hydrazone as directing group.

Keywords: C-H activation; *N*-acyl hydrazones; directing group; isoquinoline

Introduction

Isoquinolines are useful *N*-heterocyclic structures found in natural products, pharmaceutical molecules, [1] PET imaging agents, catalyst ligands, and OLED materials (Figure 1).[2] Traditionally, syntheses of isoquinolines using classical protocol such as Bichler-Napieralski,[3] Pomeranz-Fritsch[4] and Pictet-Spengle rreactions,[5] often suffer from multistep process and harsh reaction conditions. To avoid the limitations of the above reactions, various synthetic approaches for isoquinolines have been developed. Recently, transition-metal-catalyzed direct C-H functionalization has emerged as a novel strategy to construct isoquinoline skeleton by C-H/N-N bond activation or C-H/N-O bond activation with nitrogen-containing directing groups including aromatic hydrazines, imines, azines oximes, *etc*.[6-9] In most cases, internal nitrogen source of isoquinolines was also provided by directing groups.

In recent years, several aromatic hydrazones (*N*-Tos, *N*-Cbz, *N*-Boc, and *N*-pyridine, *etc*.) have been explored in rhodium(III),[10] cobalt(III),[11] cobalt(II),[12] and ruthenium(II)[13] -catalyzed annulations with alkynes through C-H/N-N bond activation to afford 1,3,4-trisubstituted isoquinolines, along with N-N bond cleavage of hydrazones (Scheme 1a). To the best of our knowledge, palladium-catalyzed C-H functionalization using aryl ketone hydrazones as directing groups for the synthesis of isoquinolines have never been reported to date. In addition, *N*-acetyl hydrazone as the directing group has not been studied in C−H activation yet. Inspired by our previous studies on palladium-catalyzed reactions,[14] we envisaged that the *N*-acetyl hydrazone as the building block could be applied to this synthetic protocol. Herein, we present a new strategy via Pd-PEPPSI-IPr catalyzed C-H/C-N bond activation employing *N*-acetyl hydrazones, which could act as a novel traceless directing group by C-N bond cleavage to afford substituted isoquinolines (Scheme 1b).

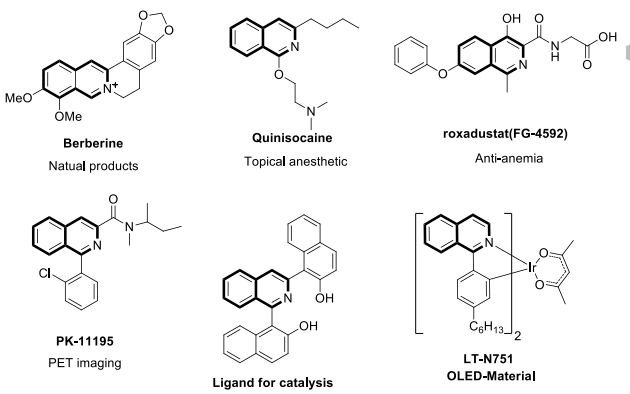
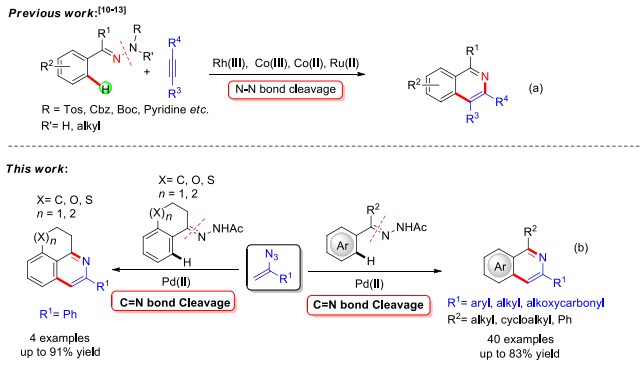


Figure 1. Representative useful molecules with isoquinoline scaffold

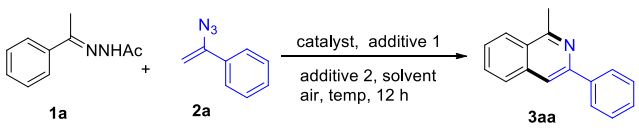


Scheme 1. Synthesis of isoquinolines via C-H activation using aryl hydrazone as directing group

Results and Discussion

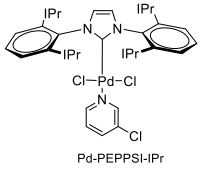
We initiated our studies by utilizing acetophenone-*N*-acetylhydrazone (**1a**) and (1-azidovinyl) benzene (**2a**) as the model substrates to optimize the reaction parameters (Table 1). When **1a** was reacted with **2a** in the presence of $Pd(OAc)_2$ (10 mol %), NaOAc (1.0 equiv), Cu_2O (2.0 equiv) in toluene at 80 °C for 12 h, the desired product **3aa** was obtained in 30% yield (Table 1, entry 1). During further screening of the catalysts, PEPPSI-IPr was indicated the most effective (Table1, entries 2-4). It was found that other acetate additives such as KOAc, AgOAc, CsOAc could not promote the reaction (Table1, entries 5-7). Further increasing the temperature to 100 °C led to the best yield of the product up to 81% (Table1, entry 9). The examination of different solvents suggested that toluene was the most effective solvent for this transformation, while other solvents such as TFE, MeCN, DMSO, DMF, and 1,4-dioxane failed to facilitate the reaction (Table 1, entries 13-17). Control experiment indicated that the reaction did not occur in the absence of Pd catalysts (Table1, entry 18). When the reaction was carried out in the presence of a stoichiometric amount of Pd without Cu_2O, only trace amount of the product was obtained (Table 1, entry 19). Finally, we found PEPPSI-IPr-NaOAc-Cu_2O catalytic system with toluene as solvent resulted in the formation **3aa** in best yields at 100 °C.

Table 1. Optimization of reaction conditions[a]



Entry	Catalyst (mol %)	Additive 1	Additive 2	Solvent	temp (°C)	yield[b] (%)
1	$Pd(OAc)_2$ (10)	NaOAc	Cu_2O	toluene	80	30
2	$Pd(TFA)_2$ (10)	NaOAc	Cu_2O	toluene	80	41
3	$Pd(OPiv)_2$ (10)	NaOAc	Cu_2O	toluene	80	27
4	PEPPSI-IPr (10)[c]	NaOAc	Cu_2O	toluene	80	56
5	PEPPSI-IPr (10)	KOAc	Cu_2O	toluene	80	45
6	PEPPSI-IPr (10)	AgOAc	Cu_2O	toluene	80	50
7	PEPPSI-IPr (10)	CsOAc	Cu_2O	toluene	80	34
8	PEPPSI-IPr (10)	NaOAc	Cu_2O	toluene	90	66
9	**PEPPSI-IPr (10)**	**NaOAc**	**Cu_2O**	**toluene**	**100**	**81**
10	PEPPSI-IPr (10)	NaOAc	BQ	toluene	100	50
11	PEPPSI-IPr (10)	NaOAc	$K_2S_2O_8$	toluene	100	41
12	PEPPSI-IPr (10)	NaOAc	DDQ	toluene	100	NR
13	PEPPSI-IPr (10)	NaOAc	Cu_2O	TFE	100	35
14	PEPPSI-IPr (10)	NaOAc	Cu_2O	CH_3CN	100	trace
15	PEPPSI-IPr (10)	NaOAc	Cu_2O	DMSO	100	trace
16	PEPPSI-IPr (10)	NaOAc	Cu_2O	DMF	100	trace
17	PEPPSI-IPr (10)	NaOAc	Cu_2O	1,4-dioxane	100	37
18	---	NaOAc	Cu_2O	toluene	100	NR
19[d]	PEPPSI-IPr (100)	NaOAc	---	toluene	100	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol %), NaOAc (1.0 equiv), Cu_2O (2.0 equiv) in the solvent (2 mL) under air atmosphere for 12 h, unless otherwise noted. [b]Isolated yield. TFE = trifluoroethanol
[c]the corresponding structure:



Pd-PEPPSI-IPr

[d] the amount of PEPPSI-IPr was 100 mol % in the absence of Cu_2O.

With the optimized reaction condition in hand, the substrate scope of the reaction was then investigated. Firstly, a broad range of *N*-acetyl hydrazones were screened to couple with (1-azidovinyl)benzene (**2a**) as shown in Scheme 2. To our delight, variation from alkyl aryl ketones to benzophenone and cycloalkyl aryl ketones hydrazones reacted smoothly with **2a** to afford isoquinolines **3aa-3ia** in 60-81% yields. Especially, cyclohexyl, cyclopentyl, cyclobutyl and cyclopropyl substituted hydrazones were compatible in this transformation (**3fa-3ia**). The substrate bearing a methyl group at the *ortho*-position of *N*-acetyl hydrazone showed the lowest reactivity and the corresponding product **3ja** was just obtained in a trace isolated yield, presumably due to the steric hindrance of *ortho* substitution.

The C-H functionalization occurred regioselectively at the less hindered site for *meta*-substituted substrate (Me, **1k**), yielding a mixture of isomers **3ka** as the target product. Diverse mono-substituted acetophenone *N*-acetyl hydrazones with either electron-donating (Me, Bu, Ph, OMe, OPh) or

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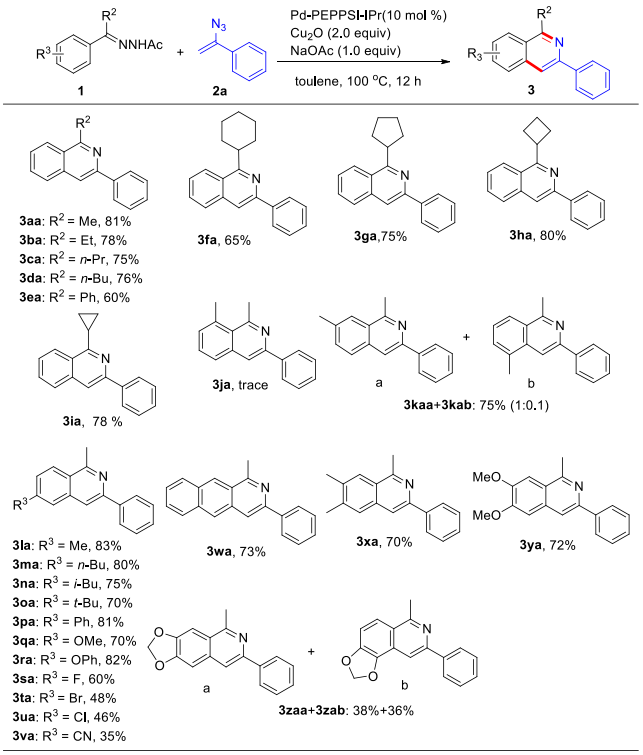
electron-withdrawing (F, Br, Cl, CN) group on the *para*-position of the phenyl ring proceeded well in this reaction and transformed to the desired products in moderate yields (**3la-3ra**, **3sa-3va**). 1-Acetylnaphthalene hydrazone was also reactive for the transformation, yielding the corresponding product **3wa**. Furthermore, this method was suitable for disubstituted *N*-acetyl hydrazones, and the desired products could be isolated in good yields with exclusive regioselectivity (**3xa-3ya**). The reaction of 3,4-methylenedioxy acetophenonehydrazone **1z** with **2a** afforded a 1:1 mixture of two regio isomer **3za** in 74% total yield.

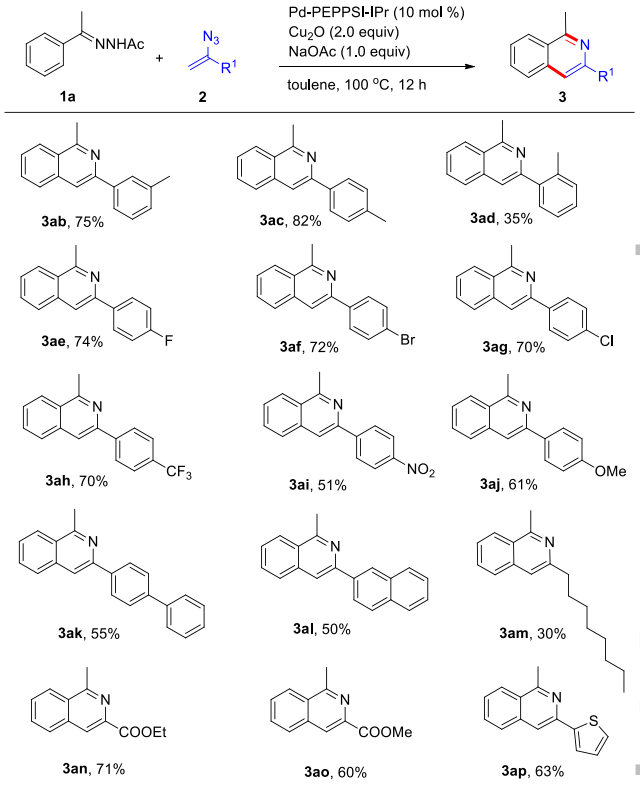
Table 2. Substrate scope of *N*-acetyl hydrazones[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol %), NaOAc (1.0 equiv), Cu_2O (2.0 equiv) in the solvent (2 mL) at 100 °C under air atmosphere for 12 h, unless otherwise noted. [b]Isolated yield.

Next, the scope of the vinyl azide in the coupling with *N*-acetyl hydrazones **1a** under the standard reaction conditions was examined (Table 3). Various substituted vinyl azides could react well with **1a**, leading to the corresponding isoquinoline products in moderate to good yields. The steric effect significantly affected this transformation. *meta*- and *para*-Methyl-substituted substrates proceeded smoothly (**3ab**, **3ac**), while *ortho*-methyl-substituted substrate was converted to the isoquinoline product **3ad** in low yield. Substitution of aryl group of vinyl azides with electron-withdrawing groups, such as fluoride and trifluoromethyl, led to isoquinoline products in 74% and 71% yields respectively (**3ae**, **3ah**). In addition, 1-naphthyl vinyl azide could transfer to the corresponding product **3al** in moderate yield. More importantly, the alkyl and alkoxycarbonyl vinyl azides were also compatible in this transformation, giving the corresponding products **3am**, **3an**, and **3ao**, respectively. Furthermore, the heteroarene vinyl azide was tolerable, converting to the desired product **3ap** in 63% yield.

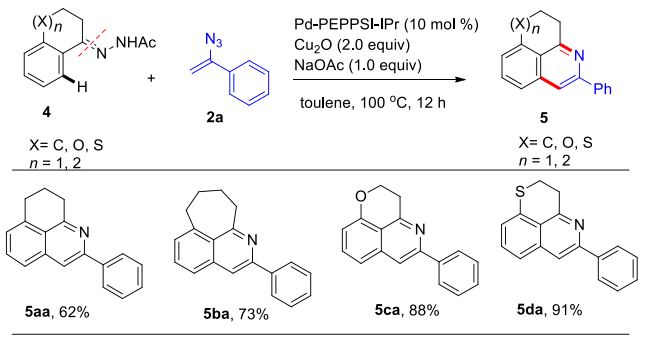
Table 3. Substrate scope of vinyl azides[a], [b]



[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol %), NaOAc (1.0 equiv), Cu_2O (2.0 equiv) in the solvent (2 mL) at 100 °C under air atmosphere for 12 h, unless otherwise noted. [b]Isolated yield.

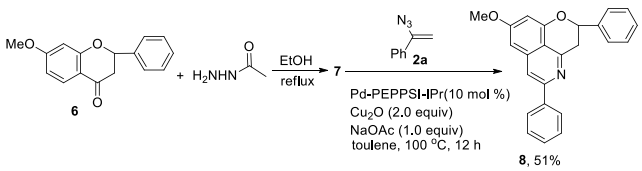
Interestingly, fused isoquinolines could be obtained by this protocol in moderate to good yields (Scheme 4). The transformations of 1-tetralone, 1-benzosuberone hydrazone proceeded smoothly to give the desired polycyclic product **5aa**, **5ba** in moderate yields. Moreover, chroman-4-one, thiochroman-4-one-hydrazone substrates could be converted to polyheterocyclic products **5ca** and **5da** in 88% and 91% yields respectively, which could be further applied to the synthesis of structurally related natural products.

Table 4. Synthesis of fused isoquinolines[a,b]



[a.]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol %), NaOAc (1.0 equiv), Cu_2O (2.0 equiv) in the solvent (2 mL) at 100 °C under air atmosphere for 12 h, unless otherwise noted. [b.]Isolated yield.

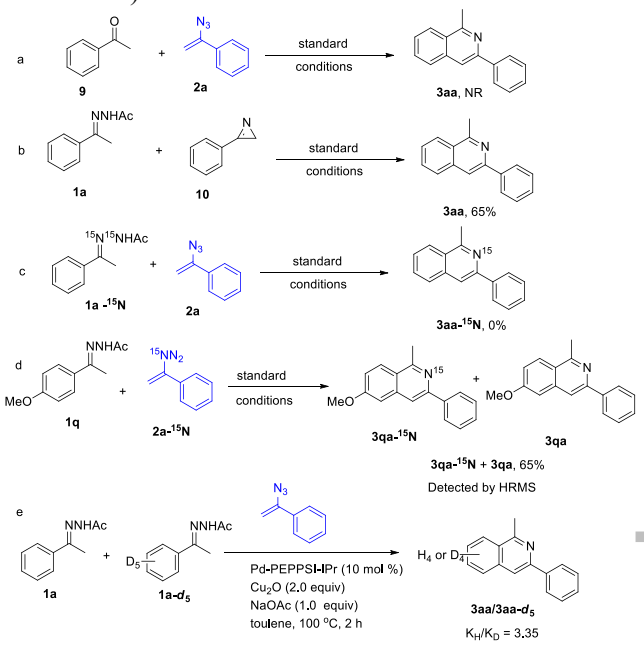
As an exploration of the application of this protocol, the synthetic transformation is shown in Scheme 2. 7-Methoxyflavanone **6**, a flavonoid natural product with a variety of biological activities,[15] could be easily converted to hydrazone **7** and reacted with vinyl azide **2a** to provide desired isoquinoline product **8** in 51% yield.



[a.]Reaction conditions: **6** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol %), NaOAc (1.0 equiv), Cu_2O (2.0 equiv) in the solvent (2 mL) at 100 °C under air atmosphere for 12 h, unless otherwise noted. [b.]Isolated yield.

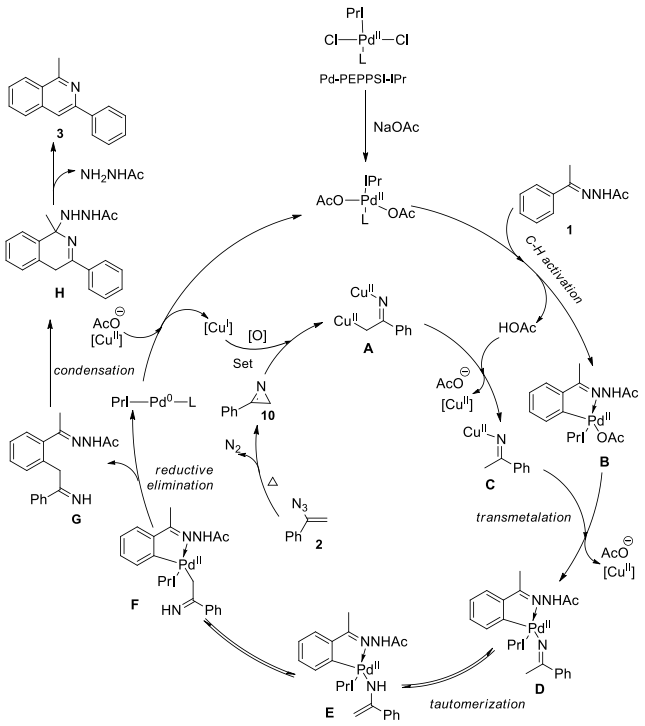
Scheme 2. Synthetic transformations of 7-methoxyflavanone

Several experiments were performed to explore the reaction mechanism. The product **3aa** could not be obtained by reaction of ketone **9** with **2a** under the standard conditions (Scheme 3a), while ary-2*H*-azirine **10** could react with **1a** to afford **3aa** in 62% isolated yield under the same conditions (Scheme 3b), suggesting that ary-2*H*-azirine **10** was an important intermediate involved in the reaction process. Furthermore, when the ^{15}N-labeld hydrazone was added to react with vinyl azide **2a** under the standard condition, the corresponding ^{15}N-labeled product could not be found (Scheme 3c). Comparatively, when using ^{15}N-labeled vinyl azide as the substrate, the ^{15}N-labeled product could be obtained (Scheme 3d). These results revealed that vinyl azide **2a** provided the sole nitrogen source to the formation of product **3aa**. In order to detect kinetic isotope effect, **1a** and deuterated *N*-acetyl hydrazones **1a-*d*$_5$** were added in an intermolecular competition reaction, and the result suggested that C-H activation of **1a** was probably involved in the rate-determining step (k_H/k_D = 3.35, Scheme 3e).



Scheme 3. Mechanistic studies

Based on these experimental results and previous reports,[16] a plausible mechanism is shown in Scheme **4**. The thermal decomposition of vinyl azide **2a** gave 2*H*-azirines **10**, which could be reduced by the Cu(I) species to afford the Cu(II) aza-enolate **A** via single-electron-transfer (SET) process. The removal and exchange the ligand from Pd-PEPPSI-IPr with NaOAc formed the active Pd(II) species. Then, coordination of the nitrogen atom to the Pd(II) center, followed by cleavage of arene *ortho* C-H bond afforded five-membered palladacycle intermediate **B** and accompanied by a release of one equivalent of HOAc. Protonolysis of **A** was proposed to offer iminyl copper species **C**. [17] The transmetalation of **C** with complex **B** gave iminyl palladium species **D**. Subsequently, tautomerization of **D** to its enamine form afforded **E**, which was in equilibrium with its C-bound Pd(II) complex **F**. Then, **F** underwent reductive elimination to provide **G** with generation of Pd(0) species. Finally, intramolecular condensation of **G** led to **H**, followed by elimination of NH_2NHAc delivered compound **3** and a redox reaction between Pd(0) and Cu(II) species regenerated the Pd(II) and Cu(I) catalyst concomitantly.



Scheme 4. Plausible reaction mechanism

Conclusion

In summary, we have developed a Pd(II)-catalyzed C-H activation/C-N cyclization reaction of *N*-acyl hydrazones with α-substituted vinyl azide. C-H bond activation and C-N bond cleavage have been realized by using hydrazone as a traceless directed group. This approach provides a new method for constructing isoquinolines with board substrate scope and functional group tolerance.

Experimental Section

General Procedure for the Synthesis of Isoquinolines

Hydrazone **1** (0.2 mmol), vinyl azide **2** (0.3 mmol), Pd-PEPPSI-IPr (0.02 mmol, 10 mol %), NaOAc (16.4 mg, 0.2 mmol, 1.0 equiv), Cu_2O (57.2 mg, 0.4 mmol, 2.0 equiv). and 2 mL of dry toluene were placed in a 10 ml tube. The reaction mixture was stirred at 100 °C (oil bath) for 12 h. The crude product was cooled to room temperature and concentrated under vacuum to give a residue, which was purified by flash column chromatography to afford the isoquinoline products (silica gel, petroleum ether/ethyl acetate: 20/1, v/v as eluent).

Acknowledgements

We thank the Ministry of Science and Technology of the People's Republic of China (2016YFA0602900), the National Natural Science Foundation of China (21420102003), State Key Laboratory of Anti-Infective Drug Development (SKLAID201803) for financial support.

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10.1002/adsc.201901394

FULL PAPER

Synthesis of Isoquinoline Derivatives via Palladium-Catalyzed C-H/C-N Bond Activation of *N*-Acyl Hydrazones with α-Substituted Vinyl Azides

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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