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Synthesis of 5-Iodo-1,2,3,4-tetrahydropyridines by Rhodium-Catalyzed Tandem Nucleophilic Attacks Involving 1-Sulfonyl-1,2,3-triazoles and Iodides

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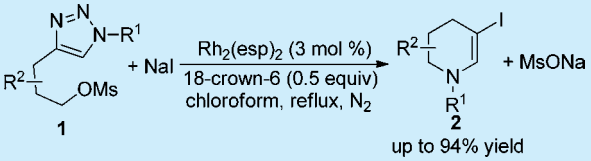
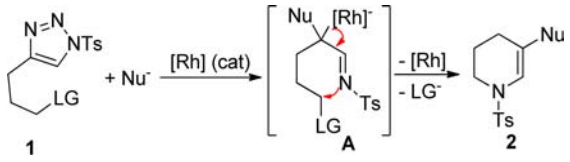
Supporting Information

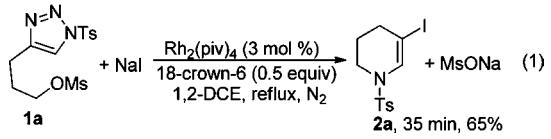
ABSTRACT: Sodium iodide is used for the first time as a nucleophile to trap an α-imino rhodium carbene, which triggers a tandem process involving intermolecular nucleophilic attack and intramolecular S_N2 reaction. A series of 5-iodo-1,2,3,4-tetrahydropyridines are obtained in high yield, and the synthetic utility of the products is demonstrated in cross-coupling reactions and the construction of biorelated polycyclic compounds.



As one of the most important intermediates, metal carbenes derived from diazo compounds or *N*-tosylhydrazones have been applied in various powerful transformations.[1] Environmentally benign approaches starting from alkynes have also been extensively studied in recent years.[2] With landmark contributions from the groups of Fokin, Gevorgyan, and Murakami[3] and subsequent research from other groups,[4] 1-sulfonyl-1,2,3-triazoles, readily available from copper-catalyzed azide–alkyne cycloaddition,[5] can now be conveniently used as precursors of α-imino carbenes. Compared with the traditional α-oxo carbene species, the increased nucleophilic activity of the nitrogen atom makes α-imino carbenes better dipoles, which participate in numerous cycloaddition reactions leading to N-heterocycles.[6] However, as far as we know, in all previous reports the electrophilic part and the nucleophilic part were installed in the same trapping reagent.[7] If the two parts can be set up in two different reagents, more opportunity could be offered for the design of efficient transformations. As part of our research on carbene-mediated chemical transformations,[8] 4-bromo-1,2-dihydroisoquinolines were obtained via intramolecular trapping of α-imino carbenes by tethered benzyl bromide.[8f] This reaction proved the strong electrophilicity of α-imino carbenes. We envisioned that if we installed a leaving group in the triazole, then intermolecular nucleophilic attack at the carbene carbon could be realized by an appropriate reactant, and the increased nucleophilicity of the nitrogen atom would facilitate the intramolecular nucleophilic substitution, leading to the formation of 1,2,3,4-tetrahydropyridines **2** (Scheme 1). It is apparent that several issues should be addressed here: (a) the participation of β-hydride migration, (b) the nucleophilic attack by the leaving group intramolecularly or intermolecularly, and (c) quenching of intermediate **A** by the counterion of the nucleophile. We believe that the nucleophilicity of Nu^- is the key factor, and after several experiments, we found that when **1a** was employed as the substrate and NaI as the nucleophile, 5-iodo-1,2,3,4-tetrahydropyridine **2a** could be obtained in 65% yield in the presence of 3 mol % $Rh_2(piv)_4$ and 0.5 equiv of 18-crown-6 (eq 1).

Scheme 1. Initial Hypothesis





The 1,2,3,4-tetrahydropyridine ring is the key substructure of various natural products,[9] and some of its derivatives are used as food additives, vacuolar pigments, or agricultural pesticides.[10] Thus, the efficient synthesis of this structure is of great importance. Moreover, the vinyl iodide moiety in **2a** provides the possibility of further functionalization using transition-metal-catalyzed coupling reactions.

With the original result in hand (Table 1, entry 1), we first screened different solvents (toluene, $ClCH_2CHCl_2$, and $CHCl_3$). When chloroform was used, the yield of **2a** increased to 88% (entry 4). Gratifyingly, the use of other Rh(II) catalysts was also efficient (entries 5–8), and the yield of **2a** was further improved to 94% when 3 mol % $Rh_2(esp)_2$ was used (entry 8). Switching 18-crown-6 to dibenzo-18-crown-6 did not result in a better yield (entry 9). When the catalyst loading was decreased to 1 mol %, **2a** was obtained in only 59% yield (entry 10). When the reaction was carried out in the presence of 0.3 equiv of 18-crown-6, the cyclization went to completion in 130 min, and **2a** was isolated in 83% yield (entry 11).

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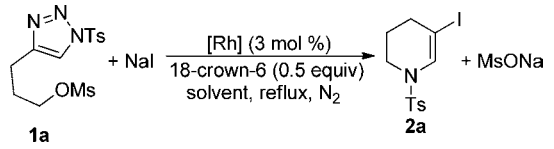
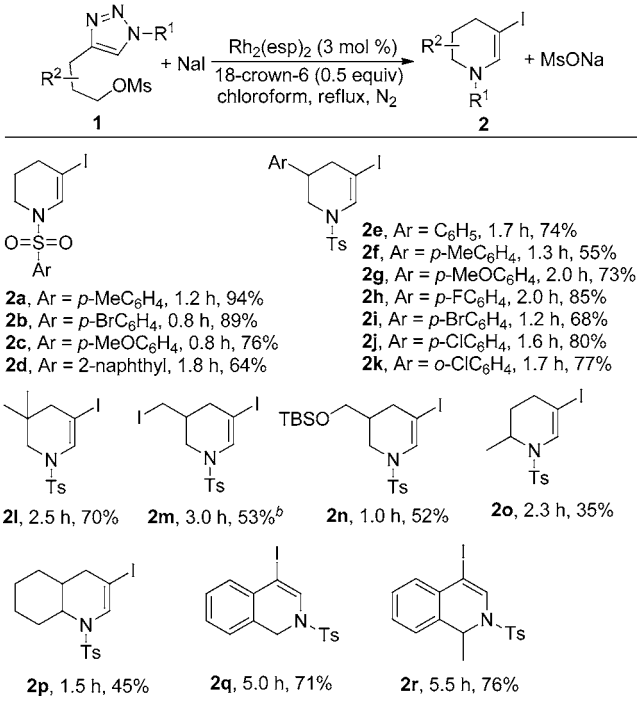
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	t (min)	yield (%)[b]
1	$Rh_2(piv)_4$	1,2-DCE	35	65
2	$Rh_2(piv)_4$	toluene	45	68
3	$Rh_2(piv)_4$	$ClCH_2CHCl_2$	70	14
4	$Rh_2(piv)_4$	chloroform	30	88
5	$Rh_2(OAc)_4$	chloroform	80	50
6	$Rh_2(oct)_4$	chloroform	60	77
7	Rh_2(*S*-nttl)$_4$	chloroform	90	61
8	**$Rh_2(esp)_2$**	**chloroform**	**70**	**94**
9[c]	$Rh_2(esp)_2$	chloroform	100	81
10[d]	$Rh_2(esp)_2$	chloroform	105	59
11[e]	$Rh_2(esp)_2$	chloroform	130	83

[a]0.2 mmol **1a**, 0.3 mmol NaI, 0.1 mmol 18-crown-6 and 0.006 mmol rhodium(II) catalyst dissolved in 2 mL of solvent and heated to reflux under N_2. [b]Isolated yield. [c]0.5 equiv of dibenzo-18-crown-6 was added instead of 18-crown-6. [d]1 mol % of $Rh_2(esp)_2$ was added. [e]0.3 equiv of 18-crown-6 was added.

Scheme 2. Reaction Scope[a]

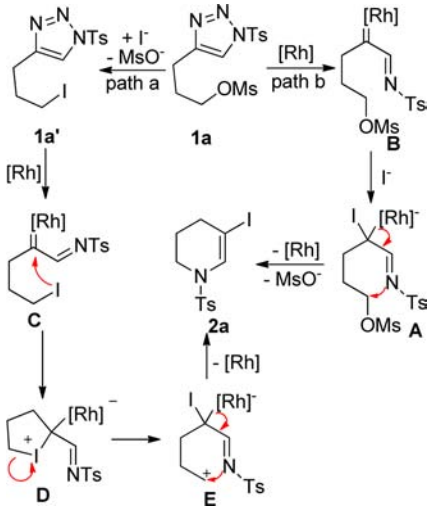


[a]Conditions: 0.2 mmol of **1**, 0.3 mmol of NaI, 0.1 mmol of 18-crown-6, and 0.006 mmol of $Rh_2(esp)_2$ were dissolved in 2 mL of chloroform, and the solution was heated to reflux under N_2. [b]0.5 mmol of NaI was used.

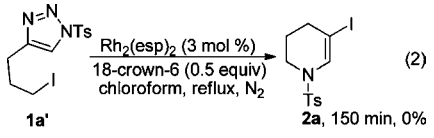
The scope of this transformation is depicted in Scheme 2. This strategy results in the practical preparation of 5-iodo-1,2,3,4-tetrahydropyridines with a high degree of functional group tolerance. Sterically and electronically different arylsulfonyl-substituted triazoles led to the formation of the corresponding products in yields ranging from 64% to 94% (**2a**–**d**). Compound **2e** with a phenyl group at the 3-position of the N-heterocycle was obtained conveniently in 74% yield. Electron-donating substituents on the aromatic ring had a negative effect on the yield of the products (**2f** and **2g**), whereas halo-substituted substrates furnished the tetrahydropyridines in better yields (**2h**, **2j**, and **2k**). When substrate **1i** bearing a *p*-bromophenyl group was treated with NaI in the presence of $Rh_2(esp)_2$, **2i** was isolated in 68% yield after 1.2 h. The substituent at the 3-position of the N-heterocycle could also be an alkyl group. **2l** and **2n** were produced in 70% and 52% yield, respectively, and the optimal conditions were compatible with the TBSO group. We also tried a substrate with two MsO groups (**1m**; see the Supporting Information). In this case, 2.5 equiv of NaI was used. One MsO group participated in the cyclization, and the other one was substituted with an iodide group (**2m**). When substrates with an alkyl group at the α-position of the MsO group were used, **2o** and **2p** were synthesized in lower yields. Finally, substrates with a phenyl linker were also tested, and 4-iodo-1,2-dihydroisoquinolines **2q** and **2r** were obtained smoothly in high yields.

As shown in Scheme 3, two plausible pathways are proposed for this novel cyclization. In path a, substitution of OMs with

Scheme 3. Proposed Mechanism



iodide leads to the formation of **1a′**, which then undergoes rhodium-catalyzed denitrogenation to afford intermediate **C**. Subsequent intramolecular attack of iodide on the carbene carbon produces iodonium ylide **D**, which undergoes cleavage of the C–I bond and nucleophilic attack to give the final product **2a**. On the other hand, in path b the rhodium carbene species **B** is generated initially. Then the attack of iodide on the carbene carbon gives intermediate **A**. Finally, reproduction of the rhodium catalyst and an intramolecular S_N2 reaction result in the formation of **2a**. We noticed that carbocation **E** is involved in path a. Thus, any factors that increase the stability of intermediate **E** should facilitate the formation of **2a**. However, **2o** and **2p** were obtained in inferior yields, which may indicate that path a is not the real mechanism. Moreover, compound **1a′** was synthesized and subjected to the optimized reaction conditions. **1a′** decomposed to an unknown complex mixture after 150 min, and no **2a** was obtained (eq 2).



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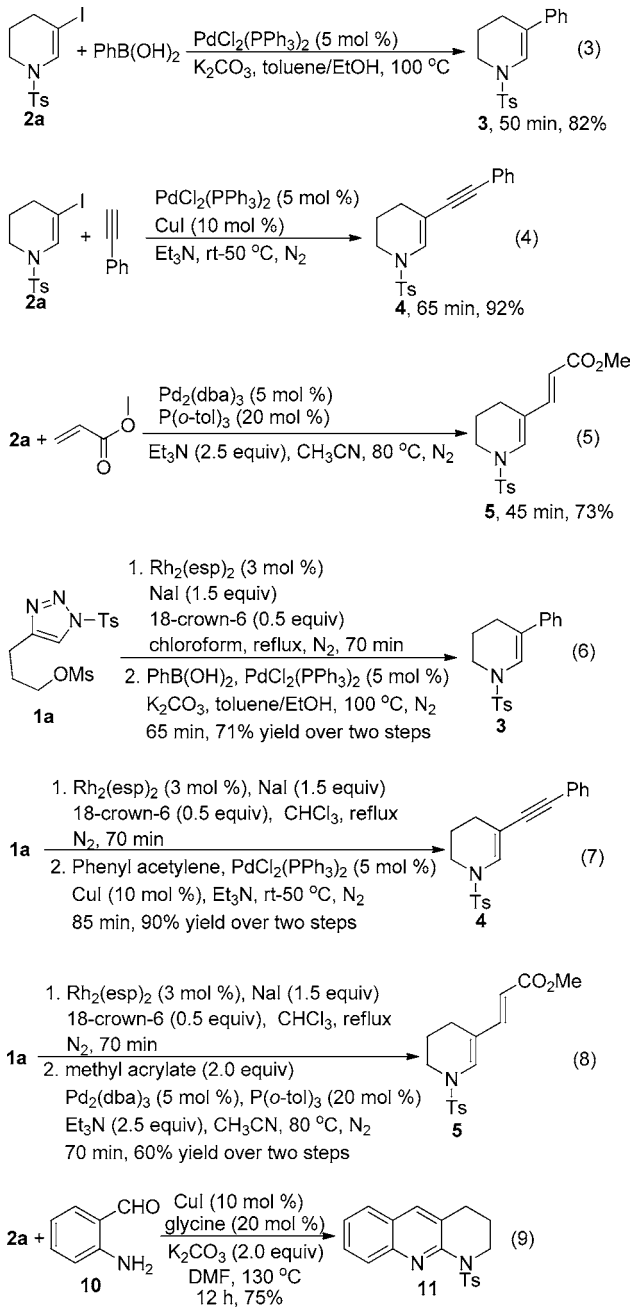
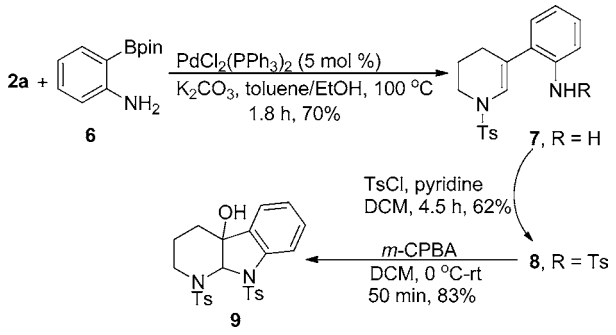


On the basis of the above experiments, path a could be ruled out and path b, which includes an intermolecular nucleophilic attack on the carbene by iodide, is the most plausible mechanism.

Compound **2a** bearing an iodovinyl group was successfully employed in several classical cross-coupling reactions. Tetrahydropyridine derivatives **3**, **4**, and **5** were obtained in high yields (eqs 3−5). To simplify the operating procedure, we tried one-pot sequential reactions.[8f] After reaction for 70 min, the reaction mixture was cooled to room temperature, and chloroform was evaporated. New catalysts and reaction reagents were added, and the reaction proceeded at certain temperature until the full conversion of **2a**. Compounds **3**−**5** were isolated in moderate to high yields (eqs 6−8). Starting from **2a** and 2-aminophenylpinacolborane (**6**), pyrido[2,3-*b*]indoline **9** could be generated via Suzuki−Miyaura coupling and subsequent oxidative cyclization (Scheme 4).[11] Moreover, in the presence of a catalytic amount of CuI and glycine, **2a** condensed with

Scheme 4. Synthesis of Compound 9



2-aminobenzaldehyde (**10**) to furnish tetrahydrobenzo[*b*][1,8]-naphthyridine **11** in 75% yield (eq 9).[12]

In conclusion, various 5-iodo-1,2,3,4-tetrahydropyridines were efficiently synthesized by a novel rhodium-catalyzed tandem process. The reaction proceeds under mild conditions, and a broad range of functional groups are well-tolerated. For the first time, NaI has been employed as a nucleophile to attack α-imino carbenes, and the nucleophilic part and electrophilic part are from different trapping reagents. A series of one-pot reactions and syntheses of several valuable polycyclic compounds have been realized, which means this work should find broad application in the construction of biologically relevant molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02428.

Experimental procedures, characterization data, and NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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