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Selective Cyclization of Arylnitrones to Indolines under External Oxidant-Free Conditions: Dual Role of Rh(III) Catalyst in the C−H Activation and Oxygen Atom Transfer

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Supporting Information

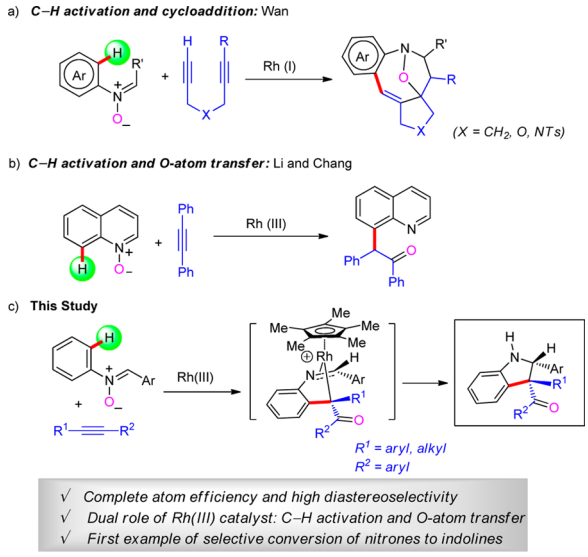
ABSTRACT: The first example of Rh(III)-catalyzed cyclization of arylnitrones to indolines under external oxidant-free conditions is presented. An intermolecular coupling of arylnitrones with internal alkynes is made possible by the dual role of the Cp*Rh(III) catalyst mediating both the C−H bond activation and O-atom transfer. Synthetically important and pharmacologically privileged indoline derivatives were obtained in good yields with high diastereoselectivity.

Transition-metal-catalyzed C−H bond functionalization has emerged as a powerful tool for synthetic innovations.[1] Due to the oxidative nature of the dehydrogenative C−H coupling reactions, stoichiometric amounts of (external) oxidants are frequently required. In this regard, development of transition-metal-catalyzed redox-neutral C−H activation procedures[2] has received much attention in which redox-active functional groups serve as a directing group as well as an oxidant.[3]

In recent years, the nitrone group has played a vital role in developing an array of notable reactions especially due to the polar nature of N−O bond.[4] In addition, one unique advantage of using nitrones as redox-active reactants is that they do not necessitate stoichiometric amounts of external oxidants and they are easy to prepare from readily available nitrobenzenes in a single step.[5] In the course of nitrone transformations,[6] versatile intermediates such as imines or metal carbenoids can be generated *in situ* which are utilized efficiently in the rapid assembly of important heterocycles through cascade reactions.[7] For instance, Wan et al. reported a Rh(I)-catalyzed efficient cyclization of diynes with nitrones (Scheme 1a).[8] While a new C−C bond forms at the *N*-phenyl ring, the bridged eight-membered heterocycles are accessed through [2 + 2 + 5]-cycloaddition. On the other hand, the catalytic O-atom transfer (OAT) from quinoline *N*-oxides to alkynyl triple bonds was reported independently by Li's and our group (Scheme 1b).[9]

During the course of our studies in developing direct C−H functionalization reactions,[10] we found new aspects of nitrones in the Rh(III)-catalyzed cyclization with internal alkynes. Described herein is the novel synthetic utility of arylnitrones in accessing indolines under external oxidant-free conditions. The rhodium catalyst was found to play a dual role in the C−H bond activation and O-atom transfer. Significantly, the imino moiety of nitrone group is incorporated into the indoline ring in a stereoselective manner (Scheme 1c).[11]

Scheme 1



We commenced our optimization study by examining a reaction of phenylnitrone (**1a**) with diphenylacetylene (**2a**, Table 1). When $[RhCp^*Cl_2]_2$ (4 mol %) was employed in the presence of $AgSbF_6$ (16 mol %), an isomeric mixture of cyclized indoline products (**3a** + **3b**) was formed with moderate efficiency and stereoselectivity (entry 1).

The structure of the major product (**3a**) was confirmed by an X-ray crystallographic analysis indicating that two phenyl groups at the C-2 and C-3 position of a newly generated five-membered ring are in an *anti* relationship. The cyclization efficiency was significantly improved by the addition of certain acids (entries 2−5; see the Supporting Information for details).[12] Among those acids screened, pivalic acid (0.5 equiv) was especially effective to provide excellent product yields together with a high diastereomeric ratio (*dr*, 87:13 of crude reaction mixture determined by ^1H NMR). Interestingly, a catalyst derivative of Rh(III) replacing Cp* with (1,3-di-*tert*-butyl)cyclopentadienyl (Cp^t)[13] was found to be also effective in this cyclization, but with lower efficiency and selectivity (entry 6). While the reaction did

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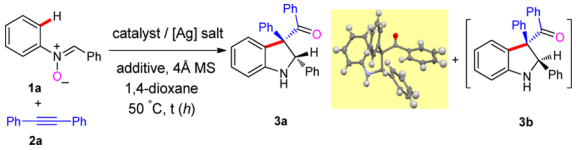
Table 1. Optimization of Reaction Condition[a]



entry	catalyst/[Ag] salt	additive	t (h)	yield (%) (**3a:3b**)[b]
1	$[RhCp^*Cl_2]_2/AgSbF_6$	–	36	42 (76:24)
2	**$[RhCp^*Cl_2]_2/AgSbF_6$**	**PivOH**	**8**	**93 (87:13)**
3	$[RhCp^*Cl_2]_2/AgSbF_6$	AcOH	10	78 (68:32)
4	$[RhCp^*Cl_2]_2/AgSbF_6$	$PhCO_2H$	8	62 (65:35)
5	$[RhCp^*Cl_2]_2/AgSbF_6$	1-AdOH	10	49 (80:20)
6	$[RhCp^tCl_2]_2/AgSbF_6$	PivOH	12	78 (60:40)
7	$[RhCp^*Cl_2]_2$	PivOH	36	N.R.
8	$Ru(p\text{-cymene})Cl_2]_2/AgSbF_6$	PivOH	36	N.R.
9	$[IrCp^*Cl_2]_2/AgSbF_6$	PivOH	36	N.R.
10[c]	$[RhCp^*Cl_2]_2/AgSbF_6$	PivOH	8	56 (61:39)
11[d]	$[RhCp^*Cl_2]_2/AgSbF_6$	PivOH	6	81 (52:48)

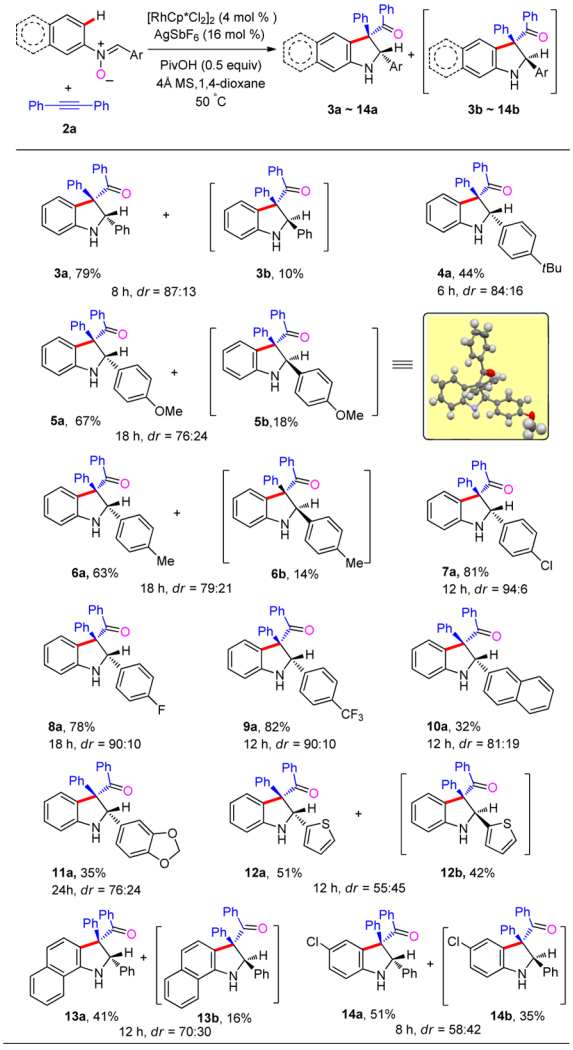
[a] **1a** (0.24 mmol), **2a** (0.20 mmol), catalyst (4.0 mol %), [Ag] salt (16 mol %), molecular sieves (4 Å), and additive (0.5 equiv) in 1,4-dioxane (1 mL). [b] Combined yield and *dr* of **3a:3b** determined by ^{1}H NMR (internal standard: 1,1,2,2-tetrachloroethane) of crude reaction mixture. [c] In 1,2-dichloroethane. [d] In benzene. PivOH = pivalic acid; 1-AdOH = 1-Adamantanecarboxylic acid. Cp* = C_5Me_5; Cp^t = (1,3-di-*tert*-butyl)cyclopentadienyl.[13] N.R. = No reaction.

not proceed in the absence of a silver salt (entry 7), other catalytic systems (e.g., Ru or Ir) which were known to mediate C−H functionalization were totally ineffective (entries 8−9). 1,4-Dioxane worked most effectively as a solvent while others such as 1,2-dichloroethene or benzene were less efficient giving moderate product yields and low diastereoselectivity (entries 10−11).

With the optimal conditions in hand, we first examined the scope of arylnitrones containing various substituents in cyclization with diphenylacetylene (Table 2). While product yields were moderate to high, the diastereoselectivity was varied depending on the substituents of arylnitrones.[14] It must be mentioned that two isomers were easily separated by silica gel column chromatography in most cases. In general, the cyclization took place with high stereoselectivity with substrates bearing electron-withdrawing substituents at the phenylimino moiety of nitrones. A similar level of selectivity was also observed with substrates having 4-*tert*-butyl, 4-methoxy, and 4-methyl groups (**4a**−**6a**, 84:16, 76:24, and 79:21, respectively). A minor isomer (**5b**) was unambiguously characterized by an X-ray crystallographic analysis to confirm its stereochemistry. Significantly, the cyclization of substrates bearing electron-withdrawing groups such as 4-chloro, 4-fluoro, and 4-trifluoro at the phenyl imino moiety of nitrones proceeded with excellent diastereoselectivities (**7a**−**9a**). However, a nitrone compound containing a 2-naphthyl group at the α-position underwent the cyclization with rather low efficiency (**10a**). While the reaction efficiency of nitrone substituted with benzodioxol was moderate (**11a**), that of a 2-thiophenyl group was smooth albeit in an almost nonselective manner (**12a**−**12b**). In addition, substrates changing the *N*-aryl moiety of nitrones with 1-naphthyl or 4-chlorophenyl also underwent the cyclization smoothly, but with variable diastereoselectivities (**13a**−**13b** and **14a**−**14b**, respectively).

The scope of the alkyne reactant was subsequently investigated (Table 3). Diphenylacetylenes bearing electron-

Table 2. Substrate Scope of Arylnitrones[a]



[a] **1** (0.24 mmol) and **2a** (0.20 mmol) in 1,4-dioxane (1 mL) at 50 °C; *dr* of crude reaction mixture determined by ^{1}H NMR (internal standard: 1,1,2,2-tetrachloroethane); isolated yields are given.

donating groups such as 4-methyl and 4-trifluoromethoxy were facile for the present cyclization with high diastereoselectivity (**15**−**16**). Halide-substituted diphenylacetylenes underwent the cyclization to afford satisfactory results. For example, when nitrone **1a** was subjected to the optimized conditions with arylalkynes bearing chloro, fluoro, or bromo substituents at the *para*-position, the desired cyclization reactions took place in high efficiency and diastereoselectivity (**17**−**19**).

We were also pleased to observe that an unsymmetrical alkyne was reacted with respectable selectivity.[15] For instance, when 1-phenylpropyne was reacted with **1a** under the standard conditions, a mixture of isomeric products **20a** and **20b** was obtained with high diastereoselectivity without detecting compound **20c**. The structure of **20a** was unambiguously confirmed again by an X-ray crystallographic analysis. A similar result was obtained with 1-phenyl-1-hexyne giving an isomeric mixture of products (**21a**−**21b**). In the cyclization of **1a** with alkylarylalkynes, moderate product yields were obtained mainly due to sluggish reaction progress. However, other types of reactants such as dialkylacetylenes, enynes, propiolates, or terminal alkynes were not reactive. On the other hand, bis(3-thienyl)acetylene was reacted with nitrone **1a** and 4-chloro α-

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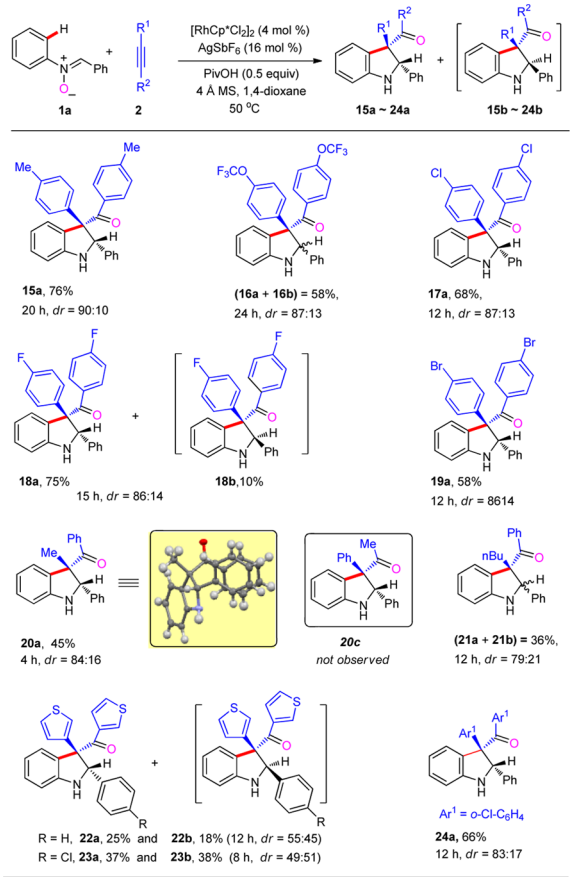
Table 3. Substrate Scope with Alkynes[a]

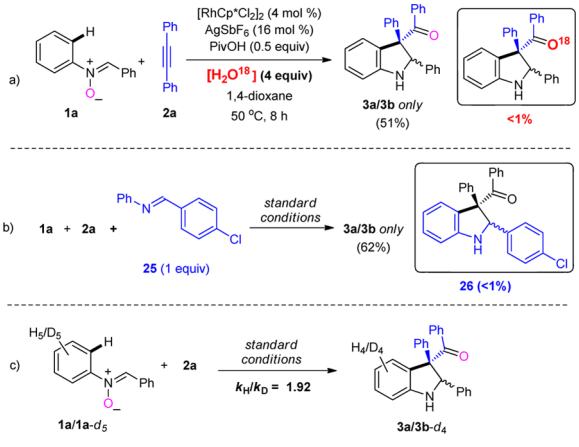


[a] **1a** (0.24 mmol) and **2** (0.20 mmol) in 1,4-dioxane (1 mL) at 50 °C; *dr* of crude reaction mixture determined by ^{1}H NMR (internal standard: 1,1,2,2-tetrachloroethane); isolated yields are given.

phenyl nitrone with low diastereoselectivity (**22**–**23**). Diphenylacetylene bearing an *ortho*-substituent was reacted smoothly with reasonable efficiency and selectivity (**24a**).

To explore the mechanistic aspects on the O-atom transfer process, a key step in the present cyclization, a reaction of **1a** with **2a** was conducted in the presence of excessive H_2O^{18} (Scheme 2a). The obtained products (51%) were analyzed to indicate that the ^{18}O atom was not incorporated. This result suggests that water is not the O-atom source and that the OAT proceeds most

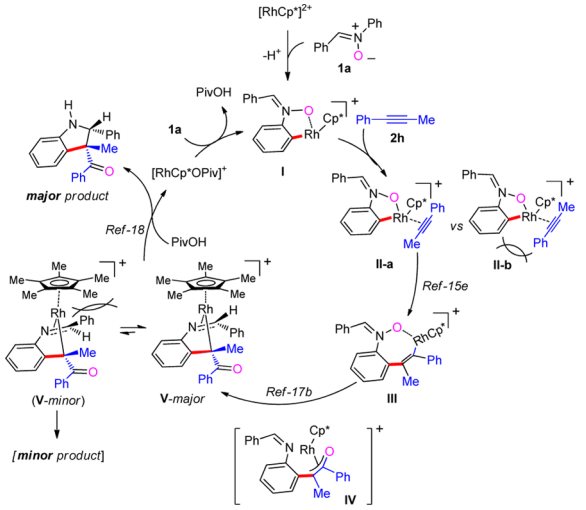
Scheme 2. Preliminary Mechanistic Studies



likely via an intramolecular manner.[9] In this line, when the cyclization was conducted in the presence of a benzylidene compound (**25**), only **3a** and **3b** were produced in moderate yield and diastereoselectivity without forming **26** (Scheme 2b). Notable kinetic isotope effects were measured (k_H/k_D = 1.92) to imply that the C−H bond cleavage may be involved in the rate-limiting step (Scheme 2c).[16]

On the basis of the preliminary mechanistic studies and precedent literature,[8,15,17,18] a plausible cyclization pathway is proposed in Scheme 3. Upon the formation of a rhodacycle **I**

Scheme 3. Plausible Mechanism



from a cationic rhodium species and nitrone,[8] an alkynyl triple bond can be inserted across the Rh−C bond to generate an alkenyl intermediate **III**.[15e] As reported by Fagnou et al.[15a,g] this insertion is assumed to be controlled by electronic as well as steric factors, favoring **II-a** instead of **II-b**. On the other hand, the alkyne insertion into the Rh−O bond cannot be completely ruled out at the present stage.[9] The subsequent O-atom transfer (OAT) is proposed to occur in two pathways: (i) cleavage of the N−O bond to form a Rh(V) oxo species that undergoes the reductive elimination to afford a Rh(III)-enolate (**IV**)[17a] or (ii) reductive elimination of **III** to form a benzoxazine[17b] and Rh(I) followed by oxidation of Rh(I) to Rh(III) via N−O cleavage leading to **IV**. A rearrangement of rhodium enolate (**IV**) and then cyclization will proceed via either **V**-*major* or **V**-*minor*, the former being the main pathway leading to the observed major diastereomers. This stereoselectivity is believed to be determined presumably by a steric factor.[18]

In summary, we have developed a Rh(III)-catalyzed coupling reaction of arylnitrones with internal alkynes under external oxidant-free conditions,[19] in which a dual role of the rhodium catalyst is proposed to operate in the C−H bond activation and O-atom transfer process. The cyclization proceeds smoothly under mild conditions giving rise to indoline products in good yields together with moderate to high diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra of products, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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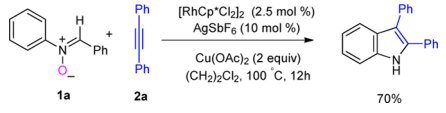
(19) In Wan's report (ref 8), the reaction of **1a** with **2a** provided 2,3-diphenylindole *in the presence of a copper additive*, indicating that the presence of external oxidants may change the reaction pathway:



1a 2a 70%

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