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Highly Stereoselective Ruthenium(II)-Catalyzed Direct C2-*syn*-Alkenylation of Indoles with Alkynes

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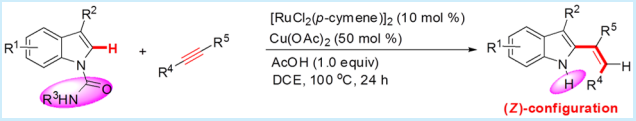
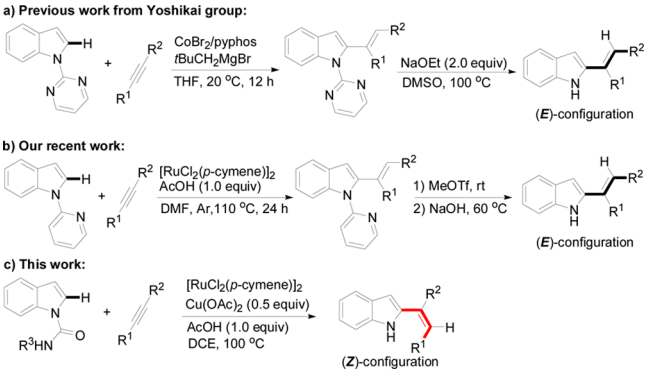
Supporting Information

ABSTRACT: A carboamide-directed ruthenium-catalyzed C2-hydroindolation of alkynes has been described. This transformation provides a rapid access to free (N−H) C2-*syn*-alkenylated indole derivatives with the assistance of copper(II) salts, in which the directing group is removed via a one-pot process.



Arylalkene derivatives belong to important structural motifs of many naturally occurring products and pharmaceutical molecules.[1] In the past few decades, traditional transition-metal-catalyzed Csp^2-Csp^2 bond-formation reactions between prefunctionalized aryl (pseudo)halides[2] or arylmetallic reagents[3] and alkenes have matured into reliable tools for constructing these compounds, except that this method is accompanied by the formation of a stoichiometric amount of hazardous heavy metal and halide salts. Recently, transition-metal-catalyzed direct cross-coupling of aryl Csp^2-H bonds with alkenyl Csp^2-H bonds or alkynyl Csp−H bonds has gained significant interest due to its high atom- and step-economy.[4] Among these various synthetic strategies, hydroindolation of alkynes through chelation assistance has already been demonstrated to enable site-selective installation of an alkenyl group into indole molecules. In this regard, Schipper, Yoshikai, and Kanai groups successively reported that Rh(III) catalysts,[5] Co(II)/Grignard reagent catalytical system (Scheme 1a),[6] or Co(III) catalysts[7] could enhance intermolecular C2-*trans*-alkenylation of indoles, in which an *N*,*N*-dimethylcarbonyl or pyrimidyl group was employed as a directing group, respectively. More recently, we also successfully employed ruthenium catalyst to realize pyridyl-directed C2-*trans*-alkenylation of indoles, and the alkyne scope was further extended to electron-poor internal alkynes and acyl- or alkyl-substituted terminal alkynes (Scheme 1b).[8] However, although directing group assisted C−H functionalizations provided an important approach to the C2-alkenylation indoles, existing methods were only limited to constructing C2-*trans* alkenylated indole derivatives, and the stereoselective C2-*syn*-alkenylation of indoles via the Csp^2-H activation process was rarely reported. Furthermore, the removal of directing groups frequently suffers from tedious reaction workup and harsh reaction conditions.[9] For example, the pyrimidyl and pyridyl directing groups from indole derivatives (Scheme 1a,b) could be removed generally using strong base (NaOEt)[6] and combined MeOTf/NaOH reagents,[8] respectively. Thus, developing one-pot chelation-assisted C2-*syn*-alkenylation of indoles/dedirecting group cascade is a subject of great importance because C2-*syn*-alkenylated indoles were widely used in synthetic organic chemistry.[10] Herein, we described a carboamide-directed C2-hydroindolation of alkynes to furnish free (N−H) C2-*syn*-alkenylated indoles[11] by using cheaply available ruthenium catalysts in which the regioselectivities from unasymmetric internal alkynes were explored (Scheme 1c).

Scheme 1. Different Approach to Free (N−H) Alkenylindoles via Csp^2-H Functionalization



It is known that the carbonyl carbon atom of urea (−HNCONH−) derivatives is easily attacked by nucleophilic reagents and leads to cleavage of the N−C bonds,[12] so we initially designed and synthesized *N*-amido-substituted indoles **1a**, **1b**, and **1c** to investigate the effect of carbamide type on the C2-Hydroindolation of the alkyne/dedirecting group cascade (HADC). First, we screened various Ru catalysts (5 mol %) including $RuCl_3$, $Ru_3(CO)_{12}$, $RuH_2(CO)(PPh_3)_2$, and $[RuCl_2(p\text{-cymene})]_2$, etc., and confirmed that $[RuCl_2(p\text{-cymene})]_2$ (**C**) could realize the C2-HADC between indole-1-carboxylic acid phenylamide **1a** and diphenylacetylene **2a** with very poor yield (5%) in the presence of KH_2PO_4 (1.0 equiv) and AcOH (1.0 equiv) using DCE as solvent at 100 °C

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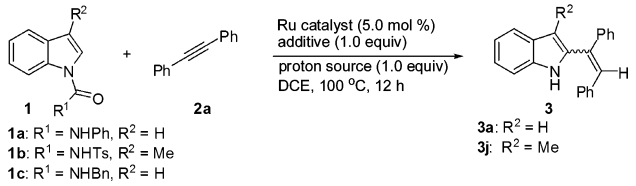
for 12 h (Table 1, compare entries 1−4 with 5). Subsequently, the dimeric species Ru(II) catalyst **C** was found to enable a

Table 1. Optimization of the Reaction Parameters[a]



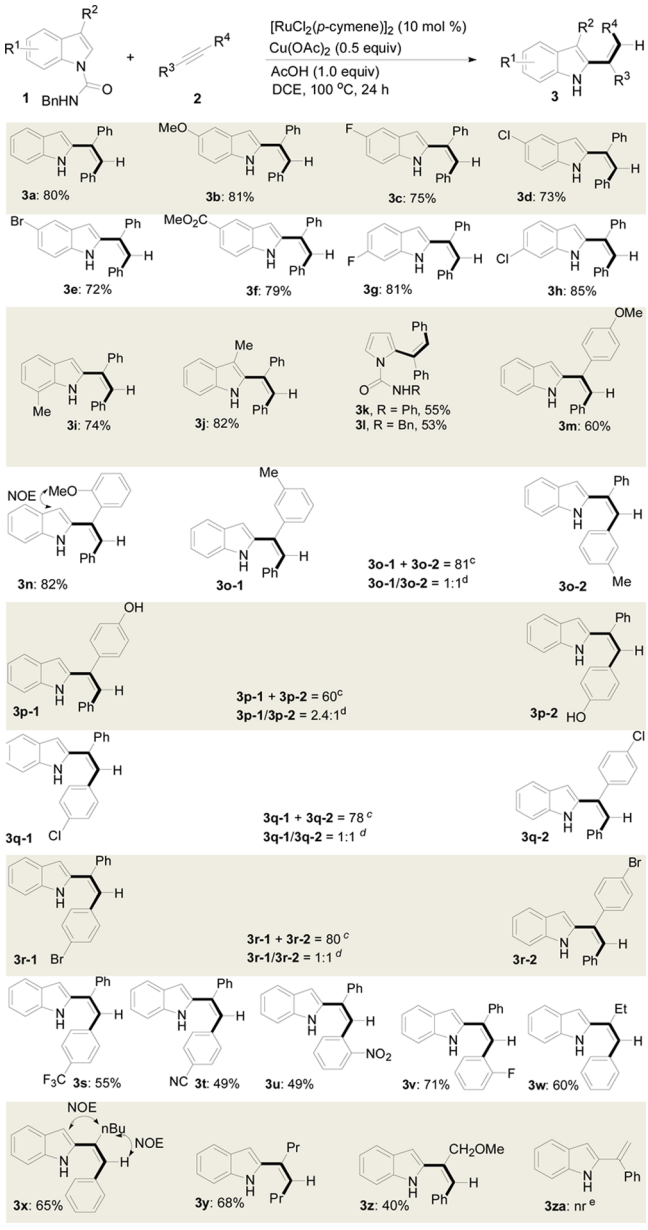
entry	Ru salts	1	additives	proton source	yield[b] (%)
1	$RuCl_3$	**1a**	KH_2PO_4	AcOH	(*E*)-**3a**, nr[c]
2	$Ru_3(CO)_{12}$	**1a**	KH_2PO_4	AcOH	(*E*)-**3a**, nr[c]
3	**A**[d]	**1a**	KH_2PO_4	AcOH	(*E*)-**3a**, nr[c]
4	**B**[e]	**1a**	KH_2PO_4	AcOH	(*E*)-**3a**, nr[c]
5	**C**[f]	**1a**	KH_2PO_4	AcOH	(*E*)-**3a**, 5
6	**C**	**1b**	KH_2PO_4	AcOH	(*E*)-**3j**, 7
7	**C**	**1c**	KH_2PO_4	AcOH	(*E*)-**3a**, 10
8[g]	**C**	**1c**	K_2CO_3	AcOH	(*E*)-**3a**, 60
9	**C**	**1c**	$NaHCO_3$	AcOH	(*E*)-**3a**, 55
10	**C**	**1c**	Ag_2CO_3	AcOH	(*Z*)-**3a**, trace
11	**C**	**1c**	AgOAc	AcOH	(*Z*)-**3a**, 43
12	**C**	**1c**	NaOAc	AcOH	(*E*)-**3a**, 60
13	**C**	**1c**	$Cu(OAc)_2$	AcOH	(*Z*)-**3a**, 67
14	**C**	**1c**	$Cu(OAc)_2$	*i*-PrOH	(*Z*)-**3a**, 53
15	**C**	**1c**	$Cu(OAc)_2$	$PhCO_2H$	(*Z*)-**3a**, 60
16	**C**	**1c**	$Cu(OAc)_2$	CH_3OH	(*Z*)-**3a**, 58
17	**C**	**1c**	$Cu(OAc)_2$	H_2O	(*Z*)-**3a**, 45
18	**C**	**1c**	$Cu(OAc)_2$		(*Z*)-**3a**, 59
19	**C**	**1c**	$Cu(OAc)_2$	AcOH	(*Z*)-**3a**, 60[h]
20	**C**	**1c**	$Cu(OAc)_2$	AcOH	(*Z*)-**3a**, 65[i]
21[g]	**C**	**1c**	$Cu(OAc)_2$	AcOH	(*Z*)-**3a**, 80[j]

[a]Unless otherwise noted, all of the reactions were carried out using *N*-acylindole (**1**) (0.10 mmol) and alkyne (**2a**) (0.20 mmol) with Ru catalyst (5 mol %) in the presence of additives (1.0 equiv) and proton source (1.0 equiv) in DCE (1, 2-dichloroethane, 2.0 mL) at 100 °C for 12 h under Ar in a sealed reaction tube, followed by flash chromatography on SiO_2. The different stereochemistries were assigned according to the results of single-crystal data of **3t** in Scheme 2 and mechanistic studies from Scheme 3. [b]Isolated yield. [c]nr = no reaction. [d]**A** = $RuH_2(CO)(PPh_3)_2$. [e]**B** = $RuHCl(CO)(PPh_3)_3$. [f]**C** = $[RuCl_2(p\text{-cymene})]_2$. [g]No product **3a** was observed in the absence of catalyst **C**. [h]The reaction temperature is 80 °C. [i]The reaction temperature is 120 °C. [j]10 mol % of Ru catalyst **C** and 0.5 equiv of $Cu(OAc)_2$ were used, and the reaction time was 24 h.

further increase of the yield of **3a** from 5% to 10% when indole-1-carboxylic acid phenylamide **1a** was switched to indole-1-carboxylic acid benzylamide **1c** (entries 5−7). Although the conversion of **1c** was very low (entry 7), these positive results further encouraged us to employ **1c** as a model substrate and investigate the effect of various additives and proton sources on this transformation (entries 8−17). Gratifyingly, we quickly found the ruthenium catalyst **C**/$Cu(OAc)_2$/AcOH system could provide us 67% yield of **3a** (entry 13). It is worth noting that 59% yield of **3a** could also be obtained in the absence of any proton sources (compare entry 13 with 18). By the way, lowering or increasing the reaction temperature led to a decreased conversion of **1c** to some degree (compare entries 19 and 20 with 13). Finally, the best yield of **3a** (80%) was obtained at 100 °C for 24 h by using 10 mol % of a Ru catalyst **C**/$Cu(OAc)_2$ (0.5 equiv)/AcOH (1.0 equiv) catalytic system (compare entry 13 with 21) (see the Supporting Informationfor more details about screening of reaction conditions).

Having established an efficient reaction protocol that enables the addition of an *N*-substituted indole C2−H bond to alkyne (**2a**), we first surveyed the reaction scope using a variety of *N*-substituted indoles and diphenylacetylene **2a**. As shown in Scheme 2, the C2-*syn*-alkenylation of various 5- or 6- or 7- *N*-benzylamido-substituted indole substrates proceeded smoothly to afford good to excellent yields of free (N−H) 2-alkenylated indoles with exclusive *Z*-stereochemistry, no matter whether

Scheme 2. Substrate Scope[a]



[a]Unless otherwise noted, all of the reactions were carried out using *N*-substituted indole or pyrrole (**1**) (0.10 mmol) and alkyne (**2**) (0.20 mmol) with $RuCl_2(p\text{-cymene})_2$ catalyst (10 mol %) in the presence of AcOH (1.0 equiv) and $Cu(OAc)_2$ (0.5 equiv) in DCE (2.0 mL) at 100 °C for 24 h under Ar in a sealed reaction tube followed by flash chromatography on SiO_2. [b]Isolated yield. [c]Total isolated yield of the mixture. [d]The ratio was determined by ^1H NMR spectroscopy. [e]nr = no reaction.

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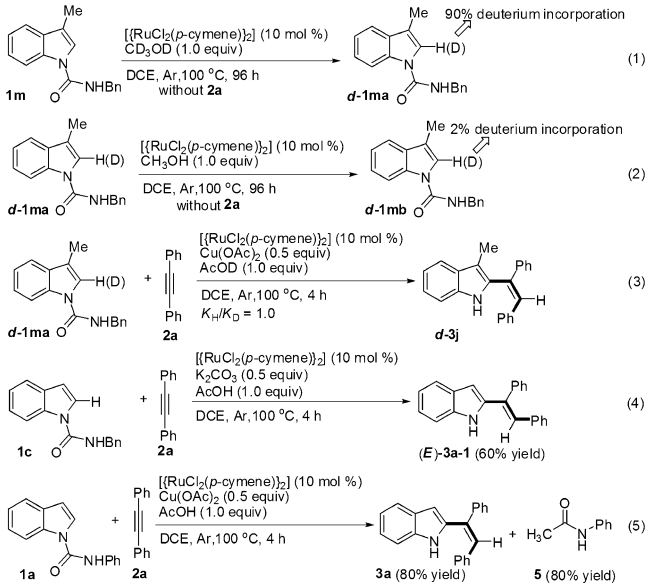
electronic-withdrawing (such as 5-CO_2Et, 5-halide, 6-halide, etc.) or electron-donating groups including 5-MeO and 7-Me are introduced to the benzene ring. For example, the C2-*syn*-alkenylation of diphenylacetylene (**2a**) with 5-ethoxycarbonyl-*N*-(benzylamido) indole and 7-methyl-*N*-(benzylamido)indole could furnish the desired alkenylation product **3f** and **3i** in 79% and 74% yield, respectively. Moreover, the 3-methyl-substituted indole could also furnish the desired *syn*-alkenylated indole **3j** in 82% yield. Interestingly, this reaction protocol could also smoothly convert *N*-(phenylamido)pyrrole and *N*-(benzylamido)pyrrole to the corresponding 2-alkenylated pyrrole **3k and 3l** in 55% and 53% yield, respectively, in which the amide directing groups were not removed.

Subsequently, the scope of the C2-HADC with regard to alkynes was then explored using **1c** as an indole source. It was found that this transformation tolerated a variety of electron-rich and electron-poor diaryl internal alkynes which could provide the desired (*Z*)-alkenylation indoles in moderate to excellent yields. Among the tested unsymmetric internal alkynes, 4-methoxylphenyl phenyl internal alkynes, 2-methoxylphenyl phenyl internal alkynes, and strong electron-withdrawing group substituted phenyl phenyl interal alkynes could high regioselectively furnish *syn*-alkenylated indoles (**3m,n,s−v**) in 49−82% yield. By the way, the lower yields of **3s−u** might be caused by the hydration of electron-poor alkynes. It is worth noting that the single crystal structure of **3t**[13] further demonstrated that C2-HADC occurred preferentially at electron-deficient Csp atom of alkyne and the alkenyl moiety belonged to *Z* conformation.[14] On the contrary, the *m*-Me-phenyl phenyl internal alkyne and 4-Cl, 4-Br, or 4-hydroxyl phenyl phenyl internal alkynes produced the desired *syn*-alkenyl products with different regioselectivity. Moreover, aryl alkyl alkynes, dialkyl alkyne, and aryl methoxymethyl internal alkyne also allowed for this transformation and afforded the corresponding (*Z*)-alkenes (**3w−z**) in good yields with high regioselectivity. Unfortunately, when terminal alkyne was applied to this reaction system, no desired 1,1-disubstituted alkene **3za** was formed.

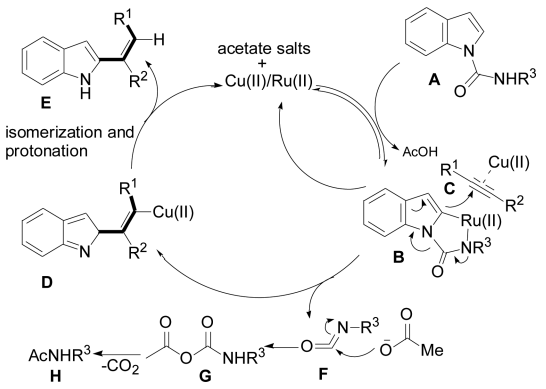
To further investigate the mechanism, the H/D exchange of **1m** was conducted in a Ru(II)/CD_3OD system for 96 h in the absence of alkyne **2a**, and 90% deuterium incorporation at C2-position was observed (Scheme 3, eq 1). It is worth noting that no H/D exchange of **1m** was observed in the absence of Ru(II) catalyst or only in the presence of AcOD. On the other hand, the content of C2-deuterium in ***d*-1ma** under the Ru(II)/CH_3OH system could be decreased from 90% to 2% (eq 2) (see the Supporting Information for the corresponding ^{1}H NMR spectrum). These results remarkably demonstrated that the first step of a reversible Csp^2−H bond cleavage process was involved in the transformation. Subsequently, the intermolecular isotope effect (K_H/K_D = 1.0[15]) further indicated that the reversible Csp^2−H bond breaking was not the rate-limiting step of the reaction (eq 3). Moreover, Ru(II)-catalyzed C-2-*trans*-alkenylation of **1c** in the absence of $Cu(OAc)_2$ confirmed that copper salts played a key role in controlling the steroselectivity of this transformation (eq 4).[16] Finally, the C2-HADC of indole **1a** with **2a** provided 80% yield of *N*-phenylacetamide **5** whose formation demonstrated that acetate salts assisted in removal of the amido group.

The possible mechanism for the C2-HADC is proposed in Scheme 4 on the basis of the above results and the (*Z*)-configuration of the indole-substituted alkenes. First, the transformation was initiated by an acetate-assisted metalation

Scheme 3. Preliminary Mechanistic Studies



Scheme 4. Proposed Catalytic Cycle



to produce the cycloruthenium intermediates **B** with concomitant loss of a proton.[17] Then, the lone-pair electrons from amide nitrogen of **B** triggered the nucleophilic attack to the alkynes (**C**) activated by Cu(II) cations to lead to the formation of the alkenylation intermediates (**D**) and isocyanates (**F**), and **F** was trapped by acetate anions to form the corresponding byproduct amides **H**[18] with the release of CO_2. Simultaneously, the alkenylation metal intermediate **D** could be further isomerized and protonated to produce the final free (N−H) (*Z*)-alkenyl indoles (**E**).

In conclusion, we have described an efficient carboamide-directed ruthenium-catalyzed C2-*syn*-alkenylation of indoles with the assistance of copper salts. This transformation was compatible with variety electron-poor and electron-rich indoles, aryl aryl internal alkynes, aryl alkyl internal alkynes, and alkyl alkyl internal alkynes. More importantly, the present reaction system allows for the rapid assembly of free (N−H) C2-*syn*-alkenylated indoles via a one-pot process. Further studies on the reaction mechanism and synthetic application of this transformation are underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Details for experimental conditions, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all isolated compounds, and the single crystal data of **3t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(11) During preparation of this work, the Kim group reported Rh (III)-catalyzed oxidative C2-*trans*-alkenylation of indoles with alkynes, in which the carboxamide directing group was also removed via a one-pot process; see: Sharma, S.; Han, S.; Shin, Y.; Mishra, N. K.; Oh, H.; Park, J.; Kwak, J. H.; Shin, B. S.; Jung, Y. H.; Kim, I. S. *Tetrahedron Lett.* **2014**, *55*, 3104.

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(13) See the Supporting Information for the single-crystal structure and data of **3t**.

(14) The NOE $^{1}H-^{1}H$ spectrum of **3n** and **3x**, as well as the single-crystal structure of **3t**, demonstrated that the configuration of the alkenyl moiety belongs *Z* stereochemistry, so the other remaining alkenylated products in Scheme 2 were also assigned the *Z* configuration by assuming an analogous reaction pathway.

(15) The KIE value (1.25) was obtained under Ru(II)/Cu(II)/AcOH system; see the Supporting Information for more details.

(16) The ^{1}H NMR of **3a-1** consisted with Co(II)-catalyzed C2-*trans*-alkenylation of indoles with alkynes; see ref 6 and the Supporting Information for more details.

(17) For a review about the carboxylated-assisted ruthenium-catalyzed C−H functionalizations, see: Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281 and references cited therein.

(18) The structure of byproduct *N*-phenylacetamide (**5**) was already confirmed by its ^{1}H NMR and ^{13}C NMR spectra; see the Supporting Information.

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