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Rhodium-Catalyzed Cyclization of 2-Ethynylanilines in the Presence of Isocyanates: Approach toward Indole-3-carboxamides

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Supporting Information

ABSTRACT: Catalytic synthesis of indole-3-carboxamides from 2-ethynylanilines and isocyanates was achieved in the presence of a rhodium catalyst through a tandem-type, cyclization–addition sequence. This tandem-type process can be performed under mild reaction conditions, affording 2,3-disubstituted indoles in a one-pot manner generally in good to excellent yields. The broad substrate scope and good functional group compatibility make the method highly efficient and widely applicable, providing a facile and entirely novel route toward variously substituted indole-3-carboxamides.

Indoles are ubiquitous in biologically active natural products and designed medicinal agents, representing an important class of heterocycles. Therefore, the development of more practical and efficient procedures for preparing functionalized indoles has long been an area of intensive research.[1] Among the range of strategies reported thus far, cyclization of 2-ethynylaniline derivatives has demonstrated high versatility and efficiency for construction of the indole scaffold. Substrates for this transformation are easily prepared via Sonogashira coupling reactions. Various reagents, including bases, ammonium fluorides, and transition metal complexes, have been employed to mediate or catalyze this cyclization process, generally producing 3-unsubstituted indoles.[1a−c,f,g] Conversely, a limited number of methods for the one-pot synthesis of 2,3-disubstituted indoles via cyclization of 2-ethynylanilines and subsequent functionalization at the C3-position are present in the literature. In most cases, palladium catalysts play a crucial role in such tandem-type processes, allowing for access to 2-substituted 3-carbonyl, 3-allyl, 3-alkyl, 3-alkenyl, or 3-arylindoles from 2-ethynylanilines.[2] Several research groups have recently demonstrated the successful use of other transition metal catalysts in a cyclization–C3 functionalization sequence for the construction of substituted indoles.[3,4] Hiroya et al. demonstrated that the use of copper catalysts enabled the cyclization of 2-ethynylanilines followed by intramolecular alkylation, affording tricyclic indole derivatives.[3a] Arcadi's group showed that a gold catalyst was able to participate in a tandem-type process consisting of cyclization and conjugate addition to α,β-enones, which resulted in the formation of 3-alkylindoles.[3b] A noteworthy example was recently reported by Lautens et al., who successfully developed a rhodium–BINAP catalytic system that effected a similar cyclization–conjugate addition reaction to afford 3-alkylindoles.[3c,d,5] Furthermore, we very recently reported the transition-metal-free synthesis of 3-carboxylated indoles via the ring-closing reaction of 2-ethynylanilines and subsequent CO_2 fixation at the C3-position.[6,7] Herein, we describe a novel catalytic cyclization of 2-ethynylanilines in the presence of isocyanates, leading to the one-pot formation of indole-3-carboxamides. This method features the use of a rhodium catalyst, which successfully affects a tandem-type process involving cyclization followed by a coupling reaction with isocyanates. Compared to previous reports regarding the synthesis of 2,3-disubstituted indoles via a cyclization–C3 functionalization process, our reactions proceed under milder conditions (room temperature). The yields are generally good to excellent, and good functional group tolerance is also observed, providing a convenient and highly applicable synthetic route toward indole-3-carboxamides.[8]

Reaction of 2-ethynylaniline **1a** in the presence of a variety of metal catalysts was first examined using propyl isocyanate as a reactant (Table 1, entries 1–6). We were pleased to find that the use of 20 mol % of a rhodium catalyst enabled the desired cyclization–addition process, providing indole **2a** in a relatively good yield in DMF (entry 6). Remarkably, the reaction

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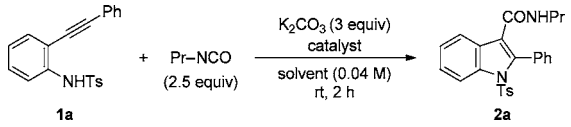
Table 1. Screening of the Reaction Parameters[a]



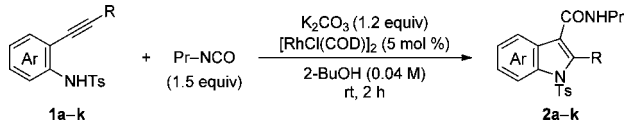
entry	catalyst (mol %)	solvent	yield[b] (%)
1	$Cu(OAc)_2$ (20)	DMF	0
2	$Pd(OAc)_2$ (20)	DMF	0
3	$Ni(acac)_2$ (20)	DMF	0
4	$RuCl_3$ (20)	DMF	0
5	$FeCl_3$ (20)	DMF	0
6	$[RhCl(COD)]_2$ (20)	DMF	56
7	$[RhCl(COD)]_2$ (20)	DMSO	56
8	$[RhCl(COD)]_2$ (20)	MeCN	54
9	$[RhCl(COD)]_2$ (20)	DME	46
10	$[RhCl(COD)]_2$ (20)	1,4-dioxane	40
11	$[RhCl(COD)]_2$ (20)	2-BuOH	76
12	$[RhCl(COD)]_2$ (10)	2-PrOH	69
13	$[RhCl(COD)]_2$ (10)	1-PrOH	73
14	$[RhCl(COD)]_2$ (10)	^{t}amylOH	39
15	$[RhCl(COD)]_2$ (10)	^{i}BuOH	48
16	$[RhCl(COD)]_2$ (10)	^{t}BuOH	46
17	$[RhCl(COD)]_2$ (10)	2-BuOH	84
18	$[RhCl(COD)]_2$ (5)	2-BuOH	84
19[c]	$[RhCl(COD)]_2$ (2.5)	2-BuOH	70
20[d]	$[RhOH(COD)]_2$ (10)	2-BuOH	62
21[c]	$Rh(OAc)_2$ (10)	2-BuOH	0
22[c,d]	$RhCl_3 \cdot H_2O$ (10)	2-BuOH	0
23[e]	$[RhCl(COD)]_2$ (5)	2-BuOH	83

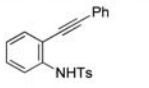
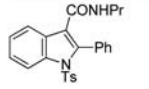
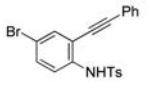
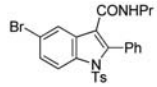
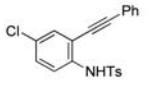
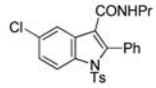
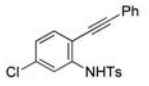
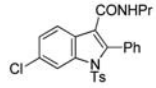
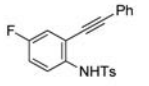
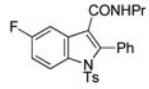
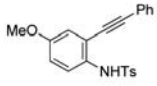
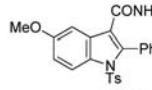
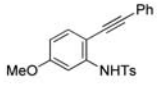
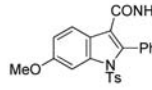
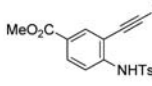
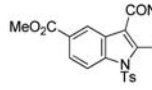
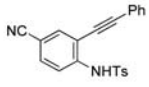
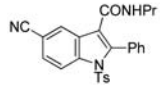
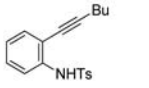
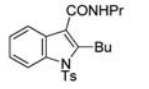
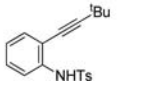
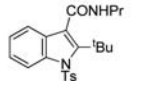
[a]Reactions were performed on a 0.14 mmol scale under an Ar atmosphere. [b]Isolated yield. [c]For 12 h. [d]At 50 °C. [e]With 1.5 equiv of Pr–NCO and 1.2 equiv of K_2CO_3.

proceeded smoothly at room temperature within a couple of hours. Addition of K_2CO_3 as the base was crucial for this transformation.[9] Encouraged by this result, we further examined the reaction using $[RhCl(COD)]_2$ as the rhodium source. Of the solvents investigated, alcoholic solvents such as 2-BuOH were found to be superior (entries 6–10 vs 11). Thus, an array of alcohols was employed as solvents for this reaction in the presence of 10 mol % of a rhodium catalyst (entries 12–17). The best result was obtained when 2-BuOH was used, affording desired indole **2a** in 84% yield (entry 17). The catalyst loading was able to be decreased to 5 mol % without a drop in yield (entry 18). The reaction with 2.5 mol % of a rhodium catalyst also resulted in the formation of **2a** in high yield, implying the efficiency of this catalytic system (entry 19). However, other rhodium sources were less active for the process (entries 20–22). Finally, it was found that the amount of both isocyanate and K_2CO_3 could be considerably reduced while still providing **2a** in high yield (entry 23).[10]

Using the optimized reaction conditions, we examined the generality of the method. These optimal reaction conditions were found to be applicable to variously substituted 2-ethynylanilines **1b–k** (Table 2). Halogen atoms, such as Br, Cl, and F, were all compatible with this transformation; indoles **2b–e** were obtained generally in high yields (entries 2–5). Moreover, the process tolerated various substituents on the benzene rings, such as the electron-donating methoxy group (entries 6 and 7) and the electron-withdrawing alkoxycarbonyl and cyano groups (entries 8 and 9). In the case of substrate **1i**, which contains a cyano group, an increased amount of the

Table 2. Substrate Scope[a]



entry	substrate	1	product	yield[b] (%)
1		**1a**		83
2		**1b**		86
3		**1c**		75
4		**1d**		77
5		**1e**		68
6		**1f**		70
7		**1g**		71
8		**1h**		67
9[c]		**1i**		68
10		**1j**		50
11[d]		**1k**		56

[a]Reactions were performed on a 0.14 mmol scale under an Ar atmosphere. [b]Isolated yield. [c]With 10 mol % of a rhodium catalyst. [d]For 5 h.

catalyst was necessary to obtain a satisfactory result (entry 9). In addition, the reactions of 2-ethynylanilines **1j** and **1k**, which have a terminal alkyl group (i.e., Bu and ^{t}Bu) on the alkyne, also successfully produced desired products **2j** and **2k**, albeit in moderate yields (entries 10 and 11).[11]

The scope of these catalytic conditions was further investigated with respect to isocyanates (Scheme 1). As in the case of propyl isocyanate shown above, alkyl isocyanates such as isopropyl and cyclohexyl isocyanates successfully participated in this process, producing the corresponding indoles **3a** and **3b** in excellent yields. The reaction using benzyl isocyanate also proceeded smoothly, affording **3c** in high yield. In addition, it was found that aryl isocyanates could be applied to this indole synthesis to give **3d** and **3e** in good yields, implying the versatility and applicability of our method.

Although the precise reaction mechanism remains to be elucidated, it seems reasonable to assume that the process occurs

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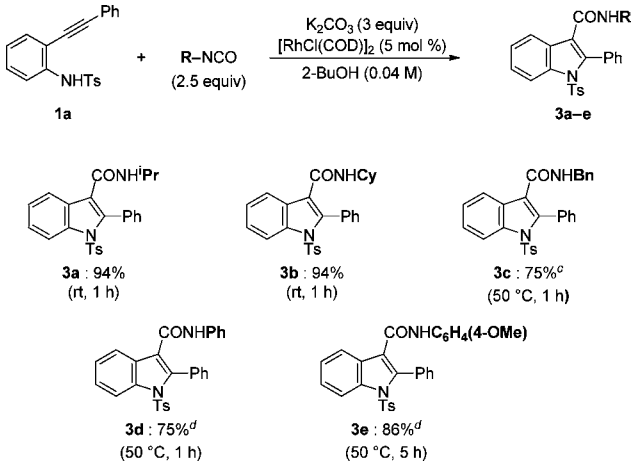
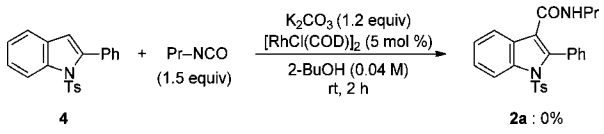
Scheme 1. Use of Various Isocyanates[a,b]



[a]Reactions were performed on a 0.14 mmol scale under an Ar atmosphere. [b]Isolated yield. [c]With 1.5 equiv of Pr−NCO and 1.2 equiv of K_2CO_3. [d]With 10 mol % of a rhodium catalyst.

via a pathway similar to that shown in the previous report by Lautens,[3c,d] in which the formation of a 3-rhodium heterocycle intermediate and the following addition reaction to electrophiles were postulated. To confirm that the formation of a 3-rhodium indole intermediate occurred during cyclization rather than after indole formation, a control experiment was also performed using 3-unsubstituted indole **4** and propyl isocyanate in the presence of a rhodium catalyst under the optimal reaction conditions. As a result, no addition product was obtained, and starting indole **4** was recovered quantitatively (Scheme 2).

Scheme 2. Control Experiment



In summary, we have reported a novel catalytic method for the synthesis of indole-3-carboxamides from 2-ethynylanilines and isocyanates through a tandem-type, cyclization−C3 carboxamidation sequence. The use of a rhodium catalyst enabled the process to be performed efficiently under mild reaction conditions. In addition to the generality of this process regarding the substrate scope, good functional group tolerance is also highly appealing. Further studies to broaden the substrate scope and increase the efficiency of the catalytic system are currently underway. Furthermore, we are applying this approach to the construction of other heterocyclic compounds, the details of which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00007.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for indoles (PDF)

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Notes

The authors declare no competing financial interest.

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(9) The use of other bases such as Cs_2CO_3 and K_3PO_4 led to decreased yields.

(10) A synthetic method for preparing indole-3-carboxamides from 2-ethynylanilines and isocyanides in the presence of a palladium catalyst was recently reported: Hu, Z.; Liang, D.; Zhao, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 7371.

(11) The effect of the substituent on the nitrogen atom of 2-ethynylanilines was also briefly examined. Whereas the cyclization of the substrate possessing a mesyl group (−Ms) proceeded in high yield (78%), *N*-acetyl and *N*-benzyl-2-ethynylanilines were completely inactive and none of the desired products were obtained. The reaction of N-free 2-ethynylaniline also did not afford the indole product.

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