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C–H Activation

Ruthenium-Catalyzed C7 Amidation of Indoline C–H Bonds with Sulfonyl Azides

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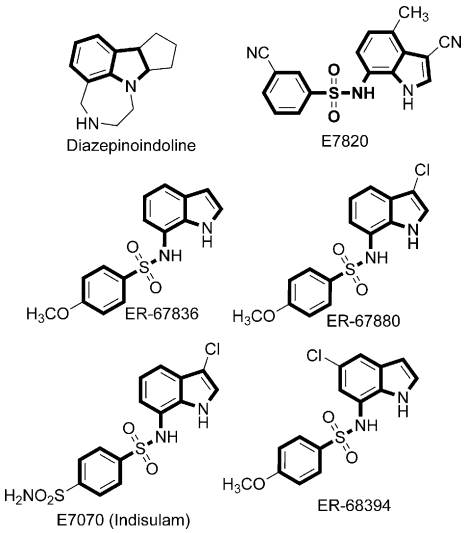
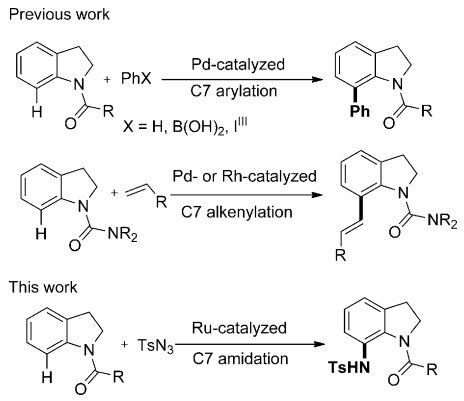
Abstract: A ruthenium-catalyzed direct C7 amidation of indoline C–H bonds with sulfonyl azides was developed. This procedure allows the synthesis of a variety of 7-amino-substituted indolines, which are useful in pharmaceutical. The good functional tolerances, as well as the mild conditions, are prominent feature of this method.

The formation of C–N bonds has been widely studied in the past decades, because C–N bonds are prevalent in numerous natural products and biologically active molecules.[1] Copper-catalyzed Ullmann and Goldberg couplings,[2] as well as palladium-catalyzed Buchwald–Hartwig aminations[3] with haloarenes have been widely accepted as the most efficient methods to construct C–N bonds. The Chan–Lam coupling reaction with boronic acids is also an efficient method that features mild reaction conditions.[4] However, prefunctionalization is required in these reactions. Undoubtedly, the direct amination/amidation of C–H bonds to form C–N bonds represents a straightforward and promising approach, because it obviates the prefunctionalization of substrates.[5] The rhodium-catalyzed C–H amidation by using sulfonyl azides as an amino source along with gaseous nitrogen as a by-product was first reported by Chang[6] and other groups.[7] Subsequently, in 2013, Chang,[8] Sahoo,[9] Jiao,[10] and Ackermann[11] independently reported the ruthenium(II)-catalyzed amidation of C–H bonds with sulfonyl azides.

The indoline scaffold is a ubiquitous structural motif found in many alkaloid natural products and bioactive molecules.[12] Many pharmaceutical scaffolds include C7-substituted indolines or their derivatives (Scheme 1).[13] Therefore, the directing-group-assisted selective C–H bond functionalization of indolines at the C7 position is synthetically attractive. For example, the *N*-acyl group was employed to accomplish the C–H arylation of indolines at the C7 position (Scheme 2).[14] Recently, Oestreich reported the Pd-catalyzed C7 alkenylation of indolines by using urea as a directing group (Scheme 2).[15] Shortly afterwards, Antonchick described a Rh-catalyzed C7 alkenylation of indolines (Scheme 2).[16] However, the C–H functionalization of indolines at the C7 position has only limited reports. Moreover, the C–H amidation of indolines at the C7 position has never been reported, although 7-amino-substituted indolines are particularly useful in pharmaceuticals (Scheme 1). Herein, we disclose a ruthenium-catalyzed direct C7 amidation of indoline C–H bonds with sulfonyl azides.



Scheme 1. Pharmaceutical scaffolds including C7-substituted indolines and their derivatives.



Scheme 2. C–H bond functionalizations of indolines at the C7 position.

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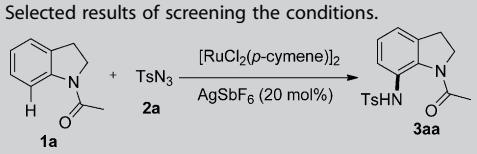
Table 1. Selected results of screening the conditions.



Entry	Additive	Solvent	T [°C]	Yield [%][a]
1	$Cu(OAc)_2$	THF	80	0
2	$Cu(OAc)_2$	CH_3CN	80	0
3	$Cu(OAc)_2$	dioxane	100	32
4	$Cu(OAc)_2$	toluene	110	16
5	$Cu(OAc)_2$	CH_3OH	80	10
6	$Cu(OAc)_2$	DMF	120	trace
7	$Cu(OAc)_2$	HOAc	120	trace
8	$Cu(OAc)_2$	DCE	80	75 (0)[c]
9	AgOAc	DCE	80	76[b](0)[c]
10	KOAc	DCE	80	trace
11	CsOAc	DCE	80	trace
12	–	DCE	80	27

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), additive (50 mol%), solvent (1 mL), 24 h, isolated yield. [b] 10 h. [c] No $AgSbF_6$ was used.

Initially, we examined the reaction of *N*-acetylindoline (**1a**) with tosyl azide (**2a**) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), and $Cu(OAc)_2$ (50 mol%). The effect of solvent is vital to this amidation reaction. Among the solvents screened, 1,2-dichloroethane (DCE) was the best, providing **3aa** in 75% yield. Other solvents such as dioxane gave only a poor yield of the product (Table 1, entry 3), whereas THF and CH_3CN were totally ineffective (Table 1, entries 1 and 2). In the absence of an additive, the reaction provided 27% yield (Table 1, entry 12). Only traces of the product were detected when KOAc or CsOAc was employed in the reaction (Table 1, entries 10 and 11). However, AgOAc enhanced the product formation and shortened the reaction time, affording **3aa** in 76% yield (Table 1, entry 9). Further studies showed that no product was obtained in the absence of $[RuCl_2(p\text{-cymene})]_2$ or $AgSbF_6$.

To evaluate the substrate scope of this protocol, the optimized reaction conditions were applied to a range of indolines. As illustrated in Figure 1, *N*-acetyl indolines bearing a series of substitutions at the C2, C3, C4, or C5 positions were compatible in this reaction, giving good yields. Halogen-substituted indolines were tolerable, affording the corresponding halogen-substituted products in good yields (Figure 1, **3ca**–**3ea**). In particular, the bromo group was kept intact during the course of the reaction, which is valuable for further transformations. Multisubstituted indolines with substitution either at C2 or C3 also provided the products in good yields (Figure 1, **3ia** and **3ja**). Moreover, *N*-benzoyl, *N*-pivaloyl, and *N*-1-butyryl indolines were readily amidated under the present conditions (Figure 1, **3ka**–**3ma**).

Next, we further explored the scope of different sulfonyl azides, and the results are summarized in Figure 2. All the reactions ran smoothly with indoline **1a**, giving good yields, and various functional groups, such as methoxy, fluoro, chloro, bromo, nitro, and trifluoromethyl groups, were tolerated. Naphthalene-2-sulfonyl azide also participated readily in the amidation process to provide the product in a good yield (Figure 2, **3aj**). Notably, thiophene-2-sulfonyl azide also worked well under the standard conditions (Figure 2, **3ak**).

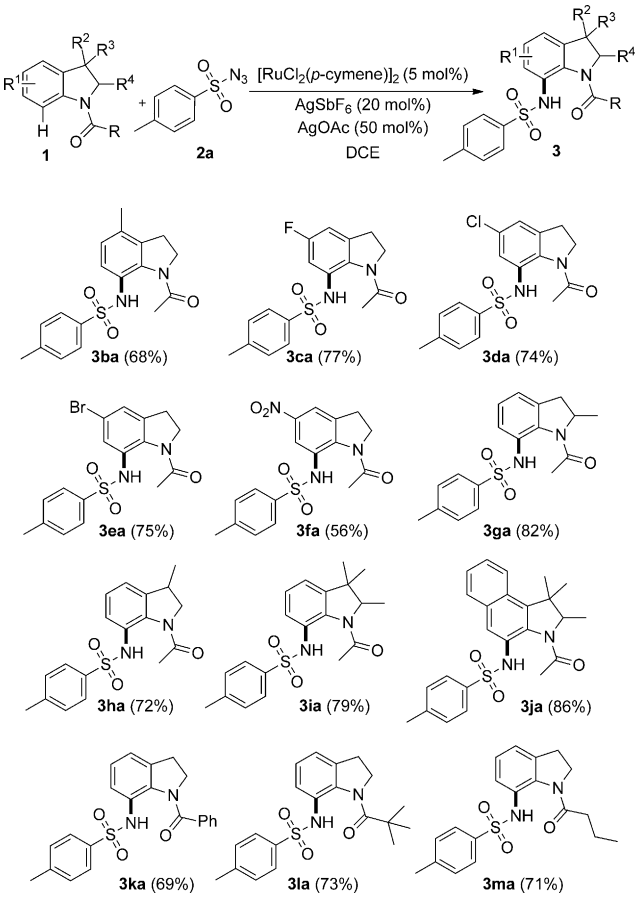


Figure 1. Ruthenium-catalyzed C7 amidation of indoline C–H bonds with tosyl azides. Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), AgOAc (50 mol%), DCE (1 mL), 80 °C, 10 h. Isolated yield.

An intermolecular competition experiment with isotopically labeled **1a″** was proposed. A kinetic isotope effect (KIE) of $k_H/k_D = 1.5$ suggested that the Ru-catalyzed C–H bond cleavage in the amidation reaction is reversible. Radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the standard procedure. However, it could not inhibit the reaction efficiency. This result ruled out the possibility of a radical-mediated mechanism. Accordingly, a possible mechanistic pathway of this Ru-catalyzed amidation reaction is proposed in Scheme 3. Initially, treatment of $[Ru(p\text{-cymene})Cl_2]_2$ with $AgSbF_6$ and OAc^- generates the active Ru^{II} catalyst. Coordination of the carbonyl oxygen with the active Ru^{II} catalyst delivers the metallacycle intermediate **A**.[17] Subsequently, coordination of the azide to **A** to form the Ru-species **B**, followed by migratory insertion of the sulfonamido moiety with evolution of N_2 gas leads to the intermediate **C**.[8] Finally, the amidation product **3aa** is produced and the active ruthenium complex is generated by protonolysis of **C**.

In conclusion, we have developed a ruthenium-catalyzed direct C7 amidation of indoline C–H bonds with sulfonyl

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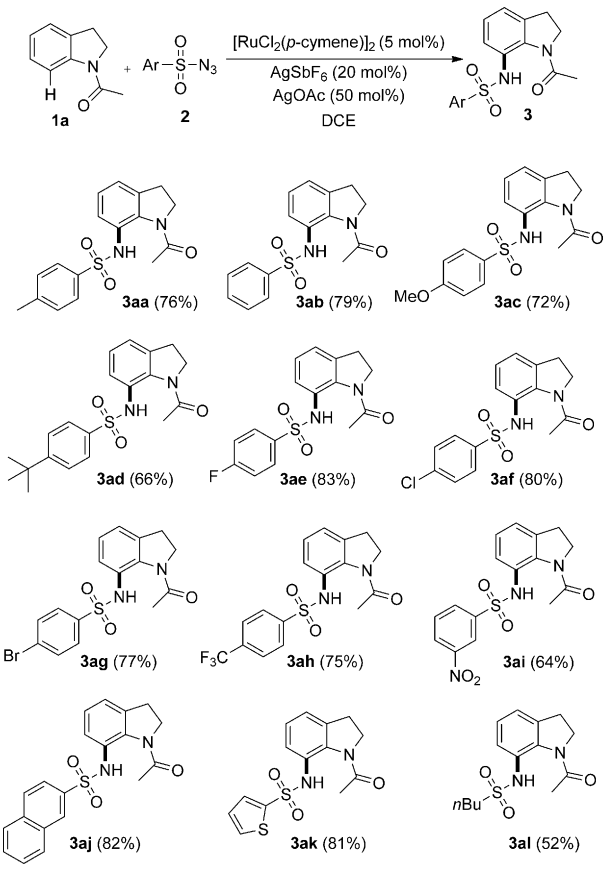
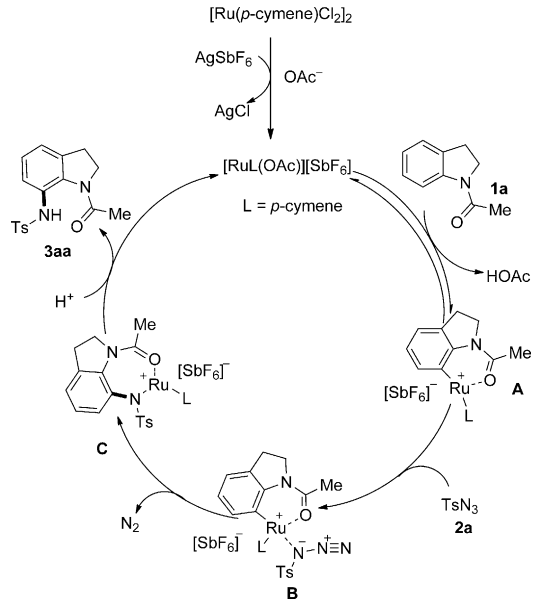


Figure 2. Ruthenium-catalyzed C7 amidation of *N*-acetyl indoline C–H bonds with sulfonyl azides. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), AgOAc (50 mol%), DCE (1 mL), 80 °C, 10 h. Isolated yield.



Scheme 3. Proposed mechanism.

azides. This procedure allows the synthesis of a variety of 7-amino-substituted indolines in good yields. The good functional-group tolerance as well as the mild conditions are prominent features of this method.

Experimental Section

Representative procedure

Under air, a Schlenk tube was charged with *N*-acetylindoline (32.2 mg, 0.2 mmol), tosyl azide (59.1 mg, 0.3 mmol), $[RuCl_2(p\text{-cymene})]_2$ (6.2 mg, 5 mol%), $AgSbF_6$ (6.8 mg, 20 mol%), AgOAc (16.6 mg, 50 mol%), and DCE (1 mL). The mixture was stirred at 80 °C for 10 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (PE/EA 2:1) to give the product **3aa** as a white solid (76%).

Acknowledgements

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Keywords: amidation · C–H activation · indolines · ruthenium · sulfonyl azides

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