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Ruthenium-Catalyzed Intramolecular Allylic Dearomatization Reaction of Indole Derivatives

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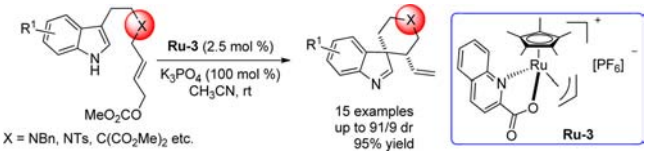
ABSTRACT



An efficient synthesis of spiroindolenine derivatives *via* a ruthenium-catalyzed intramolecular allylic dearomatization reaction has been developed. This method features a wide substrate scope, mild reaction conditions, and an operationally simple procedure.

The dearomatization reaction[1] serves as an attractive synthetic strategy to provide various ring systems, particularly heterocyclic skeletons, which frequently exist in natural products and pharmaceuticals.[2] There is continuing interest in reactions that allow for indole functionalization[3] due to the prevalence of natural products based on the indole core. Among them, the transition-metal-catalyzed allylic substitution reaction has been demonstrated successfully in a Friedel–Crafts type allylic alkylation reaction of indoles.[4,5] In addition, transition-metal-catalyzed allylic dearomatization reactions of indole derivatives have also

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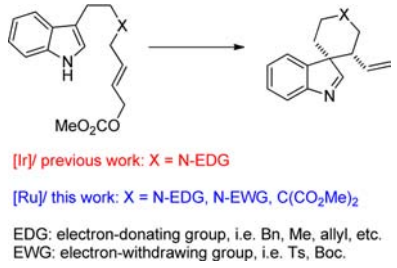
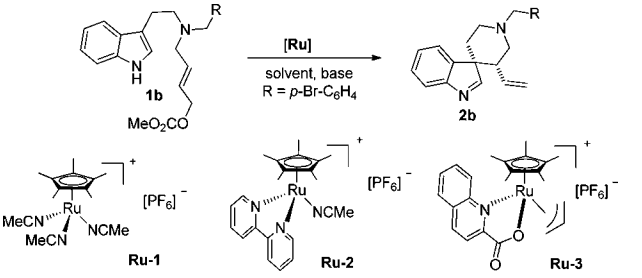
gained rapid progress recently.[6] Our group revealed several straightforward protocols to construct spiro or bridged compounds *via* dearomatization processes.[6d−g] One of the most representative examples is the construction of spiroindolenines by an intramolecular Ir-catalyzed allylic alkylation reaction.[6d] This methodology allows entry to the synthesis of spiroindolenines bearing two chiral centers in excellent yields. However, the substrate scope was limited to the allylic carbonates with an electron-donating protecting group (Bn, *p*-Br-$C_6H_4CH_2$, Me, allyl) on the linking N atom. No reaction occurred when allyl carbonates with an electron-withdrawing protecting group (i.e., Boc, Ts) on either the linking N atom or C-linker were used as substrates for six-member ring formation. Meanwhile, no reaction occurred when a *cis*-allyl carbonate substrate was used.

Scheme 1. Transition-Metal-Catalyzed Intramolecular Allylic Dearomatization Reaction of Indole Derivatives



Recently, tremendous developments have been made in ruthenium-catalyzed allylic substitution reactions.[7−9] The high tolerance of functionalized substrates is a notable feature of the ruthenium catalytic system. Given our continuing interest in dearomatization reactions, we recently found that the intramolecular allylic dearomatization reaction of indole derivatives could be realized by a ruthenium complex.[10] The reaction proceeded smoothly with a broad range of substrates including the ones not tolerated in the iridium catalytic system (Scheme 1). Herein, we report our results on this subject.

Table 1. Optimization of the Reaction Conditions[a]



entry	Ru	solvent	base	temp (°C)	time (h)	conv (%)[b]	dr[b]	yield (%)[c]
1	**Ru-1**	CH_3CN	K_2CO_3	50	20	10	94/6	N. D.
2	**Ru-2**	CH_3CN	K_2CO_3	50	20	41	80/20	N. D.
3	**Ru-3**	CH_3CN	K_2CO_3	rt	30	95	82/18	70
4[d]	**Ru-3**	CH_3CN	K_2CO_3	rt	72	<5	N. D.	N. D.
5[e]	**Ru-3**	CH_3CN	K_2CO_3	rt	12	>95	83/17	80
6[f]	**Ru-3**	CH_3CN	K_2CO_3	rt	3	>95	84/16	77
7	**Ru-3**	CH_3CN	K_3PO_4	rt	3	>95	84/16	84
8	**Ru-3**	CH_3CN	Cs_2CO_3	rt	3	>95	74/26	64
9[g]	**Ru-3**	CH_3CN	DABCO	rt	3	>95	70/30	29
10[g]	**Ru-3**	CH_3CN	TBD	rt	20	>95	81/19	29
11	**Ru-3**	CH_3CN	–	rt	20	81	80/20	69
12	**Ru-3**	THF	K_3PO_4	rt	20	80	73/27	53
13	**Ru-3**	dioxane	K_3PO_4	rt	8	95	55/45	47
14	**Ru-3**	DCM	K_3PO_4	rt	2	>95	78/22	70
15	**Ru-3**	Et_2O	K_3PO_4	rt	20	>95	69/31	59
16	**Ru-3**	toluene	K_3PO_4	rt	20	68	56/44	36
17	**Ru-3**	H_2O	K_3PO_4	rt	20	20	68/32	N. D.
18	**Ru-3**	acetone	K_3PO_4	rt	20	88	85/15	61
19	**Ru-3**	CH_3OH	K_3PO_4	rt	2	>95	80/20	46

[a] Reaction conditions: ruthenium complex (2.5 mol %), base (0.2 mmol, 100 mol %), **1b** (0.2 mmol, 100 mol %), solvent (2 mL), rt. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Isolated yield. [d] The reaction was carried out under air. [e] 2.5 mol % of water was used as the additive. [f] 110 mol % of water was used as the additive. [g] The substrate was partially decomposed. N. D. = not determined.

Our investigation was launched with the examination of different ruthenium complexes. To our delight, the desired product was observed in the presence of several ruthenium catalysts (entries 1−3, Table 1). The ruthenium(IV) complex **Ru-3**[8d] could lead to an almost full conversion, which proved much more effective than the ruthenium(II) complexes **Ru-1**[8b] and **Ru-2**[8c] in this transformation. No reaction occurred when it was carried out in an open flask mainly due to the sensitivity of the ruthenium system to air (entry 4, Table 1). However, when water was added to the system, the reaction proceeded smoothly affording satisfactory results (entries 5−6, Table 1). This revealed that ruthenium catalysts had a good tolerance of water. Different bases such as K_2CO_3, K_3PO_4, Cs_2CO_3, DABCO, and TBD were screened, and K_3PO_4 was found to be

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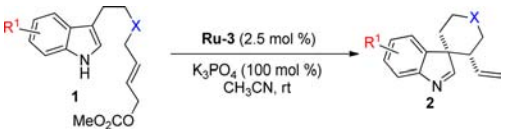
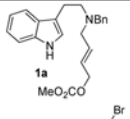
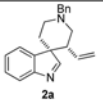
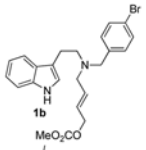
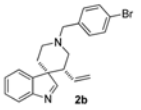
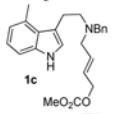
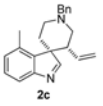
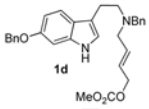
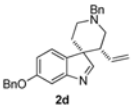
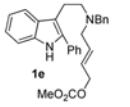
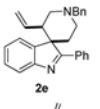
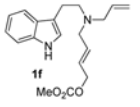
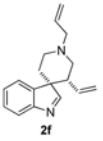
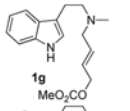
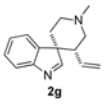
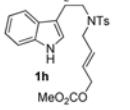
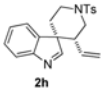
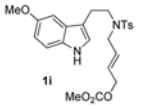
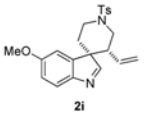
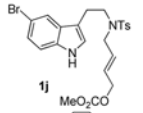
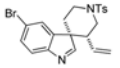
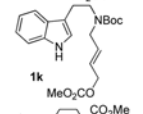
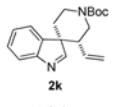
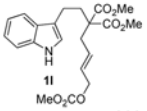
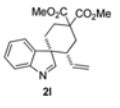
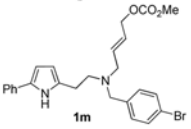
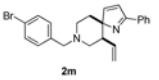
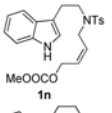
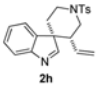
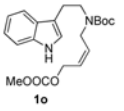
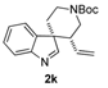
Table 2. Substrate Scope[a]



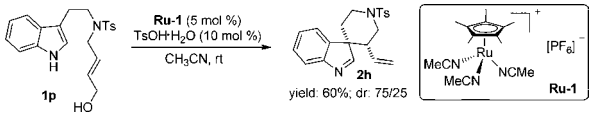
entry	substrate	product	dr[b]	yield (%)[c]
1			81/19	87
2			84/16	84
3			91/9	95
4			80/20	86
5[d]			70/30	95
6			83/17	59
7			73/27	89
8			87/13	87
9			91/9	97
10			79/21	85
11[d]			64/36	77
12[d]			90/10	71
13[d]			83/17	74
14[d]			68/32	91
15[d]			76/24	77

[a] Reaction conditions: **Ru-3** (2.5 mol %), K_3PO_4 (0.2 mmol, 100 mol %), **1** (0.2 mmol, 100 mol %), CH_3CN (2 mL), rt. [b] Determined by ^1H NMR of the crude reaction mixture. [c] Isolated yield. [d] 2.5 mol % of **Ru-3**, 100 mol % of K_2CO_3, and 100 mol % of **1** in 2 mL of CH_3CN, reflux.

optimal (entries 3, 7−10, Table 1). Notably, the reaction without any base also occurred smoothly with a slightly decreased conversion (entry 11, Table 1). Next, varying the solvent (CH_3CN, THF, dioxane, DCM, Et_2O, toluene, H_2O, acetone, CH_3OH) showed that CH_3CN was the best solvent (entries 7, 12−19, Table 1).

With the optimal conditions (entry 7, Table 1) in hand, we began to explore the substrate scope. The results were summarized in Table 2. Various substrates with an electron-donating protecting group (Bn, *p*-Br-$C_6H_4CH_2$, Me, allyl) on the linking N atom were first attempted in this reaction giving the desired spiroindolenine products with good yields and modest *dr* (84−95% yields, 70/30−91/9 *dr*, entries 1−7, Table 2). Our following efforts focused on the substrates that were not well-tolerated in our previous Ir-catalytic system.[6d] We were pleased to find that the reaction of substrate **1h** with an electron-withdrawing group such as Ts on the linking N atom occurred with high conversion as well as a slightly better *dr* (87% yield, 87/13 *dr*, entry 8, Table 2). Full conversions could be obtained with substrates bearing either an electron-donating group (5-OMe) or electron-withdrawing group (5-Br) on the indole core (85−97% yields, entries 9−10, Table 2). Substrate **1k** with an easily removable Boc group on the linking N atom was also compatible in this transformation (77% yield, entry 11, Table 2). Using *C*-linker substrate **1l** instead of the *N*-linker ones, the desired dearomatization product could be obtained in 71% yield (entry 12, Table 2). The pyrrole derivative **1m** also accommodated under these conditions (entry 13, Table 2). In addition, when substrates **1n**, **1o** with a *cis* double bond instead of a *trans* one were used, the desired dearomatization products were obtained in good yields and modest *dr* (entries 14−15, Table 2). In general, the Ru-catalytic system provides lower

Scheme 2. Ru-Catalyzed Intramolecular Dearomatization Reaction of Allylic Alcohol Substrate



diastereoselectivities compared with those of the Ir-catalytic system except for 2-susbtituted indoles such as **1e**.[6d]

The corresponding allylic alcohol was also chosen as the substrate to test the activity.[10] In the presence of 5 mol % **Ru-1** and 10 mol % $TsOH \cdot H_2O$, the reaction led to the desired product in 60% yield and 75/25 *dr* (Scheme 2).

In conclusion, an efficient synthesis of spiroindolenine derivatives *via* a ruthenium-catalyzed intramolecular allylic dearomatization reaction has been developed. There are several notable features of the Ru-catalytic system compared with the Ir-catalytic system. These include (1) a cheap and easily prepared catalyst; (2) high reactivity; (3) a moderate *dr*; (4) a broad substrate scope given the compatibility with *cis*-allyl carbonate and allyl alcohol; (5) insensitivity to water; and (6) mild conditions.

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Supporting Information Available. Experimental procedures and analysis data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.