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Site-Selective Functionalization of 7-Azaindoles via Carbene Transfer and Isolation of *N*-Aromatic Zwitterions

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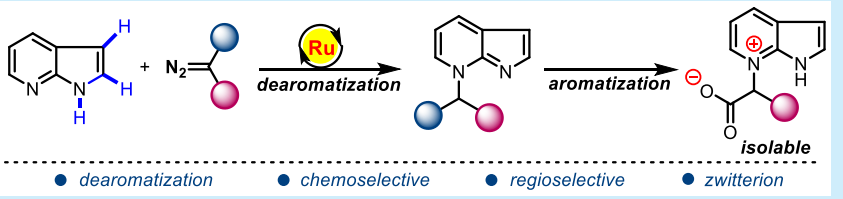

ABSTRACT: The first systematic study on metal-carbene transfer reaction of 7-azaindoles has been conducted, and the unprecedented dearomative N7-alkylation reaction has been accomplished via ruthenium catalysis. Importantly, through a sequential dearomatization−aromatization process, an isolable, and new class of azaindole-based *N*-aromatic zwitterions has been discovered from the reaction of 7-azaindoles and diazoesters.

7-Azaindoles are widely spread heterocycles in pharmaceuticals, and they are leading compounds in drug discovery.[1−7] Molecules containing a 7-azaindole moiety exhibit diverse activities, such as antitumor,[1] antifibrotic,[2] and antiautoimmune activities (Figure 1).[3] Typically, the replacement of CH group with a N atom in heterocycles can bring about significantly beneficial effects on pharmacological profiles.[4] Furthermore, it was reported that the N7-substituted 7-azaindoles have also been explored as drug candidates in medical research[5] and useful ligands in organic synthesis.[6] In view of the importance of 7-azaindoles in drug discovery, a considerable amount of methods have been developed for their synthesis.[7]

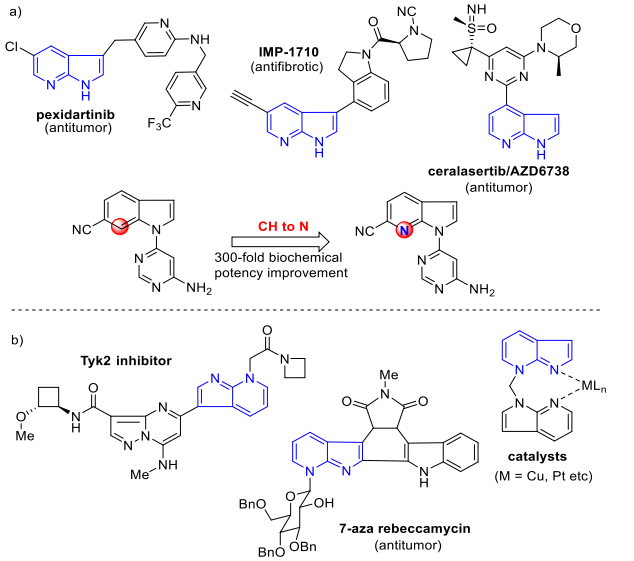

Figure 1. Bioactive molecules contain a 7-azaindole moiety.

Clearly, the direct functionalization of 7-azaindoles via carbene-transfer remains the most straightforward way to produce 7-azaindole derivatives. However, the selective functionalization of azaindoles lags far behind indoles in organic synthesis.[8] Compared with the well-established carbene-transfer reactions for indoles,[9] such as C2/C3-alkylation,[10] cyclopropanation,[11] and others,[12] the systematic investigation on 7-azaindoles with carbene precursors has never been reported. Especially, the existence of azine and azole rings in 7-azaindoles might give rise to more-complicated selectivities than indoles. In continuation with our research interest in metal-carbene chemistry, especially in dearomatization of heterocycles via carbene transfer, we recently reported a gold-catalyzed C3-olefinic dearomatization of indoles,[13a] rhodium-catalyzed dearomative N^2-alkylation of benzotriazoles,[13b] and rhodium-catalyzed dearomative rearrangement of pyridines.[13c] Herein we wish to report the unprecedented dearomatization of 7-azaindoles with diazo compounds under ruthenium catalysis. Moreover, upon the choice of suitable N1-substituents, the selective C3-alkylation and cyclopropanation have also been realized. (See Scheme 1.)

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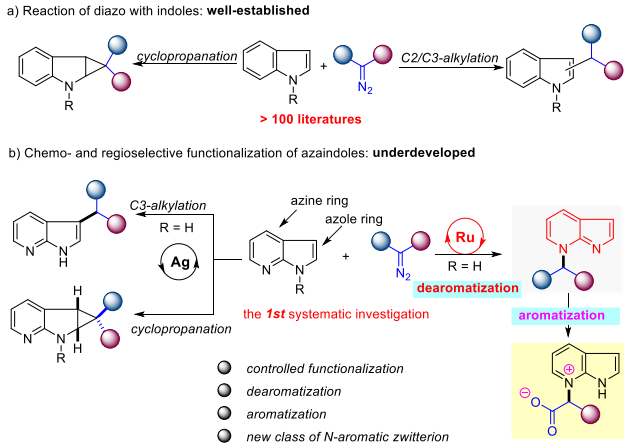
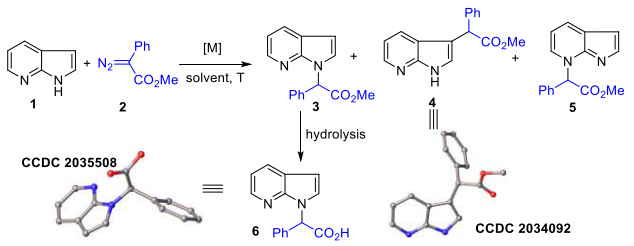
Scheme 1. Previous Reports and Our Discovery



We initiated our studies by the reaction between 7-azaindole (**1**) and diazoacetate (**2**) using $Rh_2(esp)_2$ as the catalyst in dichloromethane at room temperature. The N7-alkylated product (**5**) was obtained in 37% yield, associated with a small amount of C3-alkylated product (**4**) (see Table 1, entry 1). Using gold salt JohnPhos $AuNTf_2$ as the catalyst led to the formation of N1-alkylated product (**3**) and (**5**) in low yield (Table 1, entry 2). The ruthenium salts $Ru(PPh_3)_3Cl_2$ and $CpRu(PPh_3)_2Cl$ then were examined, from which no alkylated products were detected (Table 1, entries 3 and 4). Switching to $[Ru(p\text{-cymene})Cl_2]_2$ afforded **5** in 10% yield (Table 1, entry 5). The yield was improved to 45% when $[Ru(p\text{-cymene})I_2]_2$ was used as the catalyst (Table 1, entry 6), and no better results were observed for other solvents (Table 1, entries 7 and 8). Increasing the amount of $[Ru(p\text{-cymene})I_2]_2$ to 5 mol % gave a 57% yield of **5** (Table 1, entry 9). Furthermore, the use of 2 equiv of diazo **2** improved the yield of **5** to 82% (Table 1, entry 10), and no **3** and **4** were formed. Interestingly, using $AgNTf_2$ as the catalyst in acetonitrile, **4** was isolated as the major product (Table 1, entry 11). The yield was slightly improved at 80 °C (Table 1, entry 12). Increasing the catalyst loading to 5 mol % provided **4** in 42% yield. Also, dilute solvent gave better yield (Table 1, entry 14). Hydrolysis of N1-alkylated product **3** yielded the carboxylic acid **6**.

Having established the optimal reaction conditions, we next explored the scope and the generality of this reaction (Scheme 2). First, a range of aryl diazoesters containing either electron-donating or electron-withdrawing groups at the *para*-position of the phenyl ring reacted well to provide the corresponding products (**7**−**13**) in good yields. Substitution at the *meta*- and *ortho*-position were well-tolerated (**14**−**17**), and a dioxolane-

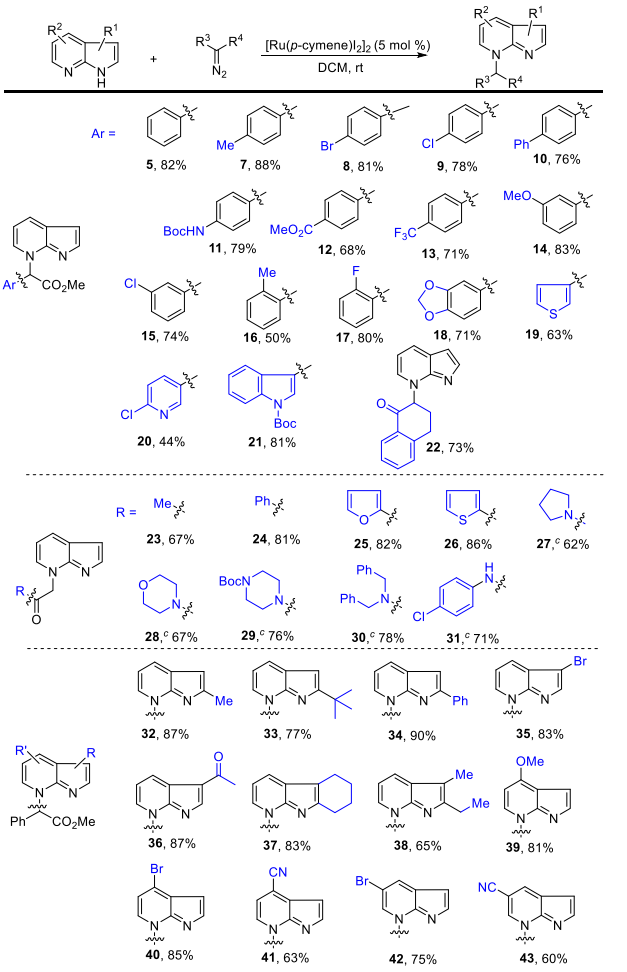
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	temperature (°C)	time (h)	yield **3**/**4**/**5** [b] (%)
1	$Rh_2(esp)_2$	DCM	25	2	0/5/37
2	JohnPhos $AuNTf_2$	DCM	25	2	10/0/18
3	$Ru(PPh_3)_3Cl_2$	DCM	25	2	–
4	$CpRu(PPh_3)_2Cl$	DCM	25	2	–
5	$[Ru(p\text{-cymene})Cl_2]_2$	DCM	25	2	0:0:10
6	$[Ru(p\text{-cymene})I_2]_2$	DCM	25	2	0:0:45
7	$[Ru(p\text{-cymene})I_2]_2$	toluene	25	2	0:0:20
8	$[Ru(p\text{-cymene})I_2]_2$	DCE	25	2	0:0:20
9[c]	$[Ru(p\text{-cymene})I_2]_2$	DCM	25	2	0:0:57
10[c,d]	$[Ru(p\text{-cymene})I_2]_2$	DCM	25	2	0:0:82
11	$AgNTf_2$	MeCN	60	4	0:31:8
12	$AgNTf_2$	MeCN	80	4	0:37:9
13[c]	$AgNTf_2$	MeCN	80	4	0:42:8
14[c,e]	$AgNTf_2$	MeCN	80	7	0:45:9

[a]Reaction conditions: **1** (0.2 mmol), catalyst (2 mol %), and **2** (0.24 mmol) in solvent (2 mL). [b]Isolated yield. [c]5 mol % catalyst. [d]**2** (0.4 mmol). [e]MeCN (4 mL).

Scheme 2. Substrate Scope for N7-Alkylation[a,b]



[a]Reaction conditions: Azaindole (0.2 mmol), diazo (0.4 mmol), $[Ru(p\text{-cymene})I_2]_2$ (5 mol %), DCM (2 mL), rt for 2 h. [b]Isolated yield. [c]Azaindole (0.2 mmol), diazo (0.3 mmol), $[Ru(p\text{-cymene})I_2]_2$ (5 mol %), DCM (2 mL), 60 °C for 5 h.

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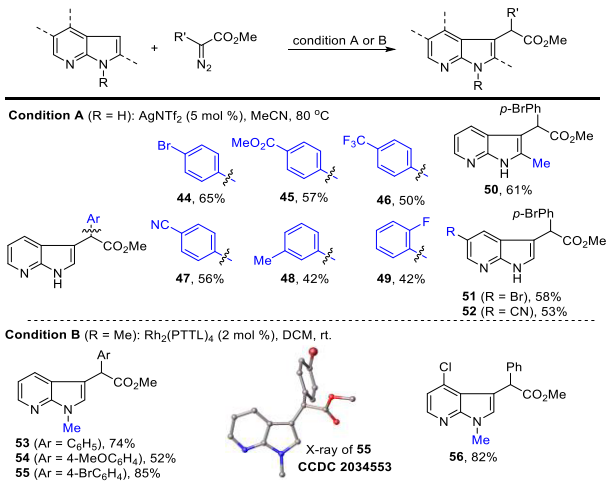
fused phenyl ring gave **18** in 71% yield. Heteroaryl-substituted diazoacetates were also compatible (**19**–**21**). A cyclic diazo substrate was used to deliver the product (**22**) in 73% yield. For α-diazoketones and α-diazoamides bearing various functional groups, the desired products (**23**–**31**) were obtained in good yields by slightly changing the reaction conditions. Further evaluation of the scope focused on 7-azaindoles. Substitution at C2/C3 position of the azole ring were all tolerated (**32**–**38**), including alkyl, phenyl, bromo, and acyl groups. With respect to the substituents at the azine ring, electron-donating (OMe) as well as electron-withdrawing groups (Br, CN) were all suitable to afford N7-alkylated products (**39**–**43**) in moderate to good yields.

Next, we turned our attention to the C3-alkylation of azaindoles with diazoesters (Scheme 3). Under silver catalysis,

Scheme 3. Scope for C3-Alkylation[a,b]

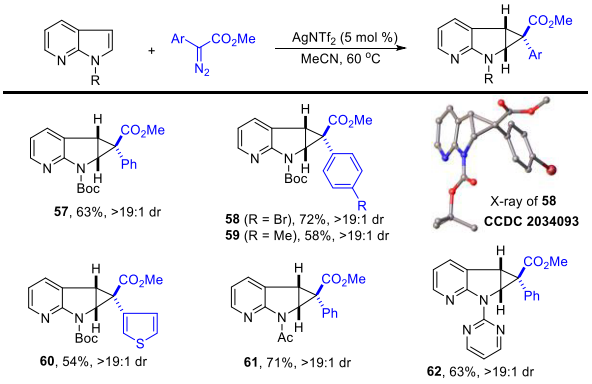


[a]Reaction conditions A: 7-azaindole (0.2 mmol), diazo (0.4 mmol), $AgNTf_2$ (5 mol %), in MeCN (4 mL), 80 °C, 7 h. Reaction condition B: 7-azaindole (0.2 mmol), diazo (0.3 mmol), $Rh_2(PTTL)_4$ (2 mol %), DCM (4 mL), rt, 0.5 h. [b]Isolated yields.

the reaction of azaindoles with aryl diazoacetates containing various groups at the *para*-, *meta*-, and *ortho*-positions of the phenyl ring proceeded smoothly to deliver the C3-alkylation products (**44**–**49**) in yields of 42%–65%. For different azaindole substrates, the reactions also gave the desired products (**50**–**52**) in moderate yields. To improve the C3-alkylation reaction, we performed further optimization by using N1-methyl 7-azaindoles as the substrates (see the Supporting Information for details). We found that when $Rh_2(PTTL)_4$ was used, the C3-alkylation reaction was improved remarkably. For example, no product was observed for the reaction between azaindole **1** and 4-methoxy phenyl diazoacetate under silver catalysis. In sharp contrast, the reaction of N1-methyl azaindole with 4-methoxy phenyl diazoaceate produced the C3-alkylation product (**54**) in 52% yield. Moreover, for the same diazo substrates used, the C3-alkylation of N1-methyl azaindole under rhodium catalysis gave much higher yields than N-free azaindoles (**4** vs **53**, **44** vs **55**).

We next investigated the cyclopropanation reaction of 7-azaindoles (Scheme 4). After detailed optimization (see the Supporting Information for details), we found that $AgNTf_2$ can effectively promote the cyclopropanation for different N1-substituted 7-azaindoles. Substitution at N1 with *t*-butyloxycarbonyl (Boc), acyl and pyrimidyl groups were all tolerated,

Scheme 4. Silver-Catalyzed Cyclopropanation[a]

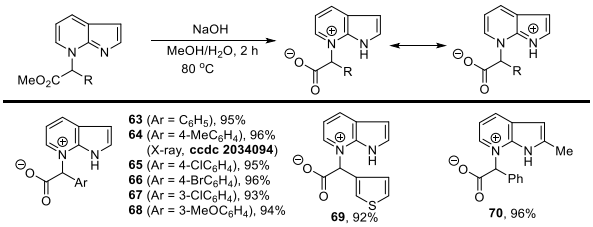


[a]Reaction conditions: 7-azaindole (0.2 mmol), diazo (0.4 mol), $AgNTf_2$ (5 mol %), in MeCN (4 mL), 60 °C for 6 h. [b]Isolated yields.

providing the corresponding products (**57**–**62**) in moderate to good yields with excellent diastereoselectivity (>19:1 diastereomeric ratio (dr)).

Unlike the widespread pyridinium salts, which are easily obtained by the reaction of pyridines with organic halides, the *N*-aromatic zwitterions are usually hard to obtain, because of the instability, and most of them have been generated in situ.[14,15] Recently, the Yoo group has developed a series of stable pyridinium zwitterions.[15] When we performed further transformation, an unprecedented pyridinium type of zwitterion has been discovered (see Scheme 5). Under basic

Scheme 5. Scope for *N*-Aromatic Zwitterion[a,b]



[a]Reaction conditions: 7-alkylated azaindole (0.2 mmol, 1 equiv), NaOH (3 equiv), $MeOH/H_2O$ (1:1, 3 mL), 80 °C, 2 h. [b]Isolated yields.

conditions, the hydrolysis of **5** gave *N*-aromatic type zwitterion **63** as a pale-yellow solid in 95% yield. Similarly, several isolable zwitterions (**64**–**70**) were obtained in almost quantitative yields. The molecular structure of **64** was characterized by single-crystal X-ray diffraction (XRD) analysis.

Further elaboration of the reactions was performed. A gram-scale synthesis was conducted, affording **5** in 81.2% yield (1.08 g) (Scheme 6a). Treatment of **57** with HCl/dioxane gave **4** in 82% yield (Scheme 6b). Next, the deuterium-labeling experiment was conducted (Scheme 6c). The reaction of **D-1** with **2** gave **D-5** only in 5% deuterium labeling, which indicated the existence of rapid proton exchange during the alkylation process. Moreover, the reaction of **71** and **72** delivered N7-alkylated product **73** in 86% yield (Scheme 6d). Finally, treatment of zwitterion **65** with dimethyl acetylenedicarboxylate (DMAD) in benzene delivered the rearrangement product **74** in 30% yield (Scheme 6e). The molecular structures of **73** and **74** were characterized by single-crystal XRD.

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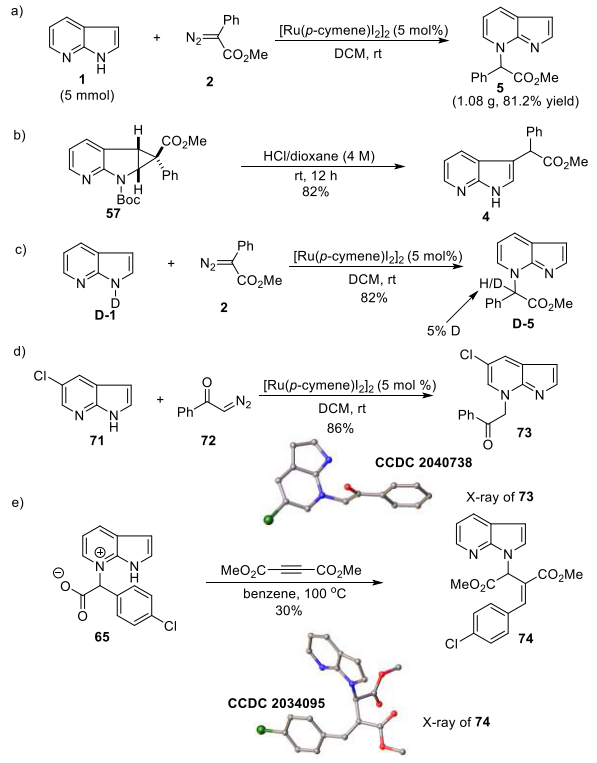
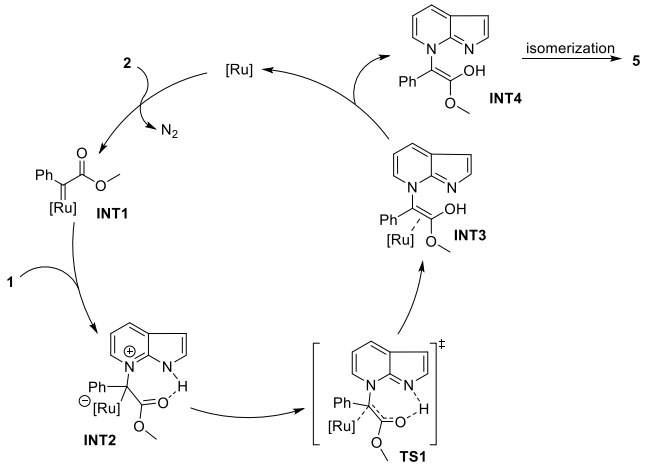
Scheme 6. Further Elaboration



Based on the common accepted mechanism for carbene insertion into X−H bonds,[16] and our previous studies on the selective N2-alkylation of benzotriazoles,[14b] we proposed a possible catalytic cycle for this ruthenium-catalyzed[17] N7-alkylation (see Scheme 7). The reaction of ruthenium complex

Scheme 7. Proposed Reaction Mechanism



with diazo (**2**) forms ruthenium carbene species **INT1** via nitrogen extrusion. The nucleophilic addition of N7 atom of 7-azaindole (**1**) to **INT1** then yields ruthenium-associated ylide **INT2**. The intramolecular [1,6]-proton shift from N-to-O might occur via a seven-membered transition state **TS1** to generate the ruthenium-associated enol intermediate **INT3**. Dissociation of the ruthenium complex from **INT3** affords free enol **INT4**. Finally, enol-to-ketone isomerization forms the final N7-alkylated product **5**.

In summary, we have developed a catalyst-controlled chemoselective and regioselective alkylation of 7-azaindoles with diazo compounds, which is the first systematic investigation on 7-azaindoles involving carbene transformation. Typically, the dearomative alkylation selectively occurs at the N7-position in the presence of a ruthenium catalyst. The selective C3-alkylation and cyclopropanation reactions have also been realized by using suitable N1-substituents and metal catalysts. Furthermore, the hydrolysis of the N7-alkylated dearomative products leads to the formation of a new class of *N*-aromatic zwitterions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03653.

Experimental procedures, along with characterizing data and copies of NMR spectra (PDF)

Accession Codes

CCDC 2034092 (**4**), 2035508 (**6**), 2034553 (**55**), 2034093 (**58**), 2034094 (**64**), 2040738 (**73**) and 2034095 (**74**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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