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Ruthenium-Catalyzed Regioselective C−H Bond Acetoxylation on Carbazole and Indole Frameworks

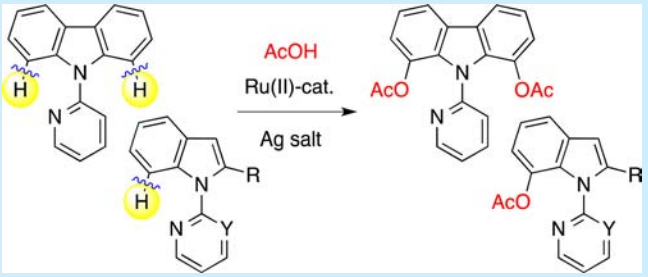
Takeshi Okada,[†] Kazunori Nobushige,[†] Tetsuya Satoh,*[,‡] and Masahiro Miura*[,†]

[†]Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[‡]Department of Chemistry, Graduate School of Science, Osaka City University, 3-3-138 Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan

Supporting Information

ABSTRACT: The regioselective C−H bond cleavage/C−O bond formation takes place smoothly upon treatment of 9-(pyridin-2-yl)carbazoles with acetic acid in the presence of a silver salt oxidant under ruthenium catalysis to afford the corresponding C1- and C8-diacetoxylated products. Under similar conditions, the acetoxylation of 2-aryl-1-(pyridin-2-yl)indoles as well as 1-aryl-7-azaindoles can also be conducted efficiently.



Functional-group-directed C−H bond functionalization under transition metal catalysis has certainly become one of the most highly useful tools in modern organic synthesis.[1] This type of reaction enables regioselective cleavage and substitution of ubiquitously existing C−H bonds in starting aromatic substrates at the proximate position to the directing group. The position is often different from that attacked in conventional aromatic electrophilic substitution reactions. For example, it was reported that carbazoles and indoles possessing a directing group on their nitrogens undergo regioselective alkenylation at the C1- and C7-positions, respectively, upon treatment with alkenes in the presence of an appropriate catalyst and an oxidant (path a in Scheme 1).[2] During the past decade, a variety of reactions involving the sequence of regioselective C−H bond cleavage/C−C bond formation have been developed. However, the processes via C−H bond cleavage/C−heteroatom bond formation have been relatively less explored. In the context of our studies on ruthenium(II)-catalyzed C−H bond functionalization,[3] we have found that the C1- and C7-acetoxylation of carbazole and indole frameworks, respectively,[4] can be performed effectively with the aid of a pyridyl or pyrimidyl directing group under ruthenium catalysis (path b in Scheme 1).[5] These oxygenated carbazoles[6] and indoles[7] are of interest because of their unique biological activities. The present procedures provide straightforward pathways toward the functionalized molecules. In addition, 1-phenyl-7-azaindoles also underwent direct acetoxylation on their phenyl ring under similar conditions (vide infra). These new findings are described herein.

Scheme 1. Regioselective Functionalization of Carbazole and Indole Frameworks

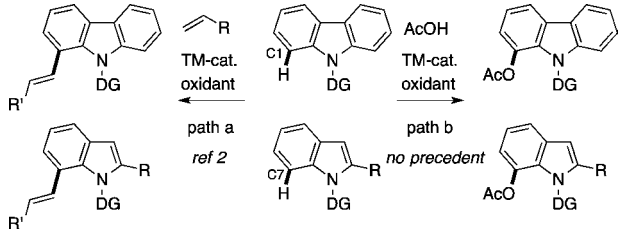
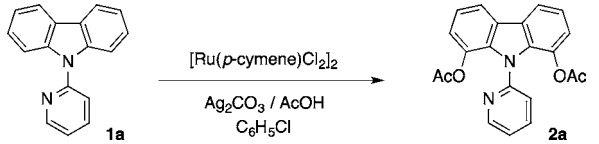


Table 1. Reaction of 9-(Pyridin-2-yl)carbazole (1a)[a]



1a 2a

entry	Ag_2CO_3 (mmol)	atmosphere	temp (°C)	yield of **2a** (%)[b]
1	0.4	N_2	140	56
2	0.4	N_2	140	48
3	0.4	air	140	63
4	0.4	O_2	140	60
5	0.4	air	160	70
6	0.44	air	140	75 (61)
7	−[c]	air	140	73
8	−[d]	air	140	0

[a]Reaction conditions: **1a** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol), AcOH (2 mmol) in C_6H_5Cl (2 mL) for 15 h, unless otherwise noted. [b]GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c]AgOAc (0.88 mmol) was used in place of Ag_2CO_3. [d]$Cu(OAc)_2 \cdot H_2O$ (0.88 mmol) was used in place of Ag_2CO_3.

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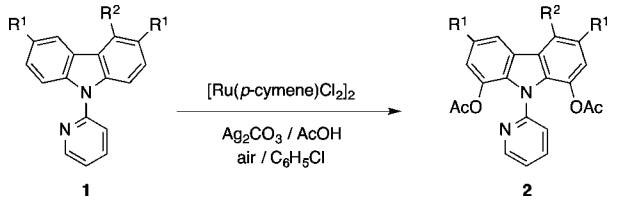
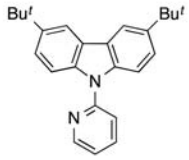
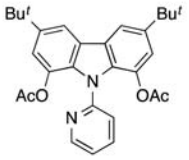
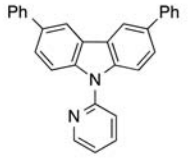
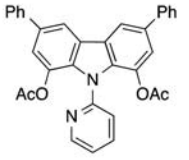
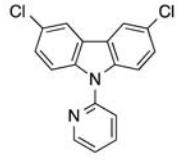
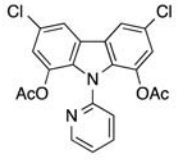
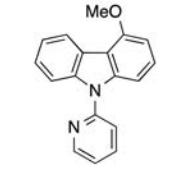
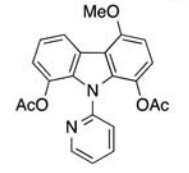
Table 2. Reaction of Substituted 9-(Pyridin-2-yl)carbazoles 1[a]

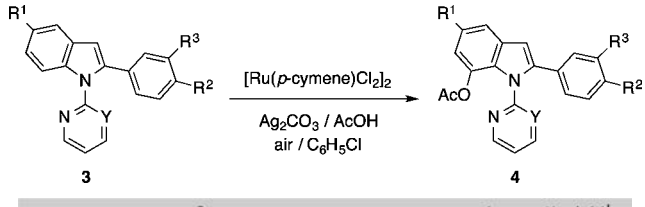


1 2

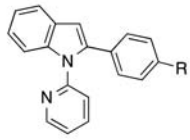
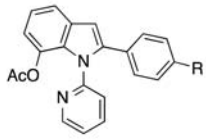
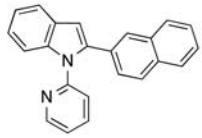
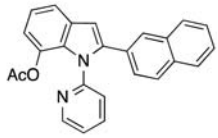
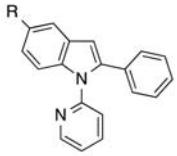
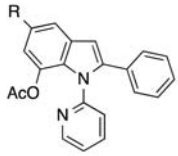
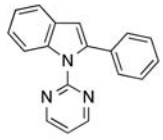
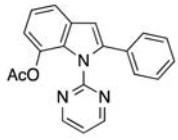
entry	1	product	% yield[b]
1	 **1b**	 **2b**	77
2	 **1c**	 **2c**	65
3	 **1d**	 **2d**	35
4	 **1e**	 **2e**	37

[a]Reaction conditions: **1** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol), Ag_2CO_3 (0.44 mmol), AcOH (2 mmol) in C_6H_5Cl (2 mL) under air for 15 h at 140 °C. [b]Isolated yield based on the amount of **1** used.

Table 3. Reaction of 1-(Pyridin-2-yl)- and 1-(Pyrimidin-2-yl)indoles 3[a]



3 4

entry	3	product	% yield[b]
1	 **3a**: R = H	 **4a**: R = H	74
2	**3b**: R = Me	**4b**: R = Me	80
3	**3c**: R = Cl	**4c**: R = Cl	79
4	**3d**: R = OMe	**4d**: R = OMe	77
5	 **3e**	 **4e**	62
6	 **3f**: R = Me	 **4f**: R = Me	60
7	**3g**: R = Cl	**4g**: R = Cl	66
8	**3h**: R = Br	**4h**: R = Br	57
9	**3i**: R = OMe	**4i**: R = OMe	39
10	 **3j**	 **4j**	61

[a]Reaction conditions: **3** (0.2 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol), Ag_2CO_3 (0.22 mmol), AcOH (2 mmol) in C_6H_5Cl (2 mL) under air for 15 h at 140 °C. [b]Isolated yield based on the amount of **3** used.

In an initial attempt, treatment of 9-(pyridin-2-yl)-9*H*-carbazole (**1a**) (0.2 mmol) in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol, 5 mol %), Ag_2CO_3 (0.4 mmol), and AcOH (2 mmol) under N_2 in C_6H_5Cl at 140 °C for 15 h gave a diacetoxylation product, 9-(pyridin-2-yl)-9*H*-carbazole-1,8-diyl diacetate (**2a**), in 56% yield (Table 1, entry 1). In the reaction mixture, a trace amount of monoacetylated product was also detected by GC-MS. In toluene, the yield of **2a** somewhat decreased (entry 2). When the reaction was conducted in C_6H_5Cl under air or O_2, the yield of **2a** was slightly improved to 63% and 60%, respectively (entries 3 and 4). Increasing the reaction temperature to 160 °C enhanced the yield of **2a** to 70% (entry 5). Even at 140 °C, the use of slightly excess Ag_2CO_3 (0.44 mmol) increased the product yield to 75% (entry 6). The reaction also proceeded smoothly in the presence of AgOAc (0.88 mmol) in place of Ag_2CO_3 (entry 7). In contrast, the reaction did not proceed at all in the presence of $Cu(OAc)_2 \cdot H_2O$ (0.88 mmol) as the oxidant (entry 8).

Under the conditions listed in Table 1, entry 6, the diacetoxylation of some substituted carbazoles **1** was next examined (Table 2). Among the cabazole substrates employed, 3,7-di(*tert*-butyl)- (**1b**) and 3,7-diphenyl- (**1c**) 9-(pyridin-2-yl)-9*H*-carbazoles underwent the reaction efficiently to afford product **2b** and **2c** in 77% and 65% yields, respectively (entries 1 and 2). The attempted reaction of 3,7-dibromo-9-(pyridin-2-yl)-9*H*-carbazole was sluggish to give a diacetylation product in ca. 10% yield. 3,7-Dichloro-substituted carbazole **1d** was found to be more reactive to produce **2d** in a moderate yield (entry 3). Treatment of 3-methoxy-9-(pyridin-2-yl)-9*H*-carbazole (**1e**) yielded the corresponding diacetylated product **2e** in a similar manner (entry 4).

Next, we examined the C7-acetoxylation of indole derivatives. When 2-phenyl-1-(pyridin-2-yl)-1*H*-indole (**3a**) (0.2

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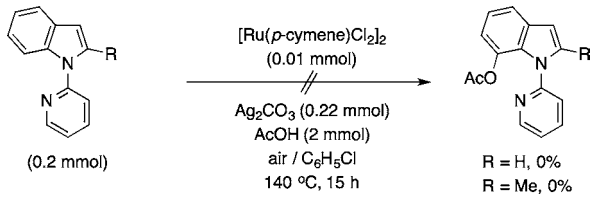
mmol) was treated in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol, 5 mol %), Ag_2CO_3 (0.22 mmol), and AcOH (2 mmol) under air in C_6H_5Cl at 140 °C for 15 h, monoacetoxylation took place as expected to selectively form 2-phenyl-1-(pyridin-2-yl)-1*H*-indol-7-yl acetate (**4a**) in 74% yield (Table 3, entry 1). The phenyl group on the C2 position of **3a** was found to be essential to conduct the acetoxylation smoothly. Thus, treatment of C2-unsubstituted- or C2-methyl-1-(pyridin-2-yl)-1*H*-indole did not give any acetoxylated product at all (Scheme 2). In contrast, a series of 2-(4-

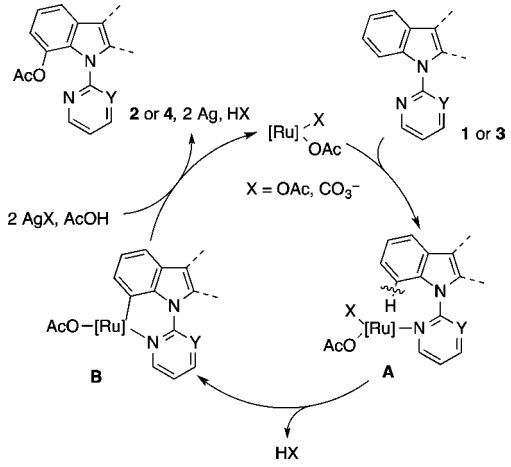
Scheme 2. Reaction of C2-Unsubstituted and C2-Methyl-1-(pyridin-2-yl)indoles



substituted phenyl)-1-(pyridin-2-yl)-1*H*-indoles **3b–d** underwent the reaction efficiently to produce **4b–d** in 77–80% yields (entries 2–4). The C2-napthtyl substrate **3e** was also transformed to **4e** in a similar manner (entry 5). The reactions of 5-substituted 2-phenyl-1-(pyridin-2-yl)-1*H*-indoles **3f–i** afforded the corresponding monoacetoxylation product **4f–i** (entries 6–9). In addition, a pyrimidyl group was found to be utilizable as a directing group in the present reaction. Thus, 2-phenyl-1-(pyrimidin-2-yl)-1*H*-indole (**3j**) underwent monoacetoxylation at the C7-position to give **4j** selectively (entry 10).

A plausible mechanism for the acetoxylation of **1** and **3** is illustrated in Scheme 3. Coordination of the pyridyl- or

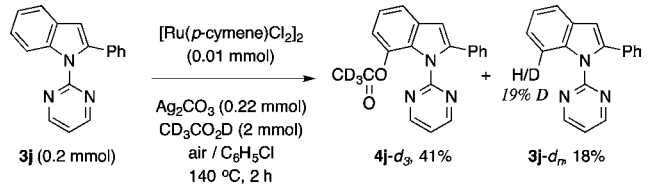
Scheme 3. Plausible Mechanism for the Reaction of 1 and 3



pyrimidyl-nitrogen of a substrate forming intermediate **A** seems to trigger regioselective C–H bond cleavage at the neighboring position to yield a six-membered ruthenacycle intermediate **B**. Subsequently, oxidation of the ruthenium center by a silver salt and reductive elimination may take place to produce **2** or **4** and with regeneration of a catalytically active ruthenium species.

To obtain mechanistic information, **3j** was treated with CD_3CO_2D under standard conditions (Scheme 4). In the early stage, H–D exchange at the C7-position of recovered **3j** was observed to some extent. This indicates that, at least partly, the

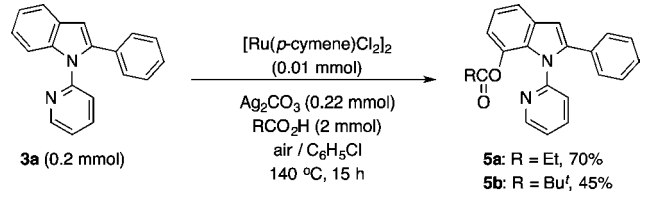
Scheme 4. Reaction of 3j with CD_3CO_2D



directed C–H bond cleavage step to form **B** appears to be reversible.

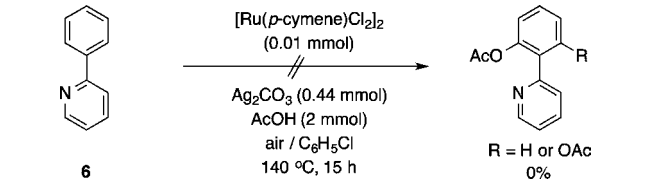
Besides acetic acid, other acids such as propionic and pivalic acids could be employed for the present C–O bond formation at the C7-position of **3a** (Scheme 5). Thus, treatment of **3a** using these acids in place of acetic acid gave **5a** and **5b** in 70% and 45% yields, respectively.

Scheme 5. Reaction of 3a with $EtCO_2H$ and Bu^tCO_2H



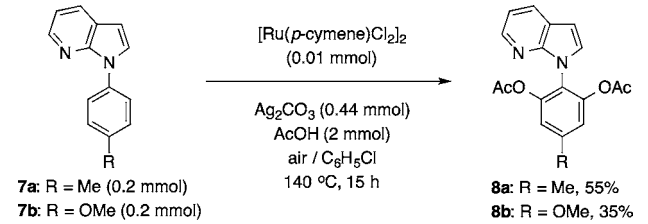
Under standard conditions, attempted acetoxylation of 2-phenylpyridine (**6**) at the 2′-position failed (Scheme 6).[8] In

Scheme 6. Reaction of 2-Phenylpyridine (6)



contrast, 1-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (**7a**) was found to undergo the reaction to give the corresponding diacetoxylated product **8a** in 55% yield (Scheme 7). The reaction of 1-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**7b**) also afforded **8b**, albeit with a moderate yield.

Scheme 7. Reaction of 1-Phenyl-1*H*-pyrrolo[2,3-*b*]pyridines 7



In summary, we have demonstrated that *N*-pyridylcarbazoles and -indoles readily underwent regioselective acetoxylation under ruthenium catalysis. This catalyst system is expected to be applicable to various dehydrogenative C–O coupling reactions. Work is underway toward further development of the catalysis.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00268.

Experimental procedures and characterization data of products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: satoh@sci.osaka-cu.ac.jp.
*E-mail: miura@chem.eng.osaka-u.ac.jp.

Notes

The authors declare no competing financial interest.

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