Coupling Reactions

Zirconium Triflate Catalyzed Direct Coupling Reaction of Lactams with Heterocyclic Arenes under Atmospheric Oxygen

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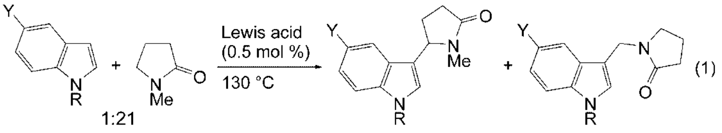
The alkylation of aromatic rings by the Friedel–Crafts reaction has become the focus of extensive research.[1] Alkyl halides or alkenes have been the substrates of choice for Friedel–Crafts reactions, even though a carbon–halide or a carbon–carbon double bond has to be introduced prior to the alkylation. Furthermore, hydrogen halides that cause environmental problems are co-produced in the use of alkyl halides. In contrast, direct use of a $C(sp^3)$–H bond of alkanes for the alkylation of arenes is apparently useful because intricate introduction of reactive functional groups can be omitted and no accompanying harmful waste is produced. Although Lewis acid mediated or catalyzed dehydrogenative coupling reactions of arenes with alkanes are also known,[2,3] poor regioselectivity with alkanes and turnover numbers (TON) of Lewis acids have so far diminished the advantages of the methodology. Herein we report the first dehydrogenative coupling reaction between lactams and heterocyclic arenes which affords lactams that are arylated exclusively at the carbon atoms adjacent to the nitrogen atom in the presence of $Zr(OTf)_4$ catalyst under atmospheric oxygen.

First, we investigated suitable conditions for direct coupling reaction of 1-methylindole (**1a**: R = Me, Y = H) with 1-methylpyrrolidin-2-one (**2a**) ([Eq. 1], Table 1). Treatment of **1a** (1.0 mmol) and **2a** (2.0 mL, 20.7 mmol) with $Zr(OTf)_4$ (0.5 mol%) at 130 °C for 5 h under O_2 (1 atm) gave a 97:3 mixture of 1-methyl-5-(1-methylindol-3-yl)pyrrolidin-2-one (**3a**) and 1-(1-methylindol-3-ylmethyl)pyrrolidin-2-one (**4a**) in 54% yield (Table 1, entry 1),[4,5] in which the carbon atoms next to the nitrogen atom in **2a** exclusively form bonds with C3 of **1a**. Notably, the TON of $Zr(OTf)_4$ was 108, which so far is the highest known for the Lewis acid catalyzed arylation of alkanes: to the best of our knowledge, the maximum TON reported is 20.3.[2h] Prolonged reaction time slightly increased the yield (Table 1, entry 2). The TON was improved up to 450 with lower catalyst loading (Table 1, entry 3). Unexpectedly, higher loading of $Zr(OTf)_4$ reduced the yield (Table 1, entry 4). Dilution of oxygen with argon retarded the coupling reaction, whereas the reaction hardly proceeded in the presence of nitrogen (Table 1, entries 5 and 6). Almost no coupling product was formed without oxygen (Table 1, entries 7 and 8). Other metal triflates also catalyzed the reaction albeit less efficiently (Table 1, entries 9–11), whereas the use of metal halides or the absence of a Lewis acid lowered the yield and the selectivity (Table 1, entries 12–14). Although triflic acid (TfOH) also effected the reaction, the TON was, unfortunately, low (Table 1, entries 15 and 16). Thus, use of $Zr(OTf)_4$ as a catalyst under O_2 was found to be important.



1 **2a** **3** **4** (1)

Table 1: Lewis acid catalyzed oxidative coupling reaction of 1-methylindole (R = Me, Y = H) with 1-methylpyrrolidin-2-one.[a]

Entry	Lewis acid	Atmosphere	Conv. [%][b]	Yield [%][b]	**3a**/**4a**[c]	TON
1	$Zr(OTf)_4$	O_2	76	54	97:3	108
2[d]	$Zr(OTf)_4$	O_2	99	58	97:3	116
3	$Zr(OTf)_4$[e]	O_2	64	45	96:4	450
4	$Zr(OTf)_4$[f]	O_2	57	31	97:3	31
5	$Zr(OTf)_4$	Ar/O_2 (4:1)	45	29	98:2	58
6	$Zr(OTf)_4$	air	19	1	99:1	2
7	$Zr(OTf)_4$	Ar	15	<1	–	<1
8	$Zr(OTf)_4$	N_2	16	1	83:17	2
9	$In(OTf)_3$	O_2	63	38	96:4	76
10	$Sc(OTf)_3$	O_2	47	31	96:4	62
11	$Zn(OTf)_2$	O_2	49	27	95:5	54
12	$ZrCl_4$	O_2	48	16	92:8	32
13	$InCl_3$	O_2	36	8	85:15	16
14	none	O_2	53	7	92:8	–
15	TfOH	O_2	14	4	99:1	8
16	TfOH[g]	O_2	39	24	98:2	12

[a] The reaction was carried out at 130 °C for 5 h with **1a** (1.0 mmol) and **2a** (2.00 mL, 20.7 mmol) using a Lewis acid or TfOH (5.0 μmol) under a certain gas atmosphere (1 atm). [b] Determined by GC using chlorobenzene as an internal standard. [c] Determined by GC. [d] The reaction was carried out for 24 h. [e] $Zr(OTf)_4$ (1.0 μmol) was used. [f] $Zr(OTf)_4$ (10.0 μmol) was used. [g] TfOH (20.0 μmol) was used.

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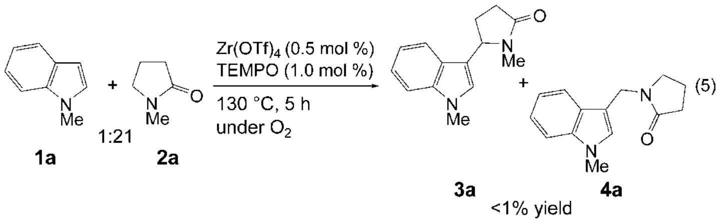
We next investigated the scope of the reaction (Table 2, [Eq. (1–4)]). Substituted 1-methylindoles reacted with **2a** with a similar high regioselectivity (Table 2, entries 1 and 2). A more-electron-rich aryl group contributed to higher yields and selectivities for **3** in the reactions of 1-aryl indoles (Table 2, entries 3–6). In the case of indole, only a single regioisomer **3** was produced (Table 2, entry 7). Indoles with an aminomethyl group at C3 are interesting in view of their biological activity.[6] A pyrrole and a thiophene also coupled oxidatively with **2a** [Eq. (2,3)]. Although 3-methyloxazolidin-2-one reacted also with **1a** exclusively at the carbon atom adjacent to the nitrogen atom but not the oxygen atom [Eq. (4)], an acyclic amide such as *N*,*N*-diethylacetamide unfortunately gave no coupling product under similar conditions.

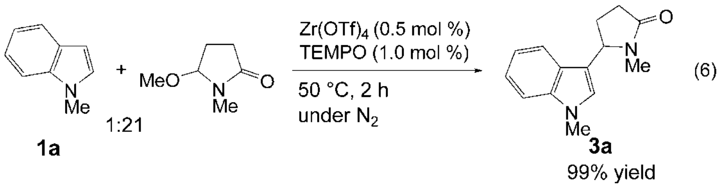
Table 2: $Zr(OTf)_4$-catalyzed oxidative coupling reaction of indole derivatives with 1-methylpyrrolidin-2-one.[a]

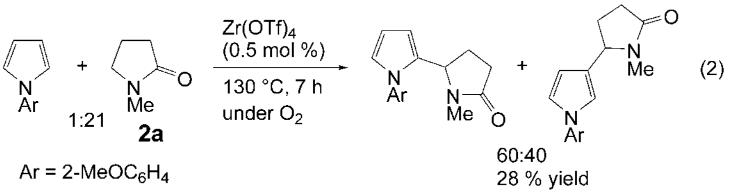
Entry	R	Y	*t* [h]	Yield [%][b]	**3**:**4**[c]	TON
1	Me	MeO	10	28	> 99:1	56
2	Me	Br	3	30	96:4	60
3	$4\text{-}MeOC_6H_4$	H	20	40	93:7	80
4	$2\text{-}MeOC_6H_4$	H	50	44	96:4	88
5	Ph	H	80	24	95:5	48
6	$4\text{-}EtOCOC_6H_4$	H	120	9	89:11	18
7	H	H	10	21	> 99:1	42

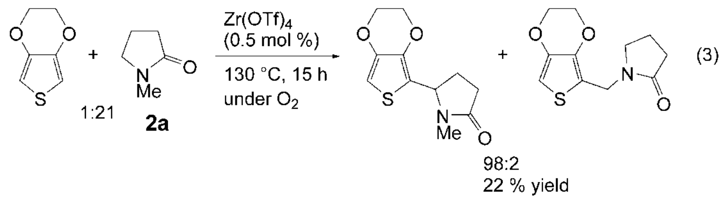
[a] The reaction was carried out at 130 °C with **1** (1.0 mmol) and **2a** (2.00 mL, 20.7 mmol) in the presence of $Zr(OTf)_4$ (5.0 μmol) under atmospheric oxygen (1 atm). [b] Yield of the isolated product based on the indole. [c] Determined by GC.

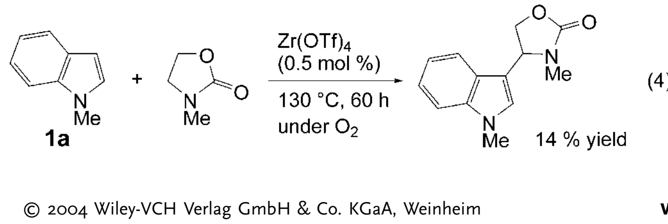
Some evidence is available to allow a discussion of the reaction mechanism. Treatment of **1a** and **2a** with $Zr(OTf)_4$ (0.5 mol %) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO; 1.0 mol %)[7] gave no coupling product, in contrast to the reaction without TEMPO ([Eq. (5)]; Table 1, entry 1). As $Zr(OTf)_4$ quantitatively catalyzed the reaction of **1a** with 5-methoxy-1-methylpyrrolidin-2-one in the presence of TEMPO [Eq. (6)],[8,9] the inability of $Zr(OTf)_4$ in the oxidative coupling reaction should not be ascribed to repression of its Lewis acidity by TEMPO. Thus, some radical species probably exist in the oxidative coupling reaction. However, the exclusive C3 selectivity of indoles observed in this case implies that the radical species is not concerned directly with the carbon–carbon bond formation because radical species are known to attack C2 of indoles.[10] On the other hand, similar preference for C3 between the oxidative coupling reaction and the reaction of the α-methoxyamide may possibly show that nucleophilic attack of an indole to an *N*-acyliminium cation is involved also in the oxidative coupling reaction.[11] Thus, it may be reasonable to consider that a possible mechanism includes stepwise single electron oxidation to give an *N*-acyliminium cation via a cation radical of **2a**. The result that treatment of **2a** (20.7 mmol) with $Zr(OTf)_4$ (5.0 μmol) at 130 °C for 10 h in the absence of **1a** under O_2 gave 0.42 mmol of an oxidized compound, 1-methylsuccinimide, might support the mechanism that includes the oxidation of **2a**.











In summary, we have disclosed the first example of a Lewis acid catalyzed oxidative coupling reaction of lactams with heterocyclic arenes. Zirconium catalyzes the coupling reaction under atmospheric oxygen, scoring the highest TON with quite high regioselectivity. Studies on the improvement of the yield of products and details of the mechanism as well as the application of the reaction to other substrates are in progress.

Experimental Section

General procedure: $Zr(OTf)_4$ (3.4 mg, 5.0 μmol) was placed in a 20-mL Schlenk tube, which was heated at 150 °C in vacuo for 2 h. The tube was cooled to room temperature and filled with oxygen. To this were added successively **2a** (2.00 mL, 20.7 mmol) or 3-methyloxazolidin-2-one (2.00 mL, 23.1 mmol) and a heterocyclic arene (1.0 mmol), and the resulting mixture was stirred at 130 °C. After the time specified in Table 2 and [Eq. (2–4)], the mixture was diluted with diethyl ether (100 mL) and washed successively with water (3 × 10 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), and then dried over anhydrous magnesium sulfate. Filtration through a pad of celite and evaporation of the solvent followed by column chromatography on silica gel gave the corresponding coupling products as a mixture of isomers. Further isolation was performed with preparative recycling column chromatography on silica gel.

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Keywords: C—C coupling · heteroarenes · lactams · Lewis acids · zirconium

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