Synthetic Methods

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Ruthenium-Catalyzed Oxidative Cross-Coupling of Chelating Arenes and Cycloalkanes**

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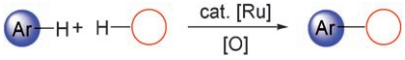
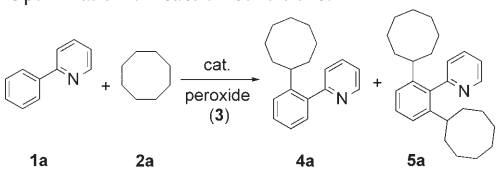
The direct conversion of C–H bonds into C–C bonds leads to a more efficient synthesis with a reduced number of synthetic operations.[1] Recently, progress has been made in the transition-metal-catalyzed activation and subsequent reaction of C–H bonds.[2,3] On the other hand, we[4] and others[5] have developed various methods to generate C–C bonds directly from two different C–H bonds in the presence of an oxidizing reagent through a cross-dehydrogenative-coupling (CDC), which is catalyzed by copper or other transition-metals. However, in all these cases, a relatively reactive C–H bond (e.g. 1,3-dicarbonyls, alkynes, and nitroalkanes) is required. Recently, an elegant cross-coupling reaction of two aryl C–H bonds to form arene–arene coupling products was reported by Fagnou and co-workers, and others.[6] We have also reported a direct alkylation of 1,3-dicarbonyl compounds by using simple alkanes in the presence of a peroxide.[7] Herein, we report an unprecedented direct oxidative cross-coupling of arenes with cycloalkanes catalyzed by ruthenium (Scheme 1).



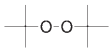
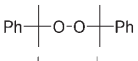
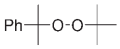
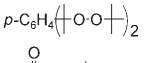
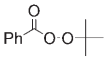
Scheme 1. Oxidative cross-coupling of arenes with cycloalkanes.

Recently, we discovered a simple methylation of 2-arylpyridine C–H bonds that is catalyzed by palladium in the presence of peroxide.[8,9] Unfortunately, the reaction is only limited to methylation. We hypothesized that direct arene–alkane coupling may be possible if we carried out the catalytic reaction by using a different combination of the alkane and the peroxide.[10] However, when 2-phenylpyridine (**1a**) was reacted with cyclooctane (**2a**) in the presence of *tert*-butyl peroxide (**3a**) under the palladium-catalyzed reaction conditions, only a trace (<1%) amount of the desired product was present as determined by GC-MS and ^{1}H NMR methods. Subsequently, we decided to search for other potential catalysts. Salts of various metals such as Fe, Co, Ir, Ni, and Rh were investigated and no desired product was observed. When $Ru(acac)_3$ was used as a catalyst, the desired product was obtained in an overall 43% yield as a mixture of both mono- and biscycloalkylation products **4a** and **5a**, respectively (Table 1, entry 4). Thus, optimization of the reaction was pursued by varying the ruthenium catalysts and the reaction conditions (Table 1). The ligand and the peroxide both showed a marked influence on the yield of the reaction. No desired product was detected in the absence of a catalyst

Table 1: Optimization of reaction conditions.[a]



1a **2a** **4a** **5a**

Entry	Catalyst	Peroxide	Yield of **4a**+**5a** [%] (**4a**/**5a**)[b]
1	—		
		3a	0
2	$Ru_3(CO)_{12}$	**3a**	0
3	$[\{RuCl_2(CO)_3\}_2]$	**3a**	0
4	$Ru(acac)_3$	**3a**	43 (1.3:1)
5	$[\{Ru(COD)Cl_2\}_2]$	**3a**	41 (2.4:1
6	$Ru(CO)H_2(PPh_3)_3$	**3a**	51 (1.5:1)
7	$[\{Ru(benzene)Cl_2\}_2]$	**3a**	40 (2.6:1)
8	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	**3a**	58 (1.5:1)
9	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		20 (4.0:1)
10	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		33 (2.0:1)
11	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		40 (1.0:1)
12	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		0
13	$[\{Ru(p\text{-cymene})Cl_2\}_2]$		0
14[c]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	**3a**	50 (1.5:1)
15[d]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	**3a**	35 (1.5:1)
16[e]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	**3a**	80 (1:1)
17[e,f]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	**3a**	0
18[e,g]	$[\{Ru(p\text{-cymene})Cl_2\}_2]$	**3a**	70 (7:1)

[a] **1a** (31 mg, 0.2 mmol), catalyst (10 mol%), cyclooctane (0.6 mL, 4.5 mmol), peroxide (2 equiv), 135 °C, 16 h in air unless otherwise noted. [b] Reaction was carried out at 120 °C. [c] Yields determined by using NMR methods in which 1,2-dichloroethane was the internal standard. [d] 5 mol% catalyst was used. [e] 4.0 equiv of peroxide used. [f] No cyclooctane was used. [g] Benzene was used instead of cyclooctane, and the yield was refers to the methylated product.

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or in the presence of complex with multiple CO ligands (Table 1, entries 1–3) when using *tert*-butyl peroxide as an oxidizing reagent. On the other hand, the use of a ruthenium catalyst bearing acac, cod, phosphine (with mono CO), or arene ligands all led to the desired mono- and bisalkylation products **4a** and **5a**, respectively (Table 1, entries 4–8).

The use of other peroxides are less effective (Table 1, entries 9–13). Decreasing the reaction temperature (Table 1, entry 14) or the amount of the catalyst (Table 1, entry 15) decreased the product yield. With 4 equivalents of peroxide, 80% of the desired product was obtained in a 1:1 ratio of the mono- and biscycloalkylation products (Table 1, entry 16). As a control, the reaction was run in the absence of cyclooctane and no product was obtained (Table 1, entry 18). Interestingly, a methylated product was obtained in good yield and regioselectivity (Table 1, entry 18) when benzene was used as the solvent.

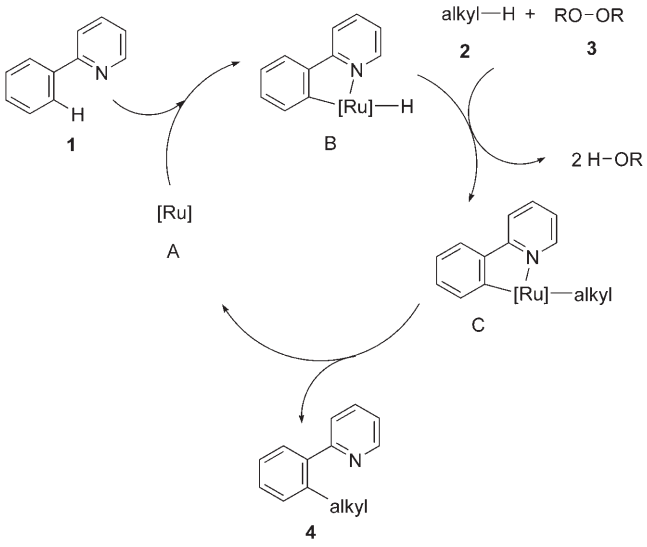
With the optimized conditions in hand, other arenes and cycloalkanes were investigated (Table 2). The reaction occurred exclusively on the non-nitrogen atom-containing aromatic ring. Various electron-withdrawing and electron-donating substituents did not affect the reaction significantly (Table 2, entries 2–8). *meta*-Substituted phenylpyridines almost exclusively afforded the monocycloalkylation products (Table 2, entries 9–11). Other N-heteroaromatic compounds also coupled with cycloalkanes regioselectively (Table 2, entries 12 and 13). Cyclohexane and cycloheptane also reacted smoothly with 2-phenylpyridine to give the desired C–H/C–H coupled products (Table 2, entries 14 and 15). Surprisingly, when the seemingly more reactive cyclooctene was used instead of cyclooctane under the standard conditions, the desired alkylation product was obtained in less than 30% yield in addition to unidentified products; and most of the 2-phenylpyridine remained unreacted.

A tentative mechanism to rationalize the product formation is illustrated in Scheme 2. The active ruthenium catalyst (A) reacts with 2-phenylpyridine (and other arenes) by a chelation-directed C–H activation to generate intermediate B.[10] The reaction of B with cycloalkane **2** and peroxide **3**[11] generates intermediate C and an alcohol. Finally, reductive elimination of intermediate C generates arene–cycloalkane coupling product **4** and regenerates active ruthenium catalyst A. Subsequent reaction of monocycloalkylation product **4** leads to biscycloalkylation product **5**. As experimental evidence to support the proposed mechanism, no [Ru]–alkyl intermediate was detected in a stoichiometric reaction between the ruthenium complex, cyclooctane, and the peroxide. In addition, deuterium isotope experiments with mono- and bisdeuterated 2-phenylpyridines **6** and **7** showed a

6 **7**

large negative kinetic isotope effect (in both cases only nondeuterated products **4a** and **5a**, respectively, were obtained, and no deuterated product was observed), which suggests that there is a fast equilibrium between starting material **1** and intermediate B, with the formation of intermediate C being the rate-limiting step.[12]

In conclusion, a novel C–C bond formation based on the direct oxidative C–H/C–H coupling involving arenes and cycloalkanes has been developed. The scope and detailed mechanism of this reaction are under additional investigation.



Scheme 2. Proposed mechanism for the ruthenium-catalyzed cycloalkylation of arenes mediated with peroxides.

Experimental Section

A representative experimental procedure (**4a** and **5a**): An oven-dried reaction vessel was charged with [{Ru(*p*-cymene)Cl_2}$_2$] (6.1 mg, 0.01 mmol), 2-phenylpyridine (**1a**, 31 mg, 0.2 mmol), *tert*-butyl peroxide (**3a**, 117 mg, 0.8 mmol), and cyclooctane (**2a**, 0.6 mL, 4.5 mmol). The reaction vessel was then sealed and the resulting solution was stirred at 135 °C for 16 h. After cooling to room temperature, the resulting mixture was filtered through a short silica gel plug in a pipette by using methylene chloride as the eluent. The volatiles were removed in vacuo and the residue was purified by column chromatography (SiO_2, hexane/ethyl acetate 9:1) to give **4a** (21 mg, 39%) and **5a** (27 mg, 36%) as pale yellow oils.

4a IR (liquid film): $\tilde{\nu}$ = 3050, 2918, 2852, 1580, 1461, 1120, 775 cm^{-1}; ^{1}H NMR (400 MHz) δ = 8.70–8.68 (m, 1H), 7.86 (s, 1H), 7.75–7.69 (m, 3H), 7.37 (t, J = 7.6 Hz, 1H), 7.26–7.23 (m, 1H), 7.20–7.16 (m, 1H), 2.90–2.85 (m, 1H), 1.93–1.77 (m, 6H), 1.69–1.59 ppm (m, 8H); ^{13}C (100 MHz) δ = 158.0, 151.3, 149.8, 139.6, 136.9, 128.9, 127.8, 126.0, 124.4, 122.2, 120.9, 45.0, 35.1, 27.1, 26.6, 26.3 ppm; HRMS calcd for $C_{19}H_{23}N$ + H 266.1903, found 266.1904.

5a IR (liquid film): $\tilde{\nu}$ = 2912, 2839, 1580, 1435, 782 cm^{-1}; ^{1}H NMR (400 MHz) δ = 8.68–8.66 (m, 1H), 7.71–7.69 (m, 2H), 7.57 (d, J = 1.6 Hz, 2H), 7.20–7.16 (m, 1H), 7.05 (s, 1H), 2.84–2.79 (m, 2H), 1.91–1.57 ppm (m, 28H); ^{13}C (100 MHz) δ = 158.5, 151.3, 149.8, 139.4, 136.8, 126.6, 123.2, 122.0, 121.0, 45.1, 35.2, 27.1, 26.6, 26.4 ppm; HRMS calcd for $C_{27}H_{37}N$ + H 376.2999, found 376.3003.

The experiments in Table 2 were carried out analogously. All products were purified by column chromatography and characterized by NMR spectroscopy and standard/high-resolution mass spectrometry.

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Table 2: Cross-coupling of various arenes with cycloalkanes.[a]

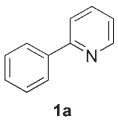
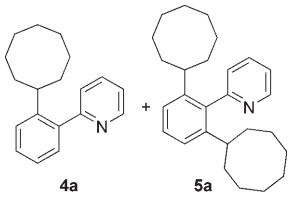
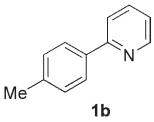
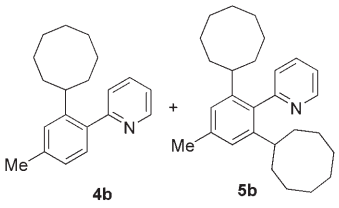
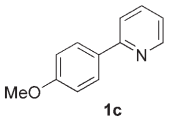
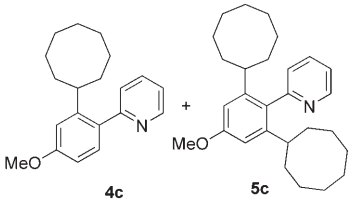
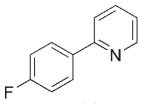
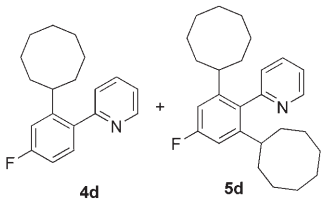
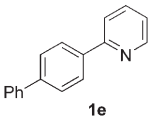
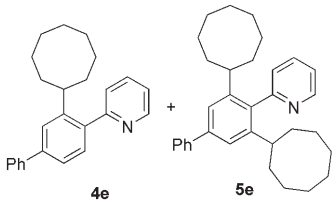
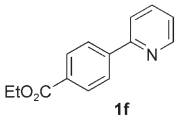
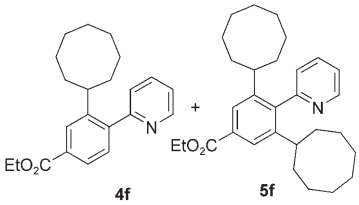
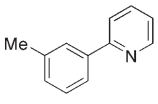
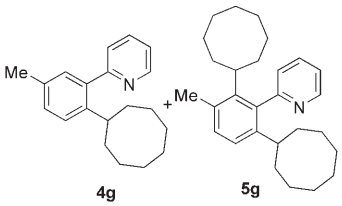
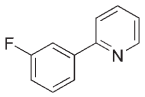
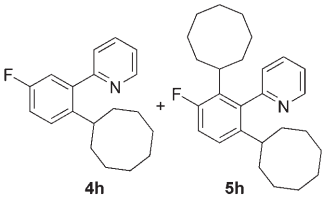
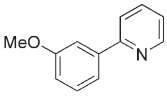
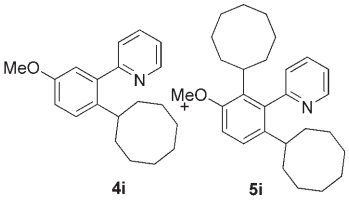
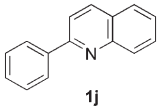
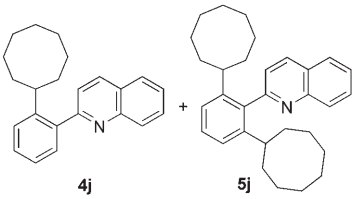
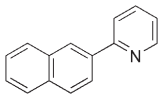
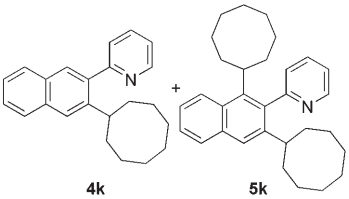
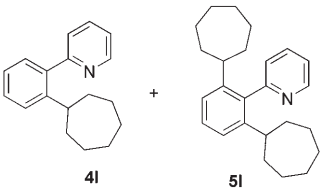
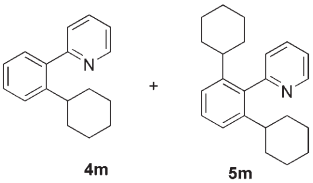
Entry	Arene	Alkane	Product	Yield [%][b]
1	 **1a**	 **2a**	 **4a** + **5a**	75 (**4a**/**5a**=1.1:1)
2[c]	**1a**	**2a**	**4a** + **5a**	56 (**4a**/**5a**=1.5:1)
3	 **1b**	**2a**	 **4b** **5b**	62 (**5b**, trace)
4	 **1c**	**2a**	 **4c** **5c**	54 (**5c**, trace)
5[d]	 **1d**	**2a**	 **4d** **5d**	71 (**4d**, trace)
6[c]	**1d**	**2a**	**4d** + **5d**	60 (**4d**/**5d**=1:1)
7	 **1e**	**2a**	 **4e** **5e**	63 (**4e**/**5e**=5:1)
8	 **1f**	**2a**	 **4f** **5f**	63 (**5f**, trace)
9	 **1g**	**2a**	 **4g** **5g**	53 (**5g**, trace)

Table 2: (Continued)

Entry	Arene	Alkane	Product	Yield [%][b]
10[c]	 **1h**	**2a**	 **4h** **5h**	64 (**5h**, trace)
11	 **1i**	**2a**	 **4i** **5i**	48 (**5i**, trace)
12	 **1j**	**2a**	 **4j** **5j**	42 (**5j**, trace)
13	 **1k**	**2a**	 **4k** **5k**	50 (**5k**, trace)
14	**1a**	 **2b**	 **4l** **5l**	70 (**4l**/**5l**=1.1:1)
15	**1a**	 **2c**	 **4m** **5m**	52 (**4m**/**5m**=1:1)

[a] **1** (0.2 mmol), *tert*-butyl peroxide (0.8 mmol), alkane (0.6 mL), 16 h in air unless otherwise noted. [b] Yields of isolated products. [c] 2 equiv *tert*-butyl peroxide was used. [d] The reaction was run for 6 h.

Keywords: alkanes · arenes · C–C coupling · C–H activation · ruthenium

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