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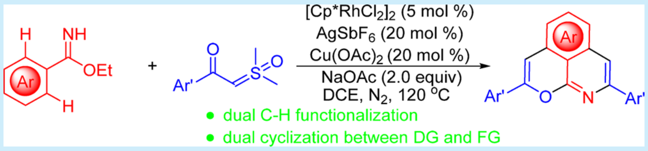
Rhodium-Catalyzed Relay Carbenoid Functionalization of Aromatic C−H Bonds toward Fused Heteroarenes

Xiaopeng Wu, Hao Xiong, Song Sun, and Jiang Cheng*

School of Petrochemical Engineering, and Jiangsu Key Laboratory of Advanced Catalytic Materials & Technology, Changzhou University, Changzhou 213164, P. R. China

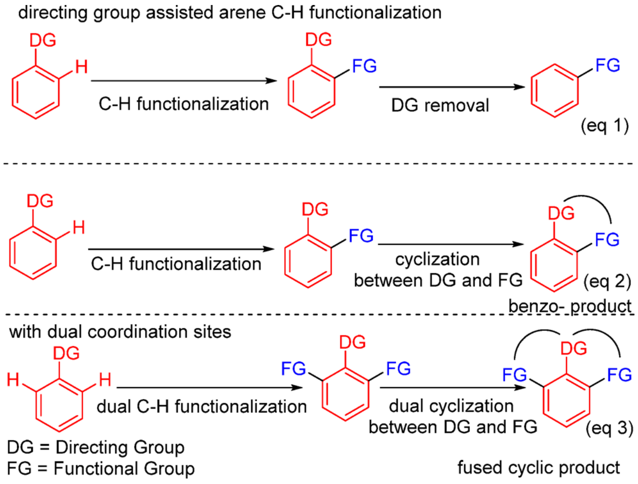
Supporting Information

ABSTRACT: A rhodium-catalyzed annulation between ethyl benzimidates and α- aroyl sulfur ylides was developed, affording a series of pyrano[4,3,2-*ij*]isoquinoline derivatives in moderate to good yields with good functional group compatibility. The procedure featured dual *ortho*-C−H functionalization and dual cyclization in one pot. The optoelectronic properties of those fused heteroarenes were tested by UV/vis and fluorescence spectrometers.



The directing group assisted functionalization of arene C−H bonds represents one of the hottest topics in organic synthetic chemistry.[1−3] However, further removal of those directing groups was required in most cases. To circumvent this, procedures employing either traceless[4] or transient directing groups[5] were developed (Scheme 1, eq 1). Alternatively, the in situ conversion of directing group into the skeleton of the final product is a better idea that allows rapid access to the target molecule with chemical complexity and diversity. As a result, the sequential directing group assisted C−H functionalization and annulation between the introduced functional group and the directing group provides a facile pathway toward benzo products (Scheme 1, eq 2).[6] Accordingly, fused aromatic frameworks could be constructed facilely through sequential dual C−H functionalization[7] and annulation with the directing group (Scheme 1, eq 3).[7] To achieve this, the selection of a proper substrate possessing dual coordination sites to ensure the secondary directing group assisted C−H functionalization is the key factor.

Scheme 1. Constructed Frameworks after *Ortho*-C−H Functionalization



Ethyl benzimidates are potential substrates since both N and O atoms may coordinate with the transition-metal catalyst in directing-group-assisted functionalization of arene C−H bonds.[8] Meanwhile, sulfur ylides[9] function as surrogates of diazo compounds in metal-catalyzed reactions due to the relatively higher security and stability of sulfur ylides.[10,11] In view of the well-developed Rh-catalyzed C−C and C−X bonds formation reactions via C−H activation,[12,13] Aïssa and coworkers pioneered a rhodium-catalyzed coupling of aromatic C(sp^2)−H with α-aroyl sulfur ylides.[14] Afterward, Li applied this strategy in the synthesis of a variety of carbocycles and *N*-heterocycles.[15]

We initially chose ethyl benzimidate (**1a**) and α-benzoyl sulfur ylide (**2a**) as model substrates to explore the dual *ortho*-C−H fuctionalization/cyclization reaction. In the presence of a catalytic amount of [Cp*RhCl$_2$]$_2$/AgSbF$_6$ (5 mol %), and NaOAc (2.0 equiv) as the base, the reaction took place at 80 °C in DCM to generate the desired pyrano[4,3,2-*ij*]isoquinoline (**3aa**), albeit in a low yield (13%, Table 1, entry 5). The reaction did not run in many solvents, such as THF, DMF, MeCN, and EtOH, even at 120 °C (Table 1, entries 1−4). To our delight, the yield increased to 55% in DCE (Table 1, entry 6). The sliver salts improved the reaction efficiency, and Cp*Rh(OAc)$_2$ was superior to [Cp*IrCl$_2$]$_2$ and CoCp*(CO)I$_2$ (Table 1, entry 7). The fused aromatic compound **3aa** was isolated in 81% yield in the presence of 0.2 equiv of Cu(OAc)$_2$ (Table 1, entry 8). Among the bases tested, sodium acetate was the best one (Table 1, entries 8−12). The yield decreased in the absence of any base (53%, Table 1, entry 13). The practicability of this method was investigated in a 1 mmol scale, and **3aa** was isolated in an acceptable 66% yield.

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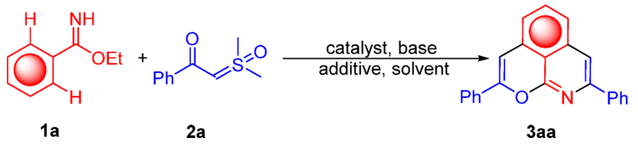
Table 1. Selected Results for Screening the Optimized Reaction Conditions[a]



entry	base	additive (equiv)	solvent	yield[b] (%)
1	NaOAc		THF	nr
2	NaOAc		DMF	nr
3	NaOAc		MeCN	trace
4	NaOAc		EtOH	trace
5	NaOAc		DCM	13[i]
6	NaOAc		DCE	55
7	NaOAc		DCE	18[c], 34[d], 77[e], trace[f], trace[g]
8	NaOAc	$Cu(OAc)_2$ (0.2)	DCE	81, 49[h], 32[i]
9	KOAc	$Cu(OAc)_2$ (0.2)	DCE	63
10	$KHCO_3$	$Cu(OAc)_2$ (0.2)	DCE	19
11	K_2HPO_4	$Cu(OAc)_2$ (0.2)	DCE	21
12	K_2CO_3	$Cu(OAc)_2$ (0.2)	DCE	<10
13		$Cu(OAc)_2$ (1.0)	DCE	53
14		$Cu(OAc)_2$ (1.0)	DCE	20[c]

[a] Reaction conditions: ethyl benzimidate **1a** (0.1 mmol), dimethyloxosulfonium benzoylmethylide **2a** (0.22 mmol), catalyst: $[Cp^*RhCl_2]_2$ (5 mol %), Cp* = 1,2,3,4,5-pentamethylcyclopenta-1,3-diene, $AgSbF_6$ (20 mol %), base (0.2 mmol), additive, solvent (2.0 mL), under N_2, at 120 °C for 12 h, in a sealed Schlenk tube, unless otherwise noted. [b] Isolated yield. [c] Without $AgSbF_6$. [d] $[Cp^*Rh(MeCN)_3)](SbF_6)_2$ (5 mol %), without Ag salt. [e] $Cp^*Rh(OAc)_2$ (5 mol %). [f] $[Cp^*IrCl_2]_2$ (5 mol %). [g] $CoCp^*(CO)I_2$. [h] 100 °C. [i] 80 °C.

With the optimized reaction conditions in hand, the scope and limitation of ethyl benzimidate derivatives were studied as shown in Figure 1. Generally, the reaction efficiency was not sensitive to the electron nature of the substituents on the aryl as substrates bearing both electron-donating (**3ba**−**ga** and **3ka**, 49−83%) and electron-withdrawing groups (**3ha**−**ja**, 65−90%) all worked well to deliver the desired products in good to excellent yields. Specially, substrates with a *meta* substituent in phenyl resulted in a mixture of two regioselective isomers (**3ba**/**3ca**, 49%, 1.3/1), and ethyl 2-methylbenzimidate failed to work. Notably, halo groups survived well under the procedure, which provided handles for potential further functionalizations. In addition, the structure of **3ha** was further confirmed by X-ray crystallography (for details, see the Supporting Information).

Next, the scope of sulfur ylides was investigated as shown in Figure 2. Generally, *α*- aroyl sulfur ylides bearing both electron-donating (**3ab**−**af**, 66−87%) or withdrawing groups (**3ag**−**ai**, 79−86%) all worked well to deliver the desired products in moderate to good yields. In addition, this procedure was applicable to sulfur ylides with 2-thiophene-yl (**2j**) and cyclohexyl (**2k**) attached in the carbonyl.

The reactivities of different alkyl benzimidates were also tested as shown in Scheme 2. As expected, the alkyl groups have little effect on the yield of **3aa** except the methyl substrate (**1l**).

The UV/vis and fluorescence emission properties of **3aa**, **3aj**, **3ae**, **3ai**, **3ia**, and **3ga** were studied as shown in Figure 3 and Table 2. All products showed similar optoelectronic properties: one absorption maxima around 340 nm and one fluorescence maximum around 465 nm. The optical properties were significantly changed by substituents. The fluorescence maxima are red-shifted (Figure 3) when the alkyl (**3aa**, 464 nm; **3ae**, 468 nm) or halogen (**3ai**, 462 nm) group is replaced by an aryl group (**3ga**, 471 nm). To our delight, the Stokes shift of **3aj** is as large as 141 nm (Table 2).

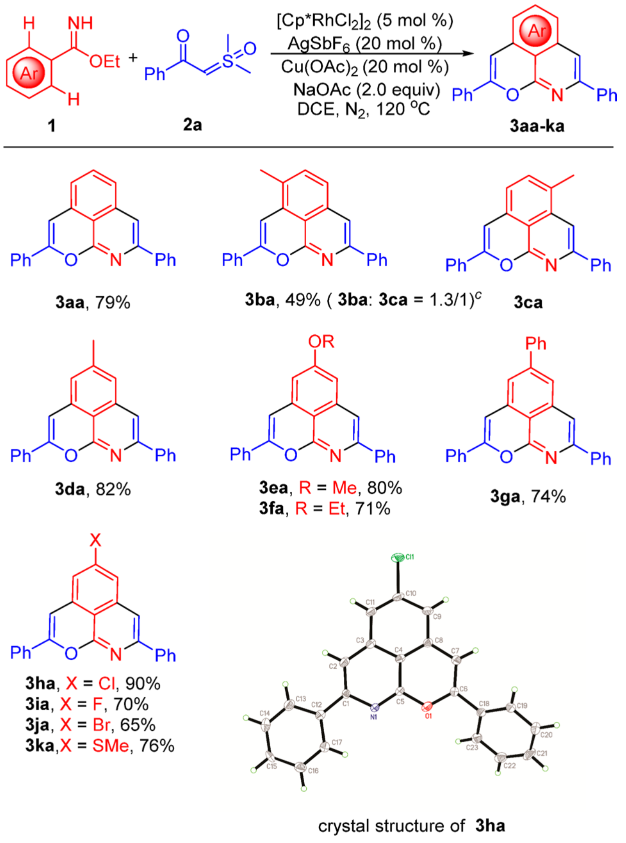


Figure 1. Scope of substituted ethyl benzimides. (a) Reaction conditions: substituted ethyl benzimidate **1** (0.1 mmol), dimethyloxosulfonium benzoylmethylide **2a** (0.22 mmol), catalyst: $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2$ (20 mol %), NaOAc (0.2 mmol), DCE (2.0 mL), under N_2, at 120 °C for 12 h, in a sealed Schlenk tube, unless otherwise noted. (b) Isolated yield. (c) It is difficult to isolate the corresponding cross-coupling mixture (**3ba** and **3ca**); their ratio data was determined by ^{1}H NMR spectrum.

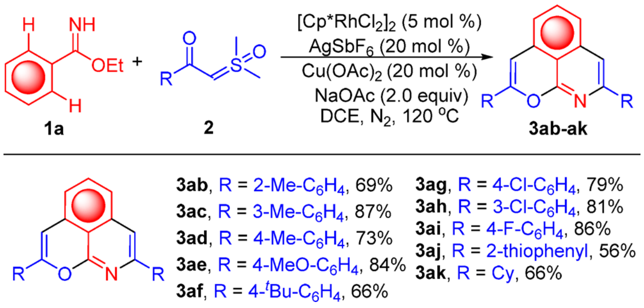
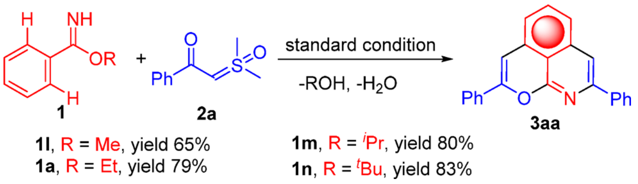


Figure 2. Substrate scope of *α*-aroyl sulfur ylides. (a) Reaction conditions: ethyl benzimidate **1a** (0.1 mmol), *α*-aroyl sulfur ylide **2** (0.22 mmol), catalyst: $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2$ (20 mol %), NaOAc (0.2 mmol), DCE (2.0 mL), under N_2, at 120 °C for 12 h, in a sealed Schlenk tube, unless otherwise noted. (b) Isolated yield.

In the control experiment (Scheme 3), 1-ethoxy-3-phenylisoquinoline (**4**) was detected at 40 °C, indicating the high reactivity of the imide group in *ortho*-C−H activation and cyclization.[15c] Intriguingly, 1-ethoxyisoquinoline (**5**) failed to deliver product **6** under the standard procedure. This result

Scheme 2. Reaction of Alkyl Benzimidate and Sulfur Ylide



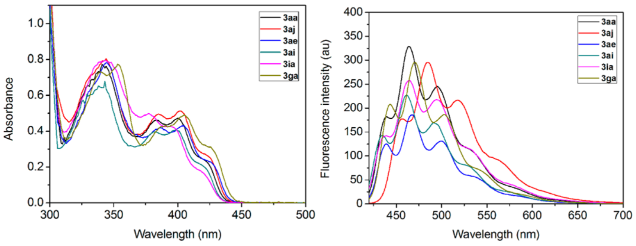


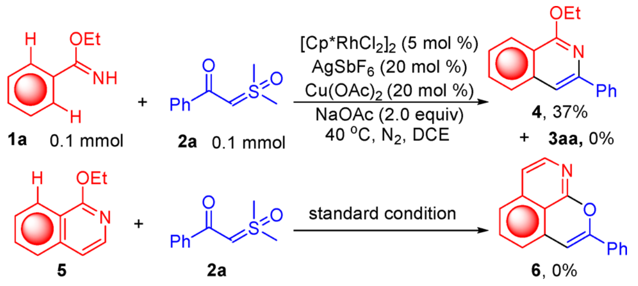
Figure 3. UV−vis (left) and fluorescence (right) spectra.

Table 2. Absorption and Emission Data[a]

	3aa	3aj	3ae	3ai	3ia	3ga
λ_{abs} (nm)	341	344	344	342	343	353
$\varepsilon_{342\ nm}$ (L $mol^{-1}cm^{-1}$)	7726	8048	7817	6870	7959	7744
λ_{em} (nm)	464	485	468	462	465	471
Stokes shift (cm^{-1})	7773	8451	7702	7595	7649	7097

[a]Solvent of all samples was DCM.

Scheme 3. Control Experiments

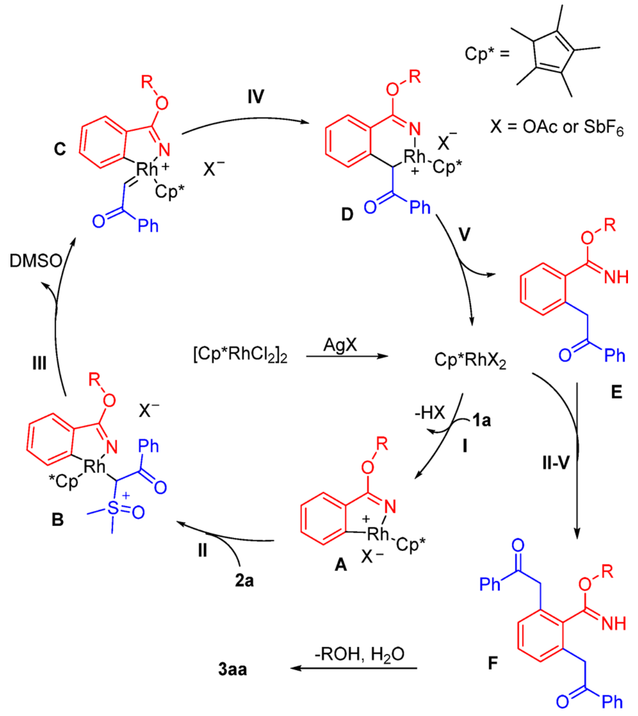


indicated that before the cyclization of imide it was the nitrogen atom rather than the oxygen atom which chelated with rhodium to facilitate the secondary cleavage of C−H bond.

On the basis of the control experiments and previous reports,[7,14,15] a catalytic cycle for the dual *ortho*-C−H functionalization and cyclization is proposed (Scheme 4). Initially, de-dimerization of $[Cp^*RhCl_2]_2$ and C−H activation of ethyl benzimide produce a rhodacyclic intermediate **A**. Then coordination of **2a** with **A** leads to a Rh(III) intermediate **B**, which transforms to a carbene species **C** by *α*-elimination of DMSO. Afterward, the migratory insertion and protonolysis afford the acylmethylated intermediate **E**. Finally, after the secondary catalytic cycle, **E** furnishes **3aa** by release of Rh(III) catalyst and a dehydrating process.

In conclusion, we have developed a rhodium-catalyzed dual *ortho*- C−H functionalization and annulation between ethyl benzimidates and *α*-aroyl sulfur ylides toward a series of functionalized isoquinazolones in good to moderate yields. The compounds are fluorescent with emission maxima around 465 nm and Stokes shifts up to 141 nm.

Scheme 4. Proposed Mechanism



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00119.

Experimental procedures along with copies of spectra (PDF)

Accession Codes

CCDC 1823329 contains 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jiangcheng@cczu.edu.cn.

ORCID

Song Sun: 0000-0002-9974-6456
Jiang Cheng: 0000-0003-2580-1616

Notes

The authors declare no competing financial interest.

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