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Dual Role of Anthranils as Amination and Transient Directing Group Sources: Synthesis of 2-Acyl Acridines

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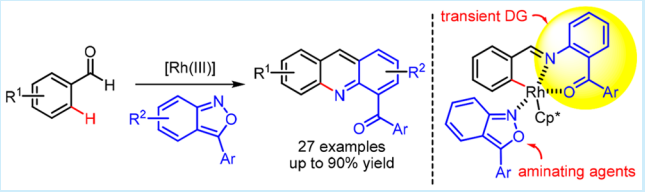
Supporting Information

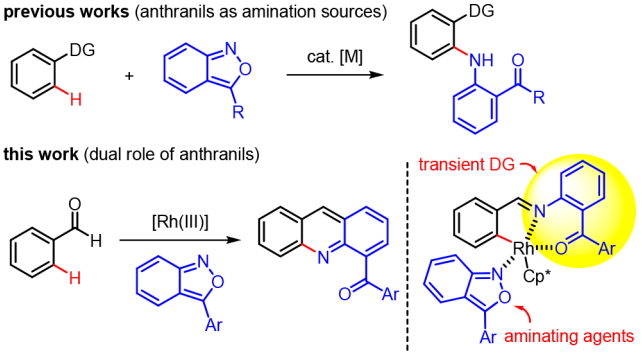
ABSTRACT: The transient directing group promoted C-(sp^2)−H functionalization of benzaldehydes with anthranils by a cationic rhodium(III) catalyst is described. Notably, anthranils have been used as both transient directing groups and amination sources to afford 2-acyl acridines through direct C−H amination followed by acid-mediated cyclization. A range of substrate scopes and functional group tolerance were observed.



The transient directing group assisted C−H functionalization of carbonyl compounds under transition metal catalysis has been recently investigated.[1] Generally, this strategy obviates extra synthetic steps for the installation and removal of the external directing groups. As a pioneering work, the transient imine-directed hydroacylation of aldehydes with alkenes by using a catalytic amount of 2-aminopicoline under rhodium(I) catalysis was reported by Jun in 1997.[2] Later, the transient imine directing groups derived from carbonyl groups with a catalytic amount of primary amines have been intensively utilized for the aromatic C−H functionalizations. For example, Jun demonstrated the Rh(I)-catalyzed hydroarylation of acetophenones with alkenes in the presence of benzylamine.[3] In addition, Kuninobu and Takai disclosed the Re(I)-catalyzed annulation reaction of aromatic ketones with α,β-unsaturated esters via the reversible in situ imine formation.[4] The transient-directed approaches have been efficiently extended to the Pd(II)-catalyzed sp^2 and sp^3 C−H functionalizations of carbonyl compounds by Yu, Jin, Sorensen, Li, Ge, and Shi.[5] In addition, the transient-imine-directed *ortho*-C−H aminations of aromatic aldehydes with organic azides and nitrosobenzenes under Ir(III) or Rh(III) catalysis were also reported.[6]

Transition-metal-catalyzed C−N bond formation via a C−H bond activation event has been of great interest in organic synthesis and medicinal chemistry.[7] In this area, anthranils have been explored as aryl amine surrogates in the C−H amination reactions of sp^2 and sp^3 C−H bonds,[8] although anthranils have been used in the coupling reaction with organozinc compounds under Ni(0) catalysis.[9] However, to our best knowledge, the dual role of anthranils as both transient directing groups and amination sources has been unexplored (Scheme 1). The acridine derivatives have been initially used as pigments and dyestuffs. Recently, acridine derivatives have been extensively explored as potential therapeutic agents for the treatment of a number of diseases, such as cancer, Alzheimer's disease, and bacterial infections.[10] In continuation of our research goal on the construction of biologically relevant heterocycles through catalytic C−H functionalization,[11] we herein present the transient-imine-directed C−H amination followed by intramolecular annulations of aromatic aldehydes with C3-aryl-substituted anthranils under cationic Rh(III) catalysis to deliver a range of 2-acyl acridines. In sharp contrast, C3-alkyl-substituted anthranils are employed for the formation of dibenzoazocinones by the intramolecular aldol condensation.

Scheme 1. Anthranils in C−H Functionalization



Our initial optimization of reaction conditions was performed by the coupling reaction of benzaldehyde (**1a**) with 3-aryl anthranil **2a**, as shown in Table 1. We were pleased to see the coupling reaction under cationic Rh(III) catalysis in the presence of a $Cu(OAc)_2$ additive in DCE at 110 °C, affording the desired 2-acyl acridine **3a** in 37% yield (Table 1,

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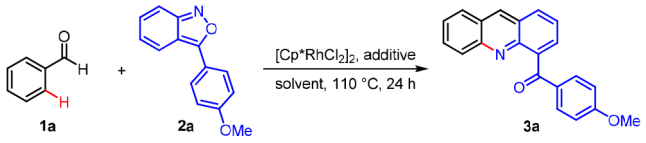
Table 1. Optimization for Reaction Conditions[a]



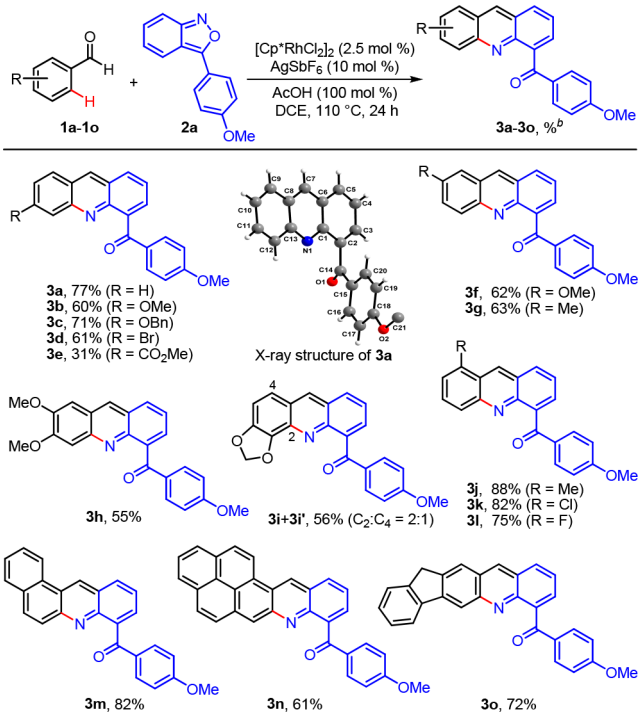
entry	additive (mol %)	solvent	yield[b]
1	$AgSbF_6$ (10)	DCE	N.R.
2	$AgSbF_6$ (10), $Cu(OAc)_2$ (50)	DCE	37
3	$AgSbF_6$ (10), $Cu(OAc)_2$ (100)	DCE	29
4	$AgSbF_6$ (10), NaOAc (50)	DCE	32
5	$AgSbF_6$ (10), LiOAc (50)	DCE	28
6	$AgSbF_6$ (10), AcOH (50)	DCE	72
7	**$AgSbF_6$ (10), AcOH (100)**	**DCE**	**77**
8	$AgSbF_6$ (10), PivOH (100)	DCE	30
9	$AgSbF_6$ (10), $AdCO_2H$ (100)	DCE	42
10	AcOH (100)	DCE	N.R.
11	$AgNTf_2$ (10), AcOH (100)	DCE	57
12	$AgPF_6$ (10), AcOH (100)	DCE	34
13	$AgSbF_6$ (10), AcOH (100)	THF	35
14	$AgSbF_6$ (10), AcOH (100)	MeCN	31
15	$AgSbF_6$ (10), AcOH (100)	DMF	20
16[c]	$AgSbF_6$ (10), AcOH (100)	DCE	N.R.
17[d]	$AgSbF_6$ (10), AcOH (100)	DCE	N.R.
18[e]	$AgSbF_6$ (10), AcOH (100)	DCE	57
19[f]	$AgSbF_6$ (4), AcOH (100)	DCE	40

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), additive (quantity noted), and DCE (1 mL) under air at 110 °C for 24 h in pressure tubes. [b]Isolated percent yield by flash column chromatography. [c]$[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol %) was used as a catalyst. [d]$[Cp^*IrCl_2]_2$ (2.5 mol %) was used as a catalyst. [e]**2a** (0.5 mmol, 2.5 equiv) was used. [f]$[Cp^*RhCl_2]_2$ (1 mol %) was used as a catalyst.

entries 1−3). Screening of acetate additives was found to be less effective in this transformation (Table 1, entries 4 and 5). Surprisingly, a loading of AcOH additive (100 mol %) displayed significantly increased reactivity to give **3a** in 77% yield (Table 1, entries 6 and 7). However, pivalic acid (PivOH) and 1-adamantanecarboxylic acid ($AdCO_2H$) were found to be ineffective in this reaction (Table 1, entries 8 and 9). In the absence of $AgSbF_6$, no formation of **3a** was observed (Table 1, entry 10). In addition, exchanging of silver additives to $AgNTf_2$ and $AgPF_6$ provided 57% and 34% yields of **3a**, respectively (Table 1, entries 11 and 12). Further screening of solvents indicated that DCE was found to be the most effective solvent (Table 1, entries 13−15). Notably, cationic Ru(II) and Ir(III) catalysts were found to be unsuccessful (Table 1, entries 16 and 17). It is mentioned that an increasing amount of anthranil **2a** afforded the decreased formation of 2-acyl acridine **3a** in 57% yield (Table 1, entry 18). Finally, a lower amount (1 mol %) of Rh catalyst resulted in a decreased yield (Table 1, entry 19).

With the optimized reaction conditions in hand, the substrate scope of aryl aldehydes was examined, as shown in Scheme 2. The reaction of *para*-substituted benzaldehydes **1b**−**1d** with both electron-donating and halogen groups was found to be good substrates in this coupling reaction, furnishing the desired products **3b**−**3d** in good to high yields. The structure of synthetic 2-acyl acridines was confirmed by X-ray crystallographic analysis of compound **3a**. However, electron-deficient benzaldehyde **1e** was found to be less reactive under the current reaction conditions. Most of starting

Scheme 2. Scope of Aryl Aldehydes[a]



[a]Reaction conditions: **1a**−**1o** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), AcOH (100 mol %), and DCE (1 mL) under air at 110 °C for 24 h in pressure tubes. [b]Isolated yield by flash column chromatography.

material **1e** and a trace amount of aldimine intermediate were detected by TLC analysis. Based on this result, we assume that relatively lower formation of **3e** might be due to the low efficiency of *ortho*-C−H activation of electron-deficient benzaldehyde. We were delighted to observe that *meta*-substituted benzaldehydes **1f**−**1h** were found to exhibit the complete site selectivity at the less hindered C−H bonds to generate the corresponding products **3f**−**3h**. However, piperonal (**1i**) was reacted with **2a**, providing a mixture of acridines **3i** and **3i′** with a 2:1 ratio in 56% combined yield. This result can be rationalized because the formation of the rhodacycle intermediate might be affected by both electronic and steric environments. In addition, *ortho*-substituted benzaldehydes showed good reactivity toward the C−H amination followed by subsequent cyclization, affording 2-acyl acridine adducts **3j**−**3l** in high yields. It should be noted that highly conjugated acyl acridines **3m** and **3n** were also formed in 82% and 61% yields under the optimal reaction conditions. Moreover, fluorene-2-carboxaldehyde (**1o**) was found to be tolerable to provide **3o** in 72% yield. However, in the case of acetophenone, *trans*-cinnamaldehyde, and 1-cyclohexene-1-carboxaldehyde, no formation of corresponding coupling products was observed.

After successful screening of aryl aldehydes, we further evaluated the scope of anthranils **2b**−**2l** with *o*-tolualdehyde (**1j**), as shown in Scheme 3. The C3-aryl-substituted anthranils **2b**−**2j**, regardless of electronic nature on C3-aryl rings, were successfully reacted with **1j**, giving 2-acyl acridine derivatives **4b**−**4j** in 67−90% yields. To our pleasure, anthranil **2k** bearing a 1-naphthyl moiety at the C3-position was found to be highly reactive under the standard reaction conditions to furnish a highly conjugated acridine **4k** in 88% yield. Additionally, 6-

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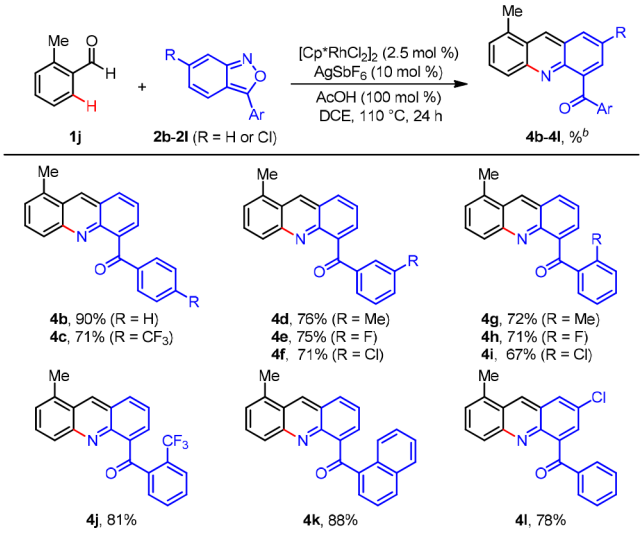
Scheme 3. Scope of C3-Aryl-Substituted Anthranils[a]

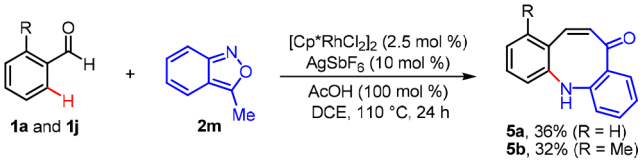


[a]Reaction conditions: **1j** (0.2 mmol), **2b**−**2l** (0.3 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), AcOH (100 mol %), and DCE (1 mL) under air at 110 °C for 24 h in pressure tubes. [b]Isolated yield by flash column chromatography.

chloro-3-phenylbenzo[*c*]isoxazole (**2l**) was found to be a good substrate in this transformation to afford **4l** in 78% yield.

Meanwhile, we also performed the reaction of C3-methyl-substituted anthranil **2m** under the optimal reaction conditions (Scheme 4). Interestingly, anthranil **2m** was coupled with aryl

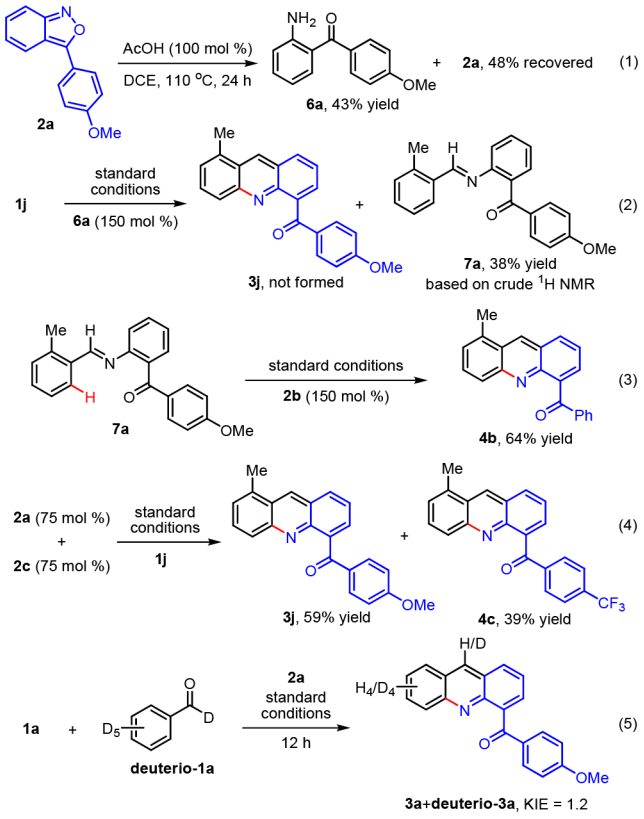
Scheme 4. Synthesis of Dibenzoazocinones



aldehydes **1a** and **1j** to furnish dibenzoazocinones **5a** (36%) and **5b** (32%), respectively. No formation of 2-acetyl acridine was observed. This observation might be rationalized by the intramolecular aldol condensation between acetyl and aldehyde groups on C−H aminated intermediate.

To recognize the formation of 2-acyl acridines, various control experiments were subjected, as shown in Scheme 5. To confirm whether aldimine intermediate is a crucial intermediate in this process, we performed the reaction of **2a** with AcOH (100 mol %) at 110 °C for 24 h, resulting in the formation of 2-benzoyl aniline **6a** in 43% yield (Scheme 5, eq 1). This result indicates that an AcOH additive can serve as a proton donor to facilitate N−O bond cleavage of anthranil. Next, treatment of **1j** with **6a** (150 mol %) provided aldimine **7a** in 38% yield based on the crude ^{1}H NMR analysis, and no formation of 2-acyl acridine **3j** was detected (Scheme 5, eq 2). Subsequently, aldimine **7a** was subjected to be coupled with **2b** to deliver **4b** in 64% yield (Scheme 5, eq 3). Based on the results, we speculated that a bidentate imine directing group[12] derived from benzaldehyde and 2-benzoyl aniline might be very crucial to initiate the C−H bond activation and subsequent insertion of anthranil. An intermolecular competition experiment using electronically different anthranils **2a** and **2c** was performed to illustrate the chemoselectivity of this

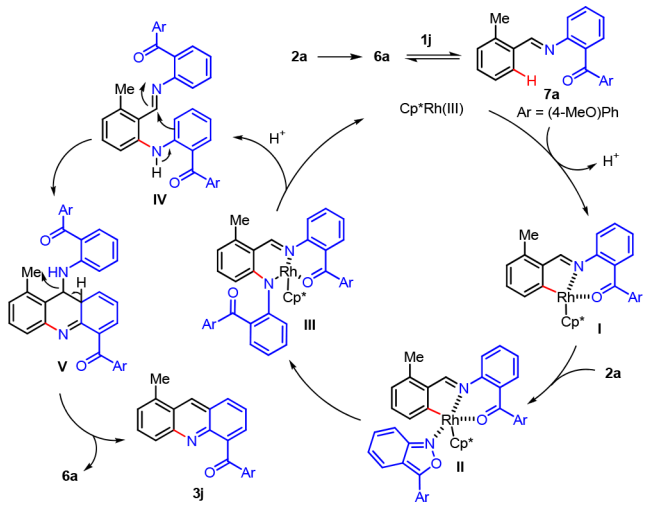
Scheme 5. Mechanistic Investigation



method (Scheme 5, eq 4). No significant distinction of product distribution between **3j** and **4c** was observed. Finally, the kinetic isotope effect experiment was carried out between **1a** and **deuterio-1a** with **2a** under standard reaction conditions for 12 h, resulting in the observed kinetic isotope effect (k_H/k_D) value of 1.2 (Scheme 5, eq 5). This result indicates that C−H bond cleavage might not be involved in the turnover-limiting step.

With the above mechanistic investigation, a proposed reaction mechanism is outlined in Scheme 6. Initially, benzaldehyde **1j** was reacted with **6a**, derived from anthranil **2a**, to afford aldimine **7a** under acidic conditions. Aldimine **7a**

Scheme 6. Proposed Reaction Mechanism



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can undergo the C−H activation step with a cationic Rh(III) catalyst to deliver a rhodacycle intermediate **I**. Coordination of **2a** and subsequent migratory insertion can take place to afford a rhodacycle intermediate **III**, which undergoes protonolysis to provide intermediate **IV** and an active Rh(III) catalyst. Next, intramolecular electrophilic cyclization followed by aromatization occurs to give 2-acyl acridine **3j**, and a regenerated 2-benzoyl aniline **6a** can be involved in the catalytic cycle for imine formation.

In conclusion, we disclosed the transient directing group-assisted Rh(III)-catalyzed C−H functionalization followed by intramolecular electrophilic cyclization between benzaldehydes and anthranils. Anthranils have been utilized for in situ formation of imine directing groups, which further underwent the reaction of the remaining anthranils as amination sources to afford 2-acyl acridines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01571.

X-ray crystallographic data of **3a**, experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

Accession Codes

CCDC 1589936 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.

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§S.K. and S.H.H. equally contributed.

Notes

The authors declare no competing financial interest.

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