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-(sp3)−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. 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 alkynes by using a catalytic amount of 2-aminopicoline under rhodium(I) catalysis was reported by Jun in 1997. 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 hydroamination of aromatic aldehydes with alkynes in the presence of benzyamine. In addition, Kuminobu and Takai disclosed the Re(I)-catalyzed annihilation reaction of aromatic ketones with α,β-unsaturated esters via the reversible in situ imine formation. The transient-directed approaches have been efficiently extended to the Pd(II)-catalyzed sp2 and sp3 C−H functionalizations of carbonyl compounds by Yu, Jin, Sorensen, Li, Ge, and Shi. In addition, the transient-imine-directed ortho-C−H aminations of aromatic aldehydes with organic azides and nitrosothiobenzenes under Rh(III) catalysis were also reported.

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. In this area, anthranils have been explored as aryl amine surrogates in the C−H amination reactions of sp2 and sp3 C−H bonds, although anthranils have been used in the coupling reaction with organozinc compounds under Ni(0) catalysis. 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 therapeutics for the treatment of a number of diseases, such as cancer, Alzheimer’s disease, and bacterial infections.

In continuation of our research goal on the construction of biologically relevant heterocycles through catalytic C−H functionalization, we herein present the transient-imine-directed C−H amination followed by intramolecular annihilations 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.

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, Table 1).

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Scheme 1. Anthranils in C−H Functionalization

previous works (anthranils as amination sources)

this work (dual role of anthranils)

transient DG

Ar aminating agents

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Surprisingly, a loading of AcOH additive (100 mol %) and 1-adamantanecarboxylic acid (AdCO2H) were respectively (Table 1, entries 11 and 12). Further screening of column chromatography.

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*Reaction conditions: 1a (0.2 mmol), 2a (0.3 mmol), [Cp*RhCl2]2 (2.5 mol %), additive (quantity noted), and DCE (1 mL) under air at 110 °C for 24 h in pressure tubes. Isolated percent yield by flash column chromatography. *Reaction conditions: 1a–1o (0.2 mmol), 2a (0.3 mmol), [Cp*RhCl2]2 (2.5 mol %), AgSbF6 (10 mol %), AcOH (100 mol %), and DCE (1 mL) under air at 110 °C for 24 h in pressure tubes. Isolated yield by flash column chromatography.

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 (AdCO2H) were found to be ineffective in this reaction (Table 1, entries 8 and 9). In the absence of AgSbF6, no formation of 3a was observed (Table 1, entry 10). In addition, exchanging of silver additives to AgNTf2 and AgPF6 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 anilanthal 2a afforded the decreased formation of 2-acetyl 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 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 acidines 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-acetyl acidine adducts 3j–3l in high yields. It should be noted that highly conjugated 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 anilanthal 2b–2l with o-toluic acid (1j), as shown in Scheme 3. The C3-aryl-substituted anilanthal 2b–2j, regardless of electronic nature on C3-aryl rings, were successfully reacted with 1j, giving 2-acetyl acidine derivatives 4b–4j in 67–90% yields. To our pleasure, anilanthal 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 acidine 4k in 88% yield. Additionally, 6-
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 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 1H 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 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 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 (kH/kD) 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 then reacts with 2b to deliver 4b in 64% yield (Scheme 6, eq 1). Subsequently, aldimine 7a was subjected to be coupled with 2c to deliver 4c in 39% yield (Scheme 6, eq 2). Based on the results, we speculated that a bidentate imine directing group 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 method (Scheme 6, eq 3). 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 (kH/kD) value of 1.2 (Scheme 6, eq 4). This result indicates that C−H bond cleavage might not be involved in the turnover-limiting step.

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can undergo the C–H activation step with a cationic Rh(III) catalyst to deliver a rhodacyle intermediate I. Coordination of 2a and subsequent migratory insertion can take place to afford a rhodacyle intermediate II, 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.orlett.8b01571.

X-ray crystallographic data of 3a, experimental procedures, characterization data, and 1H and 13C 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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Notes
The authors declare no competing financial interest.

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