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Ruthenium- and Rhodium-Catalyzed Chemodivergent Couplings of Ketene Dithioacetals and α-Diazo Ketones via C−H Activation/Functionalization

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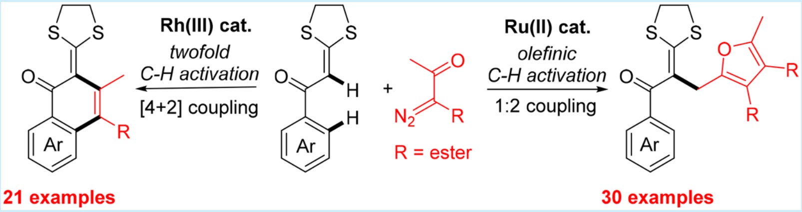
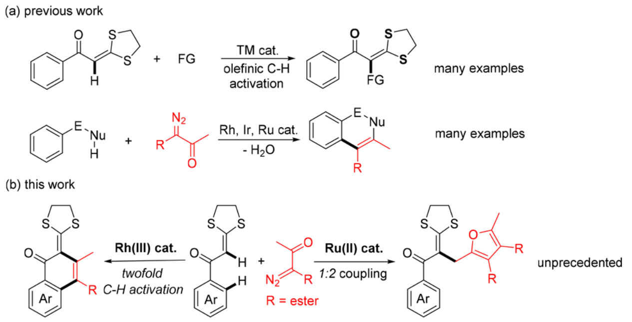
Supporting Information



ABSTRACT: Chemodivergent coupling of α-acylketene dithioacetals with diazo compounds has been realized under catalyst control. The Ru(II)-catalyzed C−H activation occurred at the olefinic position, and 1:2 coupling with α-diazoketoesters leads to furfurylation. In contrast, the Rh(III)-catalyzed C−H functionalization occurred at both the olefinic and the *ortho* C(aryl)−H positions, and [4 + 2] annulation afforded naphthalenones. Synthetic applications have been performed to demonstrate the usefulness of the coupling system.

C−H activation of arenes has been established as an increasingly important strategy for the construction of complex organic products.[1] In particular, high-valent complexes of Ru(II) and Rh(III) have exhibited high catalytic activity in functionalization of a diverse array of arenes.[1f,g,i] Despite tremendous progress, with the presence of different types of C−H bonds in arenes, the regio- and chemoselectivity represents a major challenge. While the *ortho* selectivity of C−H activation can be readily realized by taking advantage of a directing group,[2] the chemoselectivity of C−H activation can be a challenge. Olefinic and aryl C−H bonds are typical subjects in C(sp^2)−H activation, and the differentiation of these C−H bonds represents a fundamental topic, especially when the C(olefinc)−H[3] and C(aryl)−H bonds are comparatively reactive. The selective functionalization of these bonds leads to molecular diversity, especially under simple condition control.

Scheme 1. C−H Activation of α-Oxoketene Dithioacetals



We selected α-benzoylketene dithioacetals as a substrate for proof-of-concept studies on selectivity (Scheme 1).[4] Previously, only catalytic *olefinic* C−H alkenylation,[5] allylation,[6] alkylation,[7] alkoxylation,[8] phosphorylation,[9] and trifluoromethylation[10] has been realized (Scheme 1a). We reasoned that the electronic effects of the substrates and nature of the catalyst can be employed for selective C(sp^2)−H functionalization. For coupling with a highly electrophilic substrate where the electronic effect is predominant, the C(olefinic)−H functionalization is expected because of the high nucleophilicity. In contrast, C(aryl)−H activation is generally favored by a high-valent metal such as Rh(III) via cyclometalation, including assistance by electron-rich olefin chelating groups.[11c] We chose diazo esters as a typical carbene precursor that can function as a C$_1$ or C$_2$ coupling partner in C−H activation−annulation, as they have been extensively employed for the construction of various (hetero)cycles by using Rh(III),[11] Ru(II),[12] and Ir(III)[13] catalysts with the C−H activation being assisted by a bifunctional nucleophilic directing group (Scheme 1a). We

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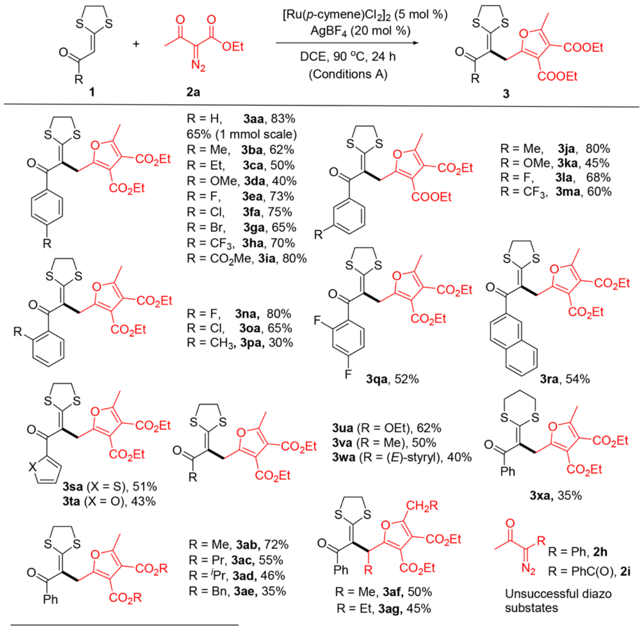
now report chemodivergent coupling of α-oxo ketene dithioacetals with diazo esters under catalyst control.

We initially studied the Ru(II)-catalyzed coupling of ketene dithioacetal **1a** with ethyl α-diazoacetoacetate **2a** (see Supporting Information (SI), Table 1). When catalyzed by $[Ru(p\text{-cymene})Cl_2]_2/AgSbF_6$ in the presence of PivOH (DCE, 50 °C), a 1:2 coupling occurred to give product **3aa** (CCDC 1825600) in 37% yield as a result of olefinic C−H furfurylation.[14] The reaction was sensitive to temperature, and the isolated yield was significantly improved to 78% when conducted at 90 °C. The yield was further improved to 83% when the PivOH was omitted. The generality of this coupling system was then explored (Scheme 2). Introduction of electron-donating and -withdrawing as well as halogen groups into different positions of the benzene ring was fully tolerated (**3aa**−**3qa**). The substrates with the 2-naphthyl, 2-thienyl, and 2-furyl moiety also gave moderate yields (**3ra**−**3ta**). Gratifyingly, we found that, under the optimized conditions, ketene dithioacetals with other types of substituents such as ester (**3ua**), alkyl acyl (**3va**), and alkenyl acyl (**3wa**) were all reactive and gave the desired products. The diazo substrate was not limited to ethyl α-diazoacetylacetate. The coupling of diazo substrates bearing other ester groups and bearing α-alkyl substituents all proceeded smoothly (**3ab**−**3ag**). The ring size of the dithioacetal had significant effects, and the yield diminished when a 1,3-dithioacetal was used (**3xa**). Moreover, when diazo substrates **2h** and **2i** were used, no desired products were obtained.

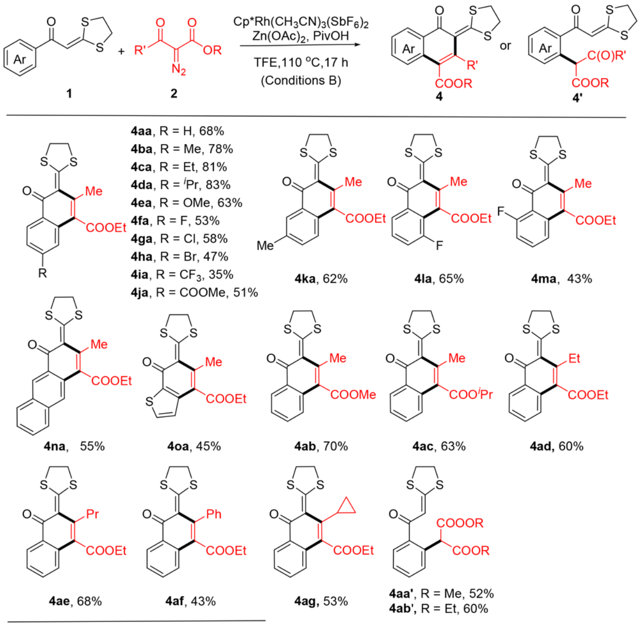
Scheme 2. Olefinic C−H Furfurylation of Ketene Dithioacetals[a,b]



[a]Reaction conditions A: **1** (0.2 mmol), **2a** (0.5 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), and $AgBF_4$ (20 mol %) in DCE (2 mL) at 90 °C for 24 h in a sealed tube under Ar. [b]Isolated yield.

Having established the Ru(II)-catalyzed coupling system, we next moved to Rh(III)-catalyzed C−H activation (Scheme 3). The higher valence of the Rh(III) catalyst conduces to chelation-assisted C−H activation and the resulting Rh(III)-C bond interacts favorably with diazo substrates. Indeed, the Rh(III)-catalyzed coupling of **1a** and **2a** in the presence of $Zn(OAc)_2$ afforded naphthalenone **4aa** as a result of [4 + 2] carbo-annulation (Reaction conditions B) and no furfurylation prouduct **3aa** was detected. The scope of this system is also broad. Ketene dithioacetals bearing halogens (**4fa**−**4ha**), electron-donating (**4ba**−**4ea**) and−withdrawing (**4ia**, **4ja**) groups at the *para* positions of the benzene ring could tolerate the reaction conditions, forming the target products in moderate to good yields (35%−83%). Introduction of different *meta* substituents is also tolerated. The reaction tends to occur at the less hindered *ortho* site when a *meta*-methyl group was used (**4ka**), whereas **4la** was obtained when a *meta*-fluoro substrate was used. Furthermore, an *ortho*-fluoro substrate was also viable (**4ma**). Besides benzoyl ketene dithioacetals, the reaction could be extended to naphthalene (**4na**) and thiophene substrates (**4oa**) under the standard conditions. α-Diazo compounds derived from other ketoesters also reacted well (**4ab**−**4ag**). In contrast, coupling of α-diazo malonates only gave arene C−H alkylation (**4aa′**, **4ab′**), indicating that the ketene dithioacetal is a directing group with possible nucleophlic cyclization contingent on the electrophilicity of the acceptor diazo substrate. Also, diazo substrates **2h** and **2i** failed to participate in the reaction under the standard conditions.

Scheme 3. Rh(III)-Catalyzed [4 + 2] Annulation of Ketene Dithioacetals with Diazo Ketoester[a,b]

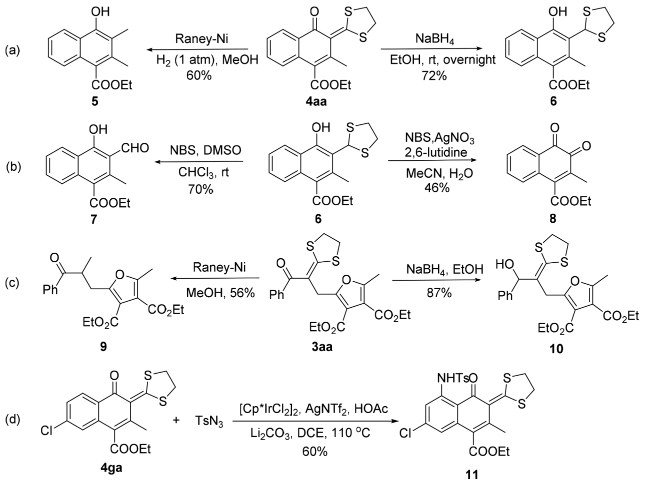


[a]Reaction conditions B: **1** (0.2 mmol), **2** (0.5 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (8 mol %), $Zn(OAc)_2$ (30 mol %), and PivOH (2 equiv) in TFE (4.0 mL) at 110 °C for 17 h under Ar. [b]Isolated yield.

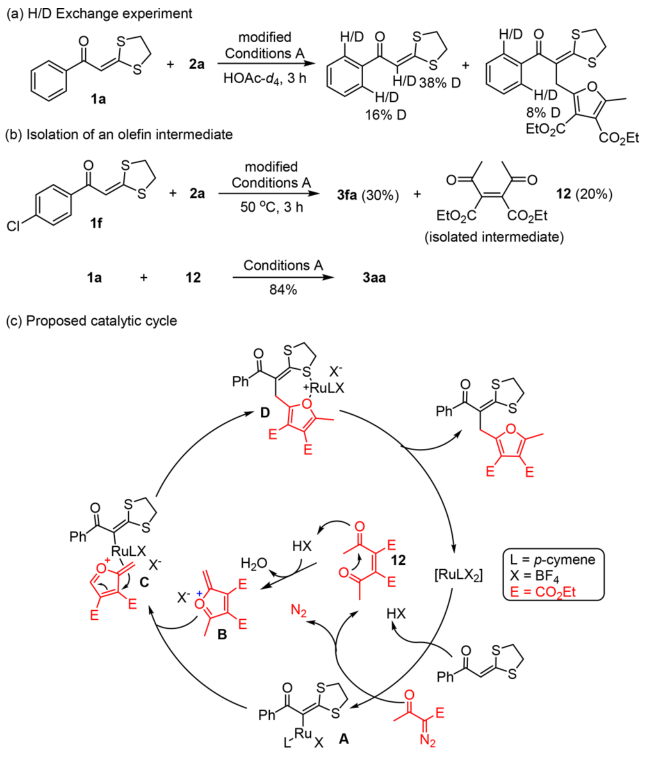
Derivatization of representative products has been performed to demonstrate synthetic applications. Hydrogenation of **4aa** and **3aa** with Raney nickel afforded the hydridesulfurization products **5** and **9**, respectively (Scheme 4). Treatment of **4aa** and **3aa** with $NaBH_4$ led to reduction of the carbonyl group, delivering phenol **6** (72%) and alcohol **10** (87%), respectively. Deprotection of **6** with NBS/DMSO afforded aldehyde **7** in 70% yield, and oxidative desulfurization gave *o*-naphthoquinone **8**. Ir(III)-catalyzed C−H amidation of **4ga** with TsN_3 delivered **11** in moderate yield.

Experimental studies have been performed to probe the reaction mechanism. In the case of ruthenium(II) catalysis

Scheme 4. Derivatization of Coupled Products

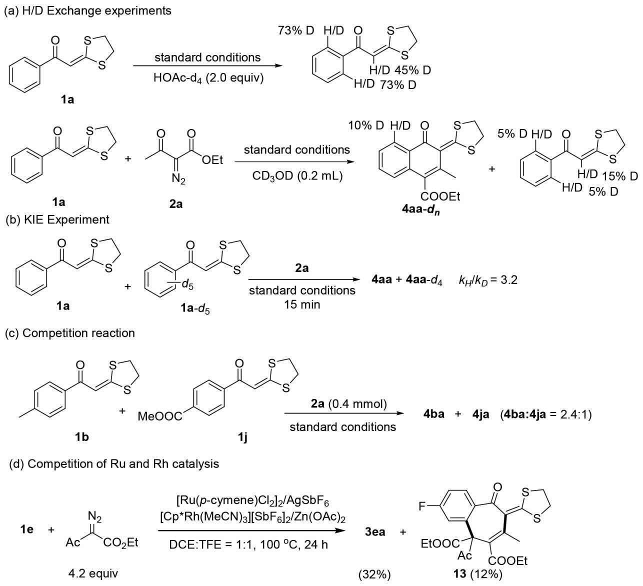


Scheme 5. Mechanistic Studies and Plausible Mechanism of Ru(II)-Catalyzed C−H Furfurylation



(Scheme 5), H/D exchange was performed for the coupling of **1a** and **2a** in the presence of CD_3COOD (Scheme 5a). Substrate **1a** was recovered with deuteration at the *ortho* (16% D) and the olefinic (38% D) positions. Meanwhile, product **3aa** was deuterated (8% D) at the *ortho′* position. These observations indicated reversibility of the C−H cleavage, although the *ortho* C−H cleavage is nonproductive. To obtain reaction intermediates, the coupling of **1f** and **2a** was performed at a lower temperature, from which a (*Z*)-olefin **12** was isolated (20%) via carbene dimerization (Scheme 5b). This olefin proved to be a reactive intermediate in that it coupled with **1a** to yield **3aa** in 84% yield. A plausible mechanism is proposed for this coupling system (Scheme 5c). Olefinic C−H ruthenation of **1a** gives intermediate **A**. Meanwhile, Ru-catalyzed denitrogenation of diazo and carbene dimerization generates olefin intermediate **12**. We cannot pinpoint the exact stage at which carbene dimerization occurs. However, it seems less likely that it occurs at the initial $RuLX_2$ catalyst because no dimerization was observed when the diazo **2a** was subjected to the catalytic conditions in the absence of a dithioacetal substrate. The carbene dimer undergoes dehydrative cyclization to give a highly electrophilic, exocyclized olefin (**B**). Driven by aromatization, attack of the more nucleophilic Ru−C(vinyl) group (instead of the Ru−C(aryl) group) at the activated olefin then furnishes the coupled product. It should be noted that the carbene dimer is a common side product in a metal-catalyzed coupling reaction of diazo compounds. However, it is efficiently utilized in the construction of a furan ring.

Scheme 6. Mechanistic Studies on Rh(III)-Catalyzed [4 + 2] Annulation of Ketene Dithioacetals with Diazo Ketoester



In the case of rhodium(III) catalysis (Scheme 6), H/D exchange was performed in the presence or absence of diazo ester **2a**. Substrate **1a** was recovered with deuteration at the *ortho* and the olefinic positions. H/D exchange was also observed at the *ortho* position of product **4aa** (Scheme 6a). These results indicate reversibility of the C−H cleavage. To further probe the C−H activation process, the kinetic isotope effect was determined by intermolecular competition experiments using an equimolar mixture of **1a** and **1a**-d_5. The value of k_H/k_D = 3.2 suggests that C−H bond cleavage is likely involved in the turnover-limiting step (Scheme 6b). Moreover, a competition experiment was conducted with an equimolar amount of **1b** and **1j**, which differ in their electronic properties. Products **4ba** and **4ja** were afforded in a ratio of 2.4:1, showing that the electron-rich arene reacted faster (Scheme 6c). Competition of ruthenium and rhodium catalysis was also performed using **1e** and diazo **2a** (Scheme 6d). The Ru-catalyzed product **3ea** was isolated, but essentially no naphthalenone was observed. Interestingly, a seven-membered ring **13** was obtained as a result of the Rh-catalyzed trapping of the intermediate **12** via olefin insertion and nucleophilic cyclization. On the basis of these observations and previous reports,[12a] a plausible catalytic cycle was given (see SI).

In summary, we have realized chemodivergent C−H activation of α-oxoketene dithioacetal and coupling with diazo compounds. The Ru(II)-catalyzed C−H furfurylation occurred at the olefinic C−H position, where dimerized carbene was identified as a key intermediate, which is usually a side product in carbene chemistry. The Rh(III)-catalyzed [4 + 2] annulation of α-benzoylketene dithioacetals with diazo compounds occurred via both aryl and alkenyl C−H bond cleavage. The tunable selectivity of C−H activation may find applications in the development of new catalytic systems. Further studies on the synthesis of other heterocycles via C−H activation and functionalization are underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01890.

> Detailed experimental procedures, characterization of new compounds, crystallographic data of **3aa**, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1825600 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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