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# Rhodium(III)-Catalyzed Oxidative Cross-Coupling of *N*-Pyrimidylindoles with Cyclic *β*-Keto Esters for Accessing All-Carbon Quaternary Centers

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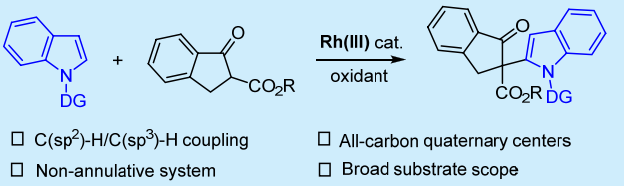
**ABSTRACT:** Rh(III)-catalyzed direct oxidative C−H/C−H cross-coupling between *N*-pyrimidylindoles and *β*-ketoesters is presented. Easily available *β*-ketoesters are used as an alkylating agent for the facile construction of all-carbon quaternary centers under mild conditions. The ester group in the product can undergo decarboxylation or decarboxylative amination.

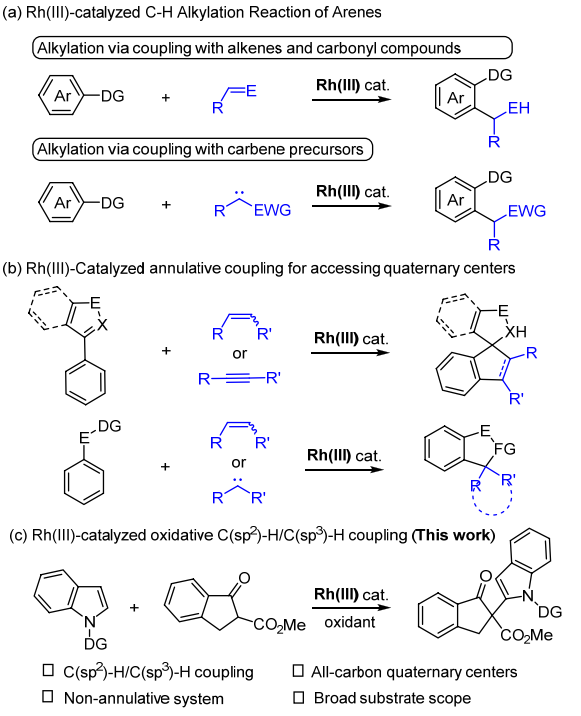





Carbon−carbon bonds are ubiquitous in nearly every organic material, and increasing attention has been devoted to the selective construction of carbon−carbon bonds starting from readily available reagents. In the past decades, owing to the abundance of arenes, metal-catalyzed C(aryl)−H bond functionalization as an atom-economic synthetic method has become a powerful strategy for C−C bond formation.[1] Among the various transition metals, rhodium(III) cyclopentadienyl complexes are outstanding catalysts for activation of a broad series of arenes under chelation assistance.[2] Significant development has been made in the field of Rh(III)-catalyzed direct alkylation of C−H bonds. In early studies (Scheme 1a), unsaturated C═C,[3] C═O,[4] and C═N[5] bonds have been predominantly used as a coupling reagent toward C−H alkylation reactions with outstanding functional group compatibility. Meanwhile, diazo,[6] hydrazone,[7] sulfoxonium ylide,[8] and other carbene precursors[9] have also been demonstrated as highly reactive coupling reagents in arene C−H alkylation, allowing introduction of both primary and secondary alkyl groups. Alternatively, our group, Cramer, Glorius, Wang, and others realized Rh(III)-catalyzed C−H alkylation with strained or reactive rings as alkylating reagents.[10,11] In addition, we and Wang have developed rhodium-catalyzed oxidative C−H alkylation of arenes using organoboron reagents.[12] Nevertheless, these systems are predominantly limited to the introduction of primary and secondary alkyl groups.

All-carbon quaternary centers are commonly found in many natural products and drug intermediates.[13] It remains a daunting challenge to access all-carbon quaternary centers via metal catalysis due to the steric effects when connecting two bulky groups. Previous studies typically relied on strategies of substrate activation and ligand promotion, such as taking advantage of reactive palladium enolates and Rh(III) carbene species to facilitate C−C coupling. In terms of C−H bond activation (Scheme 1b), synthetic methods have been limited

**Scheme 1. Rh(III)-Catalyzed C−H Alkylation Reaction**

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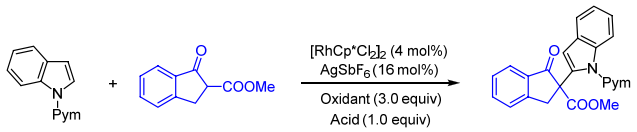
to annulation reactions upon participation of a directing group, where migratory insertion typically serves as a key step to introduce an alkyl group. Thus, by following this strategy, arenes bearing a heteroatom directing group reacted with unsaturated reagents such as alkynes and alkenes to give various spirocyclic skeletons (Scheme 1b).[14] Additionally, utilizing the nucleophilicity of directing groups to achieve dearomative oxidative annulation is also an effective method.[15] Moreover, Rh(III)-catalyzed [4 + 1][16] and [5 + 1][17] annulation systems between arenes and diazo compounds, difluoroalkynes, allenes, or alkenes have been realized (Scheme 1b). However, Rh(III) catalyzed C−H functionalization to form quaternary carbon centers is mainly restricted to annulation reactions. Thus, it is necessary to exploit new coupling patterns to fulfill the demand of all-carbon quaternary center synthesis. Our approach was to effect C−C coupling via direct C−H alkylation using a nucleophilic methine that involves challenging C−C reductive elimination, where β-ketoesters have been designed as the alkylating reagent.[18] We now report Rh(III)-catalyzed oxidative C($sp^2$)−H/C($sp^3$)−H cross-coupling of *N*-pyrimidylindole with β-ketoesters for the efficient construction of all-carbon quaternary centers (Scheme 1c).

To ensure the reactivity of β-ketoesters, cyclic ketoesters were our first choice. Our initial studies were performed using *N*-pyrimidylindole **1a** and β-ketoester **2a** in the presence of $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), AgOAc (3.0 equiv), and AcOH (1.0 equiv) at 70 °C (Table 1). Fortunately, the desired product **4a** was obtained in 59% yield, and the yield was slightly affected by the silver carboxylate additive or acid additive (entrie 1−3). AgF has been identified as the optimal oxidant, while other oxidants ((Cu(OAc)$_2$, $Ag_2O$, and $Ag_2CO_3$) only led to lower coupling efficiency (entries 5−8). Screening of the solvent gave DCE as the optimal medium (entries 8−11). PivOH proved to be the optimal acid; switching to other acids such as PhCOOH, MesCOOH, and 1-AdCOOH only led to a lower coupling efficiency (entries 12−15). By contrast, reducing or increasing the reaction temperature can lead to poorer results (entries 16 and 17).

Under the optimal reaction conditions, we then investigated the substrate scope of C($sp^2$)−H/C($sp^3$)−H coupling (Scheme 2). First, the scope of *N*-pyrimidylindoles was explored; indole rings with electron donating, electron withdrawing, and halogen groups were completely compatible (**3a**−**3w**). Furthermore, 5,6-disubstituted indole (**3x**) was also a suitable substrate. To our delight, a pyrrole substrate was amenable to this transformation, delivering desired product **3y** in 58% yield. Notably, extension of the directing group to an *N*-pyridyl ring resulted in somewhat lower efficiency (**3z**), indicating that the directing group has a direct impact on reaction efficiency.

The coupling of *N*-pyrimidylindole **1a** with various cyclic β-ketoesters **2** was next examined (Scheme 3). β-Keto esters

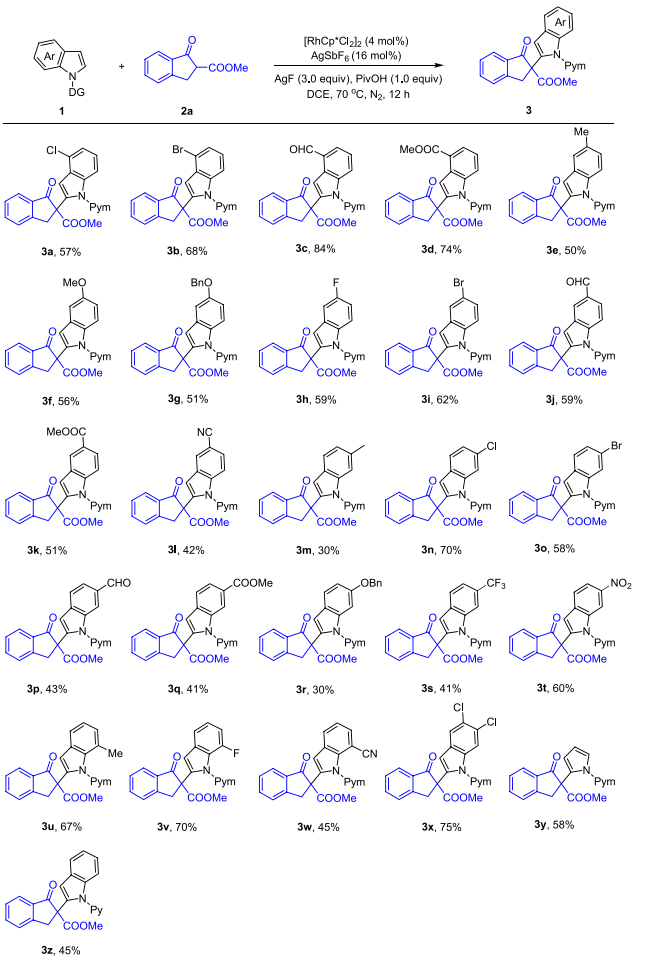
**Table 1. Optimization Studies**[a]




| entry | solvent | oxidant | acid | yield[b] (%) |
|---|---|---|---|---|
| 1 | DCE | AgOAc | AcOH | 59 |
| 2 | DCE | AgOAc | − | 50 |
| 3 | DCE | AgOPiv | PivOH | 56 |
| 4 | DCE | Cu(OAc)$_2$ | AcOH | trace |
| 5 | DCE | $Ag_2O$ | AcOH | 48 |
| 6 | DCE | $Ag_2CO_3$ | AcOH | 60 |
| 7 | DCE | AgF | AcOH | 64 |
| 8 | $CHCl_3$ | AgF | AcOH | 24 |
| 9 | TCE | AgF | AcOH | 33 |
| 10 | PhCl | AgF | AcOH | 39 |
| 11 | TFE | AgF | AcOH | 53 |
| 12 | DCE | AgF | $PhCO_2H$ | 42 |
| 13 | DCE | AgF | $MesCO_2H$ | 50 |
| 14 | DCE | AgF | 1-Ad$CO_2$H | 72 |
| **15** | **DCE** | **AgF** | **PivOH** | **78** |
| 16[c] | DCE | AgF | PivOH | 58 |
| 17[d] | DCE | AgF | PivOH | 70 |

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.05 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), oxidant (3.0 equiv), acid (1.0 equiv), solvent (0.5 mL), 70 °C, under $N_2$ for 12 h. [b]Isolated yield. [c]50 °C. [d]90 °C.

**Scheme 2. Scope of Indoles in C($sp^2$)−H/C($sp^2$)−H Coupling Reaction**[a,b]




[a]Reactions conditions: β-indanone ester **1a** (0.2 mmol), indole **2** (0.1 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), AgF (3.0 equiv) and PivOH (1.0 equiv) at 70 °C in DCE (1.0 mL) under $N_2$ for 12 h. [b]Isolated yields.



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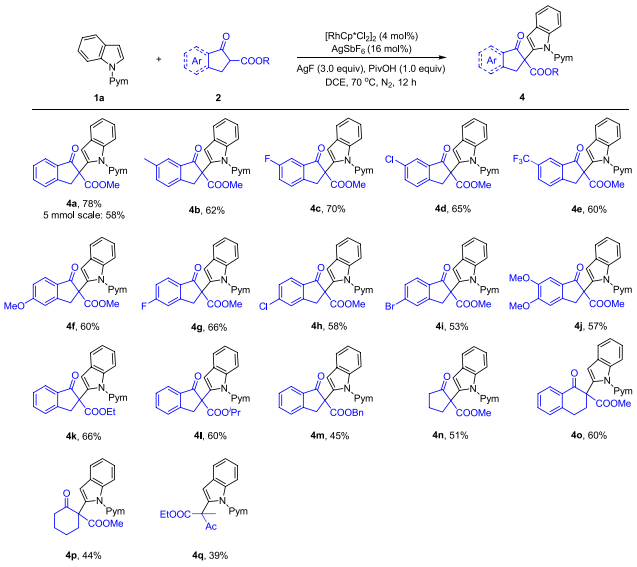
**Scheme 3. Scope of Cyclic β-Ketoester Compounds in C(sp²)−H/C(sp²)−H Coupling Reaction**[a,b]

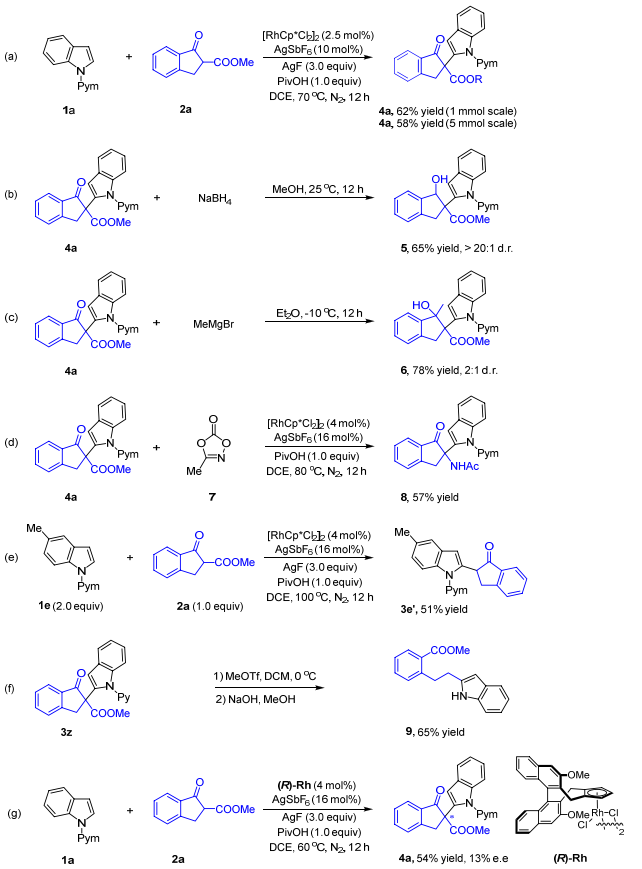



[a]Reactions conditions: α-substituted cyclic β-ketoester **1** (0.2 mmol), *N*-pyrimidylindole **2a** (0.1 mmol), $[RhCp^*Cl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), AgF (3.0 equiv) and PivOH (1.0 equiv) at 70 °C in DCE (1.0 mL) under $N_2$ for 12 h. [b]Isolated yields.

derived from 6-substituted 1-indenone with various functional groups were suitable for coupling, and the corresponding products **4b**−**e** were isolated in 60−70% yields. Meanwhile, 5-substituted 1-indanone derived β-ketoesters also performed well, and the corresponding products were isolated in moderate to good yields (**4f**−**i**). Of note, dimethoxy-substituted β-ketoester **1j** reatcted to give **4j** in 57% yield. Diverse ester groups were also tolerated in this C(sp²)−H/C(sp³)−H coupling reaction, providing the corresponding products in 45%−60% yields (**4k**−**m**).

To our delight, the β-keto esters derived from cyclopentanone were also a viable substrate for this transformation, affording the corresponding product **4n** in moderate yield. It is worth noting that six-membered β-ketoesters and an acyclic β-ketoester were also applicable, furnishing the related products **4o**-**q** in acceptable outcomes. In order to verify the synthesis efficiency of the coupling reaction, scaled up reactions have been achieved, and product **4a** was isolated in 62% (1 mmol) or 58% yield (5 mmol) under a reduced catalyst loading (Scheme 4a). The derivation and transformation of coupling products have also been briefly demonstrated (Scheme 4). Treatment of **4a** with $NaBH_4$ generated the corresponding alcohol **5** in 65% yield with excellent diastereoselectivity (Scheme 4b). The nucleophilic addition of a methyl Grignard reagent to **4a** took place well, giving product **6** in 78% yield (2:1 d.r., Scheme 4c). $[Cp^*RhCl_2]_2$-Catalyzed decarboxylative amidation of **4a** with 1,4,2-dioxazol-5-one afforded product **8** in 57% yield (Scheme 4d). In particular, by increasing the reaction temperature and changing the proportion of substrates, the decarboxylated product **3e′** was obtained in 51% yield (Scheme 4e). Selective removal of the *N*-directing group afforded product **9** in 65% yield, which may involve a retro-Claisen reaction and decarboxylation (Scheme 4f). By following modified racemic reaction conditions, an asymmetric coupling was attempted using Cramer's chiral catalyst (***R***)-**Rh**, affording product **4a** in moderate yield but low enantioselectivity (Scheme 4g). Future studies on this enantioselective coupling are ongoing.

**Scheme 4. Derivatization of Coupled Products**




The mechanism of this C(sp²)−H/C(sp³)−H coupling reaction was briefly explored. Using prepared rhodacycle **10** as the catalyst precursor under otherwise the same conditions, product **4a** was obtained in 65% yield. This indicated that complex **10** might be a reactive intermediate or a close analogue in the reaction (Scheme 5a and 5b). The stoichiometric reaction between complex **10** and **2a** in the presence of different bases did not give any product **4a**, which may suggest that the C−C forming reduction elimination is likely oxidation-induced (Scheme 5c).[19] The H/D exchange reaction between **1a** and $CD_3COOD$ produces the product with 43% deuterization at the 2-position, suggesting the reversibility of the initial C−H activation (Scheme 5d). Besides, competitive experiments were conducted using equimolar mixtures of **1e** and **1k** that exhibit different electronic effects. $^1H$ NMR analysis of the product mixture showed that the ratio of **3e** to **3k** in the product was 1.3:1, which revealed a slightly higher reactivity of the more electron-rich indole (Scheme 5e).

Based on mechanism experiments and literature reports, a possible catalytic cycle of the oxidative coupling has been proposed (Scheme 6). **2a** undergoes C−H activation with the active $[RhCp^*(OAc)X]$ (X = $SbF_6$ or OPiv) species (**A**) to generate intermediate **B**. Next, **B** reacts with β-ketoesters **2a** to produce an O-bound enolate intermediate **C** with the assistance of a base. Intermediate **C** is oxidized by a Ag(I) oxidant to give a cationic Rh(IV) intermediate **D**, which further undergoes reductive elimination to release the desired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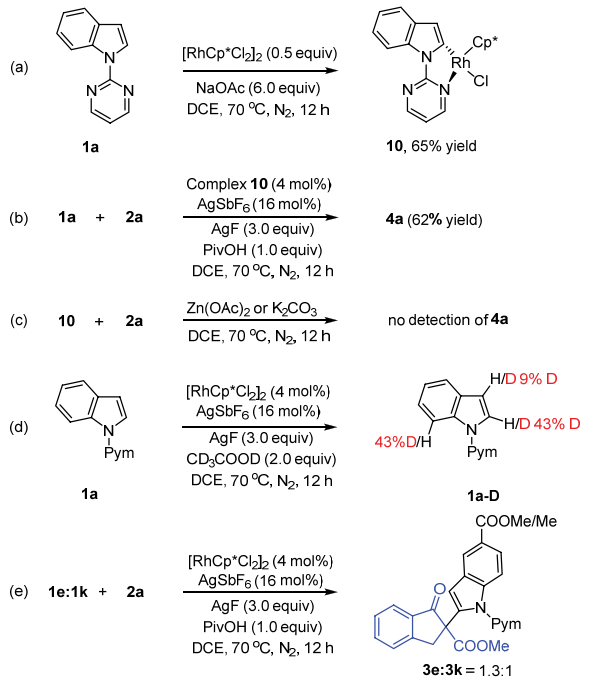
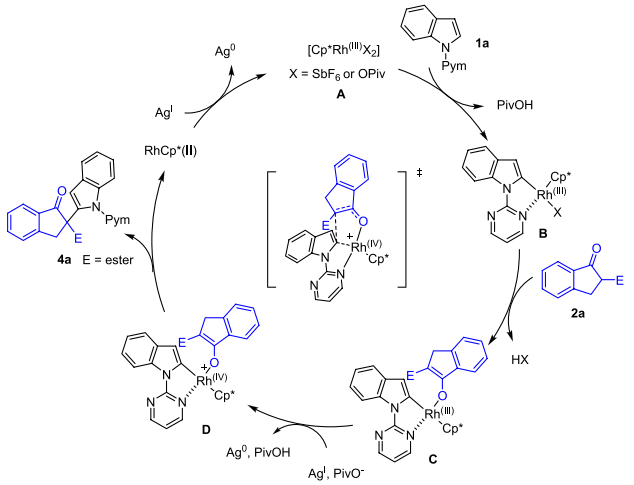
**Scheme 5. Mechanistic Studies**




**Scheme 6. Proposed Mechanism**




product **4a**. The reductive elimination likely proceeds through a 5-membered ring TS[20] with oxygen participation. Finally, the Rh(II) intermediate is reoxidized to Rh(III) by Ag(I) to complete the catalytic cycle.

In summary, we have demonstrated oxidative C−H/C−H cross-coupling reactions of *N*-pyrimidylindoles and *β*-ketoesters via Rh(III)-catalyzed C−H activation. The *β*-ketoesters as alkylating agents exhibited decent reactivity. This coupling has the advantages of mild conditions and good functional group compatibility. The ester group in the product can be functionalized. This system offers a rare example of C−H activation−alkylation using a methine group in nonannulative systems.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c01631.

Detailed experimental procedures, characterization of new compounds, and copies of NMR spectra. (PDF)

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### Notes

The authors declare no competing financial interest.

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