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Rhodium(II)-Catalyzed Regioselective Remote C−H Alkylation of Protic Indoles

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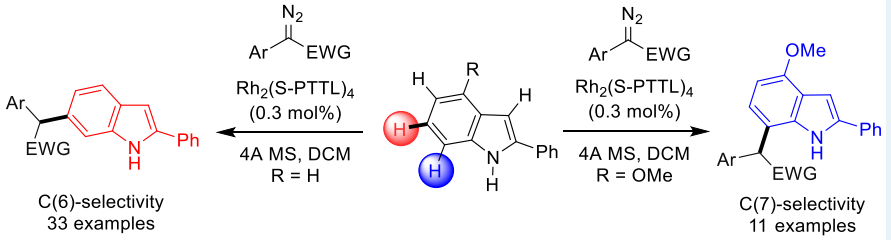


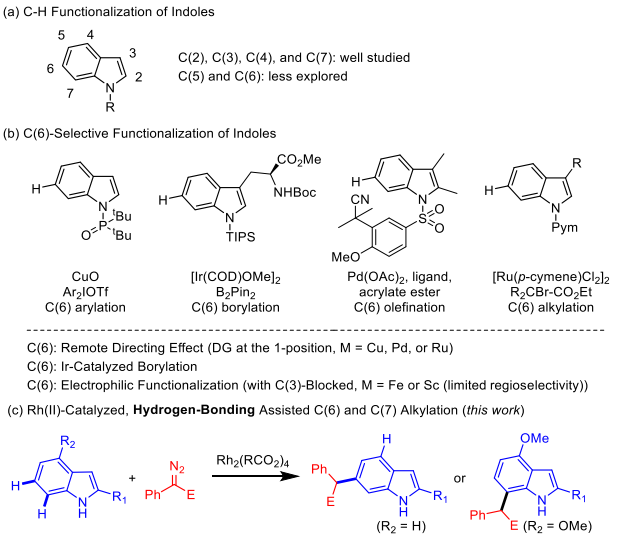
ABSTRACT: Control of regioselectivity that defies the intrinsic reactivity of arene C−H bonds remains a formidable challenge. In this work, dimeric Rh(II) complexes have been applied as an efficient catalyst for the regioselective coupling of NH indoles with diazo compounds. Two-substituted indoles mostly reacted with C(6) selectivity. Mechanistic studies revealed that the regioselectivity results from the hydrogen-bonding directing effect, and the C−C bond formation proceeds via the Friedel−Crafts-type attack of indole toward the Rh(II) carbene species. In contrast, the reaction of 4-methoxyindoles occurred exclusively with the complementary C(7) selectivity.

KEYWORDS: *rhodium, remote C−H functionalization, indole, diazo, alkylation, hydrogen bonding*

Catalytic C−H activation/functionalization has been established as an increasingly important strategy to access value-added aromatics owing to the high atom and step economy.[1] Given the presence of multiple C−H bonds in most arenes, regioselectivity generally poses a significant challenge. Several strategies have been adopted to ensure regioselectivity. Among them, the installation of a directing group seems predominant in delivering *ortho* selectivity.[2] To overcome the limitation of *ortho* selectivity, other strategies such as molecular recognition, transient mediator approaches, and radical addition have been employed to offer efficient protocols via remote C−H activation.[3]

In addition to the above strategies, the intrinsic reactivity of electron-rich arenes has been adopted to ensure regioselectivity. Indoles are representative electron-rich heteroarenes, and the C−H activation of indoles has been extensively explored (Scheme 1).[4,5] Indoles typically undergo C(3)−H functionalization when catalyzed by various metals.[6] By following a N-directing effect, both C(2) and C(7) activation can be enabled.[7] Of note, seminal C(2)-selective borylation has also been realized under boron-catalyzed conditions, as pioneered by Shi.[8] Similarly, C(4) selectivity has also been realized using a directing group at the C(3) position.[9] Catalytic C(5) functionalization has also been enabled under copper- or enzyme-catalyzed conditions.[9a,10] In contrast, C(6)-selective functionalization is rather rare.[11] Shi reported the copper-catalyzed remote C(6)-selective arylation of indoles with diaryliodonium as an arylating reagent using a directing group

Scheme 1. Regioselective C−H Activation of Indoles (DG = Directing Group)



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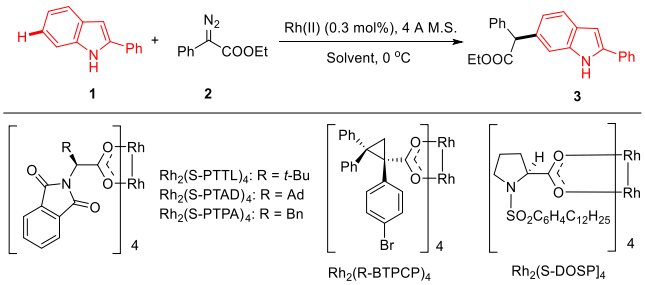
at the *N* position.[11d] Baran reported the Ir(III)-catalyzed C(6)-selective borylation of tryptophan esters.[11c] Despite the progress, remote C(6)−H activation remains a formidable challenge.

Previous studies on the C−H activation of indoles mostly focused on *N*-protected indoles. We reasoned that NH indoles may open up a new avenue toward selectivity control in that the NH may serve as a noncovalent directing group via hydrogen bonding with the catalyst, which obviates the reliance of the common directing group strategy that requires the extra steps of DG installation and removal. On the contrary, dimeric Rh(II) carboxylates are well known to catalyze the insertion of carbene species into the C−H bond.[12] Whereas the Rh(II)-catalyzed C−H alkylation of *N*-protected indoles has been independently studied by Davies and Fox,[13] the regioselectivity is limited to the C(3) position, as governed by the intrinsic reactivity. We speculated that the hydrogen bonding between the indole NH and the ligand may play a significant role to override the inveterate C(3) selectivity. We now report the C(6)-selective alkylation of protic indoles under Rh(II) catalysis, where the regioselective is enabled by the judicious choice of the substrates and the Rh(II) catalyst.

Optimization studies were then conducted for the coupling of 2-phenylindole (**1**) and a diazo ester (**2**, Table 1). Typical

Table 1. Optimization Studies[a]



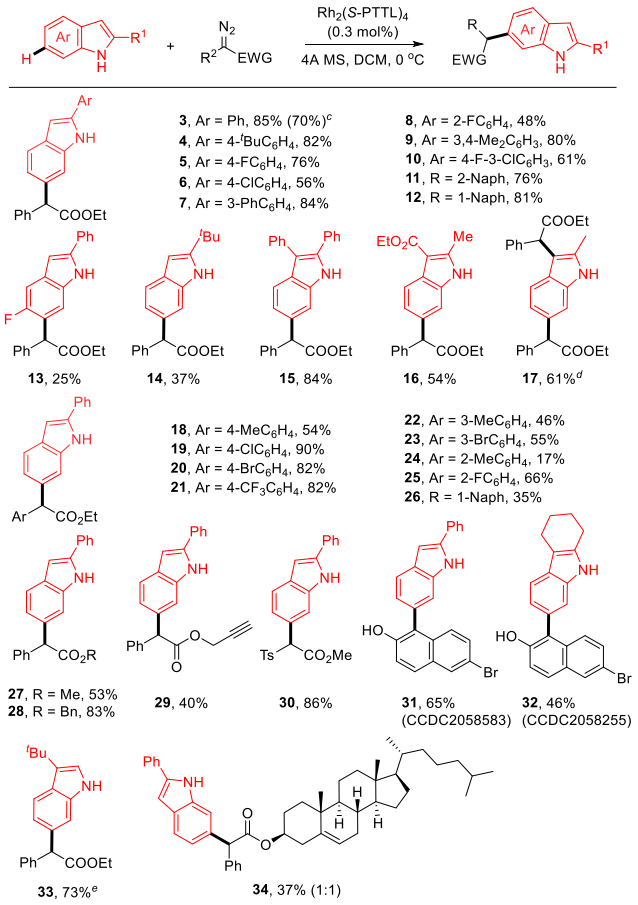
entry	catalyst (0.3 mol %)	solvent	yield (%)[b]
1	$Rh_2(OAc)_4$	DCM	<5
2	$Rh_2(AdCOO)_4$	DCM	<5
3	Rh_2(*S*-PTTL)$_4$	DCM	87 (85)[c]
4	Rh_2(*S*-PTTL)$_4$	DCE	78
5	Rh_2(*S*-PTTL)$_4$	Ph−F	75
6	Rh_2(*S*-PTTL)$_4$	Ph−Cl	76[c]
7	Rh_2(*S*-PTTL)$_4$	Ph−Me	42
8	Rh_2(*S*-PTTL)$_4$	Ph−OMe	72
9	Rh_2(*S*-PTAD)$_4$	DCM	81
10	Rh_2(*S*-PTPA)$_4$	DCM	75
11	Rh_2(*R*-BTPCP)$_4$	DCM	36
12	Rh_2(*S*-DOSP)$_4$	DCM	45

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.25 mmol), catalyst (0.3 mol %), and 4 Å MS (100 mg) in 2 mL of solvent, 0 °C for 12 h without exclusion of air or moisture. [b]NMR yield using 1,3,5-$(OMe)_3C_6H_3$ as an internal standard. [c]Isolated yield.

dimeric Rh(II) catalysts have been screened in a halogenated solvent. The employment of $Rh_2(OAc)_4$ afforded a messy reaction, from which the 6-alkylated product (**3**) was isolated in low yield. Whereas a low yield was also realized using $Rh_2(AdCOO)_4$ as a catalyst, significant improvement was made when Rh(II) catalysts bearing other bulky carboxylates were used (entries 3−12). Among all of the catalysts screened, Rh_2(*S*-PTTL)$_4$ exhibited optimal activity and selectivity, affording the essentially racemic product **3** in 85% isolated yield in DCM (entry 3). Of note, no NH, C(3), or other C−H functionalization product has been detected.

With the optimized reaction conditions in hand, the scope and limitation of this coupling system were next explored (Scheme 2). It was found that protic indoles bearing diversified

Scheme 2. Scope of the C6 Alkylation[a,b]



[a]Reaction conditions: indole **1** (0.2 mmol), diazo **2** (0.25 mmol), Rh_2(*S*-PTTL)$_4$ (0.3 mol %), and 4 Å M.S. (100 mg) in DCM (2 mL) at 0 °C for 12 h without exclusion of air or moisture. [b]Isolated yield. [c]5 mmol scale reaction. [d]At 25 °C with **2** (2.2 equiv). [e]Rh_2(*S*-PTTL)$_4$ (0.3 mol %), chiral acid A (1.0 equiv).

2-aryl groups all reacted with **2** in good to high yields (**3**−**10**). The 2-aryl group was also successfully extended to naphthyls (**11** and **12**). A 5-fluoro-substituted indole was also amenable to the standard reaction conditions, albeit with a lower yield. In contrast, 2-methylindole underwent 1:2 alkylation with the diazo reagent **2** at the three- and six-positions (**17**), possibly due to the reduced steric effect of the methyl group. Indeed, 2-*tert*-butylindole reacted with the expected regioselectivity in 37% yield (**14**). Extension of the indole substrates to 2,3-disubstituted ones also proved successful (**15** and **16**).

The scope of the diazo reagent was next examined using **1** as the indole substrate. The introduction of various electron-donating and -withdrawing groups into different positions of the benzene ring of the diazo reagent was generally tolerated, and the coupled products were isolated in moderate to high yields (**18**−**25**). The presence of an *ortho* group in the substrate tended to give a reduced yield due to the steric effect

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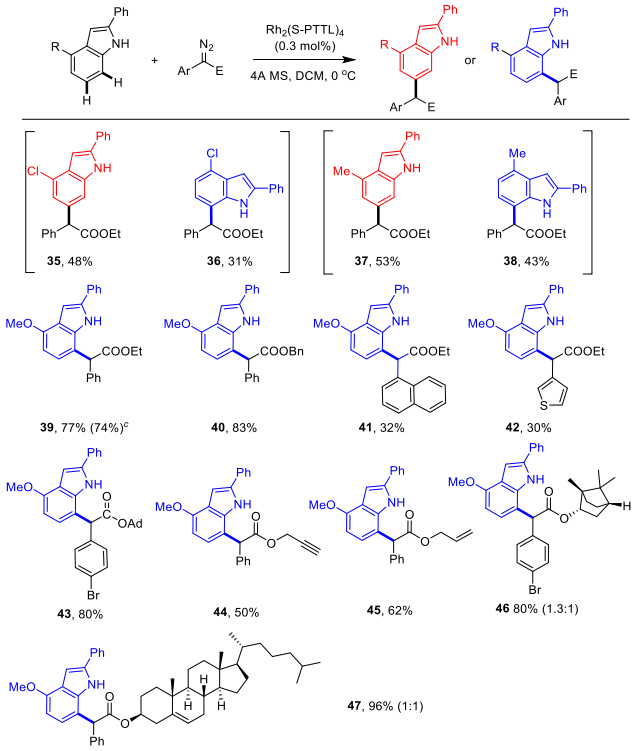
(**24**−**26**). Variation of the ester group in the diazo reagent was also successful (**27**−**30**), and an 86% yield was obtained when an acceptor−acceptor reagent was used (**30**). The reaction also tolerated a cyclic diazo reagent (**31** and **32**) and 3-*t*Bu-substituted indole (**33**), and this protocol was also applicable to the late-stage functionalization of a natural product-derived diazo reagent (**34**, 1:1 dr).

A different scenario was observed in the reaction of four-substituted indoles (Scheme 3). It was found that 4-chloro and

Scheme 3. Scope of the C(7) Alkylation[a,b]

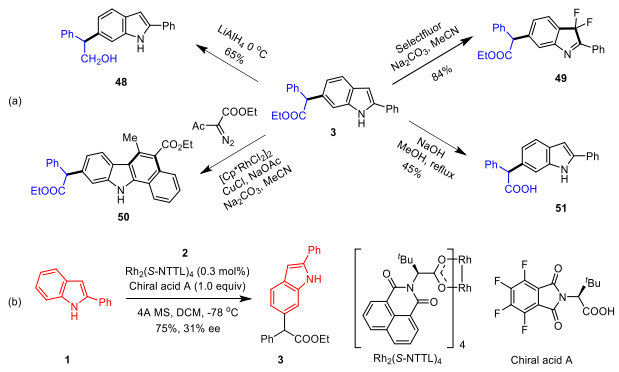


[a]Reaction conditions: indole **1** (0.2 mmol), diazo **2** (0.25 mmol), Rh_2(*S*-PTTL)$_4$ (0.3 mol %), and 4 Å M.S. (100 mg) in DCM (2 mL) at 0 °C for 12 h without exclusion of air or moisture. [b]Isolated yield. [c]Chlorobenzene solvent.

4-methylindoles underwent coupling to **2** to give mixed products that correspond to the competing C(6) and C(7) alkylation with low regioselectivity. Inspired by this observation, we moved to a more donating group. Thus a 4-methoxyindole coupled to **2** in exclusive C(7) selectivity, indicating the strong electronic effect. The scope of this C(7) alkylation reaction was then briefly explored using different diazo reagents. A variety of donor−acceptor diazo reagents, including those tagged with a natural product, underwent smooth coupling in moderate to excellent yields (**35**−**47**).

Derivatization reactions of product **3** have been conducted to demonstrate the synthetic utility of this coupling system (Scheme 4). The scale-up synthesis (5 mmol) of **3** was readily achieved in 70% yield. The reduction of **3** gave alcohol **48** in 65% yield. The ester group in **3** was hydrolyzed to give acid **51**. The NH group could serve as a directing group in the Rh(III)-catalyzed annulation of **3** with a diazo acetylacetate to afford **50**. The treatment of **3** with Selectfluor delivered the difluorinated product **49** in 84% yield. In addition, an essentially racemic product was obtained for the coupling of

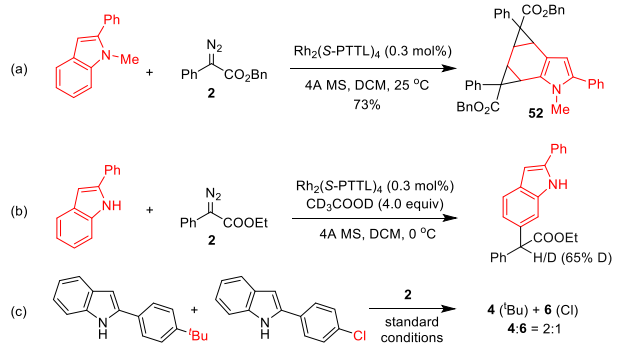
Scheme 4. Synthetic Applications and Attempts of Enantioselective Synthesis



1 and **2** under our standard conditions. It was found that a combination of Rh_2(*S*-NTTL)$_4$ and a chiral carboxylic acid offered low enantioselectivity (31% ee, Scheme 4b). The low enantioselectivity may be ascribed to the distinct mechanism of proton transfer during C−H bond formation (*vide infra*).

Preliminary studies have been conducted to explore the reaction mechanism (Scheme 5). The coupling of *N*-methyl-2-

Scheme 5. Mechanistic Studies



phenylindole under the standard reaction conditions afforded only the dicyclopropylated product **52** in 73% yield.[14] This observation suggests the necessity of the NH group in delivering the C(6) selectivity, possibly by hydrogen bonding. In addition, the donating effect of the *N*-Me group may favor two-fold cyclopropylation. To probe the C−H formation process, the coupling of **1** and **2** was conducted in the presence of AcOD. ^{1}H NMR analysis indicated significant H/D exchange at the alkyl position (Scheme 5b), which suggests the unlikelihood of concerted C−H to C−M ligand-to-ligand hydrogen transfer (LLHT). In addition, competitive studies indicated that an electron-rich indole is kinetically more reactive (Scheme 5c).

Density functional theory (DFT) studies have been conducted to further explore the regioselectivity (Figure 1). Coordination of the diazo reagent **2** is followed by dediazotization to give a Rh(II) carbene species with an overall barrier of 11.6 kcal/mol via **TS3**. NH···O hydrogen-bonding between indole **1** and one of the amide carbonyl group was detected. The subsequent alkylation of 2-phenylindole was found to occur via successive Friedel−Crafts-type addition and intramolecular deprotonation. The Rh(II)−carbene intermediate **Int-4** adds electrophilically onto the C6 position of 2-phenylindole via transition state **TS-5** with an

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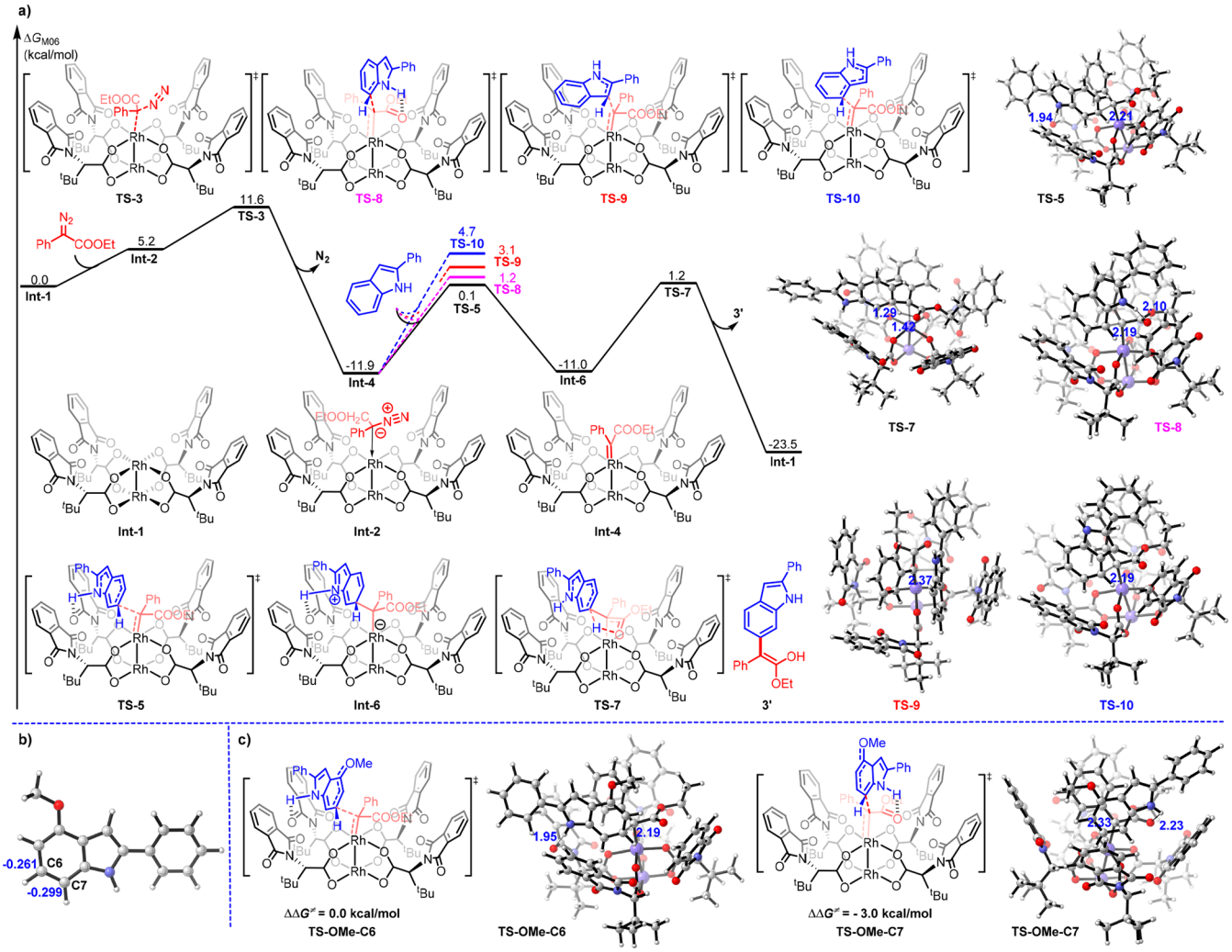

Figure 1. (a) Calculated free-energy profiles for the regioselective alkylation of 2-phenylindole. (b) NPA charge distribution of 4-methoxy-2-phenylindole. (c) Optimized key transition states **TS-OMe-C6** and **TS-OMe-C7**. The favored pathway is labeled by solid lines. The values given in kilocalories per mole are the relative free energies calculated by the SMD/M06/def2-TZVP//SMD/M06/def2-SVP method in chlorobenzene.

energy barrier of 12.0 kcal/mol to give the dearomatized zwitterion intermediate **Int-6**. Subsequently, intramolecular ester-assisted proton transfer (via **TS-7**) affords the C6-alkylated enol **3′** and regenerates the active catalyst Rh(II). The calculated energy barriers of the alternative intramolecular 1,2-H transfer and the carboxylate ligand-assisted proton transfer are both higher. The calculated free energy of C−C coupling via C(7), C(3), or C(4) attack (via **TS-8**, **TS-9**, or **TS-10**, respectively) is >13.1 kcal/mol, which is higher than that via C(6) attack (via **TS-5**). The calculated results are consistent with our experimental observation.

The optimized geometric information analysis (Figure 1a) indicates significant hydrogen bonding between the NH and the amide carbonyl in the **TS-5** (NH···O = 1.94 Å), which directs the C6 alkylation. The electrophilic addition of the Rh(II)-carbene intermediate **Int-4** onto the C6 or C7 position of the 4-methoxy-2-phenylindole was also considered. With the aid of natural bond orbital (NBO) analysis, the natural population analysis (NPA) charges distributed at the C6 or C7 position of 4-methoxy-2-phenylindole were −0.216 and −0.299, respectively, indicating that the nucleophilicity of the C7 position is more nucleophilic (Figure 1b). In the case of 2-phenyl-4-methoxyindole, DFT studies revealed hydrogen bonding between the NH and the diazo ester group, which directs the attack of the most nucleophilic C(7)−H position (via **TS-OMe-C7**) with a barrier that is 3.0 kcal/mol lower than for the C(6)−H attack (via **TS-OMe-C6**). Consistent conclusions have been reached between experimental and theoretical studies.

In conclusion, we have realized the Rh(II)-catalyzed regioselective C−H insertion of NH protic indoles into carbenes. The regioselectivity is substrate-dependent. Four-unsubstitituted indoles tend to undergo rare C(6) alkylation, whereas 4-methoxyindoles predominantly react with C(7) selectivity. Mechanistic studies suggest that the C−C formation occurs via Friedel−Crafts attack of the C(6) position at the carbene ligand, and this attack is assisted by hydrogen bonding of the NH moiety. Subsequent ester-assisted proton transfer furnishes the enol form of the coupled product. The remote C−H functionalization mode and the substrate-controlled selectivity may offer new insight into the development of other remote modes of C−H activation.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c01052.

X-ray crystallographic data for **31** (CIF)
X-ray crystallographic data for **32** (CIF)
Detailed experimental procedures, characterization data, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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