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Rhodium(III)-Catalyzed Selective Monoarylation of β or γ C(sp^3)–H Bonds Assisted by a Trimethylpyrazole Group

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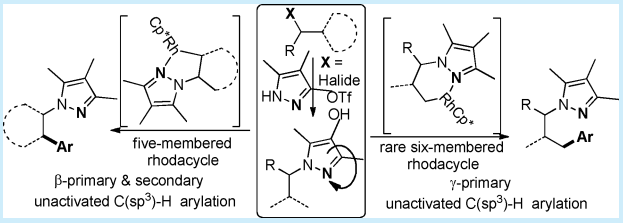
Supporting Information

ABSTRACT: The selective arylation of unactivated β or challenging γ primary and secondary β-C(sp^3)–H bonds has been developed with a Cp*Rh(III) catalyst assisted by a trimethylpyrazole group. A rarely reported six-membered rhodacycle has been identified in rhodium-catalyzed C(sp^3)–H activation reactions. Preliminary mechanistic studies have revealed that a concerted metalation–deprotonation pathway might be involved in the C–H activation step.



Over the past decades, transition-metal-catalyzed C–H activation reactions have seen rapid development and now provide straightforward approaches to many important synthetic units.[1−5] Among the reported procedures, rhodium(III)-catalyzed C–H functionalization has attracted considerable attention in recent years due to its high selectivity, good functional group tolerance, and high efficiency.[6] To date, numerous of Rh-catalyzed C(sp^2)–H functionalizations have been developed, leading to carbon–carbon and carbon–heteroatom bond formation.[7] Despite these great achievements, only limited reports have been concerned with the rhodium(III)-catalyzed C(sp^3)–H functionalization, which may be due to an incomplete understanding of pertinent mechanistic aspects.

In 2010, Glorius' group reported pioneering work on the rhodium(III)-catalyzed allylic C(sp^3)–H activation of enamines in coupling with alkynes to form pyrazoles.[8] Later, Wang's group showed 8-methylquinolines to be suitable substrates for rhodium(III) catalysts in activating C(sp^3)–H for alkenylation reactions.[9] Since then, several examples of selective functionalization of C(sp^3)–H bonds with Cp*Rh(III) as catalyst have been developed by the groups of Glorius,[10] You,[11] and Li.[12] However, the substrates have been limited to 8-methylquionline-type benzylic C–H bonds or oxime-directed β-Me C–H bonds. There have been few examples of functionalization of unactivated primary and secondary C(sp^3)–H bonds. In particular, to the best of our knowledge, there has been no example of rhodium-catalyzed γ-C(sp^3)–H bond functionalization, presumably because an unstable six-membered rhodacycle would need to be formed during the catalytic cycle. Herein, we report a rhodium(III)-catalyzed selective monoarylation of C(sp^3)–H bonds assisted by a trimethylpyrazole group. Preliminary results have revealed that rhodium(III) can not only promote functionalization of β-Me C–H bonds but also of less activated methylene C(sp^3)–H bonds. Further study has revealed that primary γ-C(sp^3)–H bonds are compatible, whereby a rarely reported six-membered Rh–C(alkyl) intermediate may be invoked for the first time.

Although pyrazole-directed C(sp^2)–H functionalizations have been well explored and various transition metals such as Rh,[13] Pd,[14] and Ru[15] have been demonstrated to be effective catalysts, there have been few examples of pyrazole-directed C(sp^3)–H activations. It is likely that the weak coordinating ability of pyrazole hinders C–H transformations.[16] Recently, Yu's group[17] has overcome this problem by employing monoprotected amino acids as ligands, which are well-known to promote C–H activation reactions with palladium catalysts. On the basis of our experience in developing new directing groups,[18] the electron density is known to greatly influence the efficacy of transition-metal-catalyzed C–H activations. We speculate that the pyrazole skeleton may provide a perfect coordinating center for C(sp^3)–H activation if its structure is slightly modified. Thus, 1-alkylpyrazole derivatives might be suitable substrates for rhodium-catalyzed C(sp^3)–H activation to form important synthetic units. Further investigation indicated that these 1-alkylpyrazoles could be easily prepared from an alkyl bromide,[19] an alcohol[20] and a (trifluoromethyl)-sulfonyloxy-protected alcohol.[21]

With these conditions in mind, we initially treated 1-isopropyl-1*H*-pyrazole (**1a**) with a triarylboroxine (**2**) in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), Ag_2CO_3 (2 equiv), and $AgSbF_6$ (0.2 equiv) in toluene for 24 h (Scheme 1, **3a**). Unfortunately, the arylated product **3a** was only observed by LC–MS in <3% yield. Next, pyrazoles bearing electron-withdrawing functional groups were tested (**3a**). However, these did not give the desired products, and only the starting material was recovered. It is probable that weakly coordinating pyrazoles have no assisting ability in promoting C–H activation. Monomethyl-substituted pyrazoles were further

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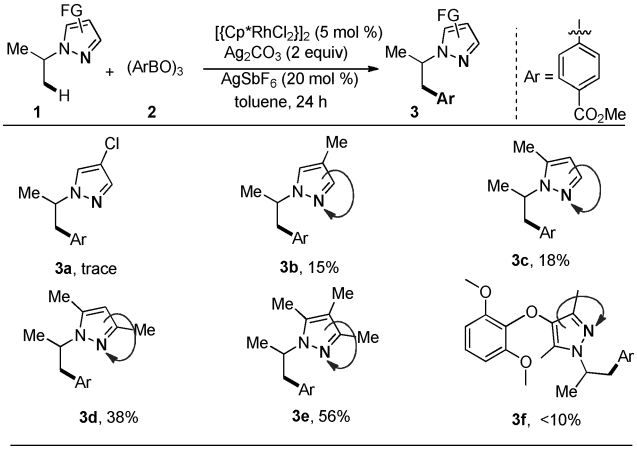
Scheme 1. Scope of Rhodium-Promoted C(sp^3)−H Activation[a]



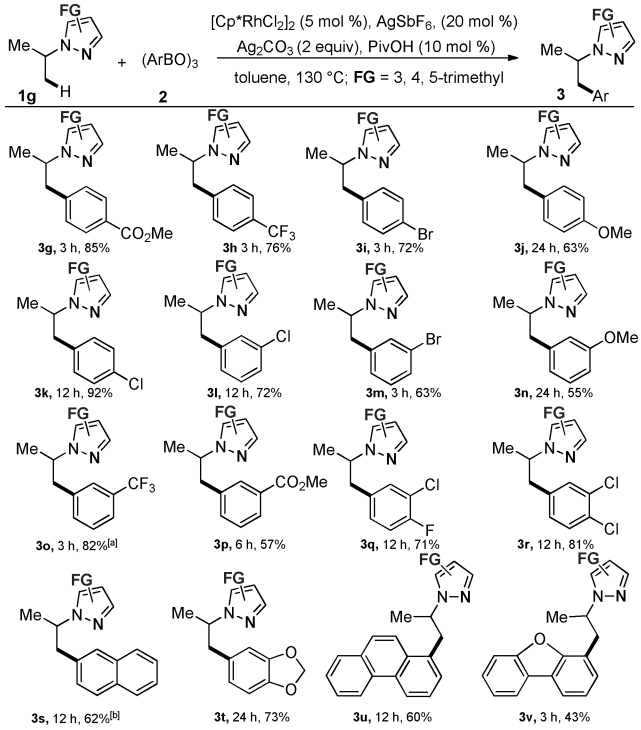
[a]FG: functional group.

screened. As we expected, monoarylated products were obtained in up to 18% yields (**3b**,**c**). Encouraged by these results, 1-isopropyl-3,5-dimethylpyrazole (**1d**) was tested. To our great delight, the arylated product **3d** was obtained in 38% yield. The 1-isopropyl-3,4,5-trimethylpyrazole was further explored, affording the monoarylated product **3e** in a rather good yield of 56%. When substrate **1h** was scanned, less than 10% of the arylated product (**3f**) was obtained.

With these preliminary results in hand, we next explored various oxidants, solvents, and additives to accomplish this β-C(sp^3) arylation reaction (see the Table S1). The results revealed that the additives NaOAc, PivOH, $(n\text{-BuO})_2PO_2H$, and 1-Ad-OH all had a promoting effect. A satisfactory isolated yield of **3g** of 85% was achieved when PivOH was used as the additive. In regard to the role of these additives in palladium-catalyzed C(sp^3)−H activation, a concerted metalation−deprotonation (CMD) pathway might be involved in activating the C(sp^3)−H bonds.[22] Several oxidants, such as $Cu(OAc)_2$, BQ, $K_2S_2O_8$, and O_2, were screened in place of Ag_2CO_3. However, none of them gave the desired products in good yields. It is worth mentioning that the monoarylated product **3g** was the only arylated product. We surmise that the rhodium(III) complex interacted weakly with the arenes, which precluded secondary C−H activation, while the steric effect is also a possible reason for the absence of a secondary arylation. In addition, palladium acetate was also tested in combination with aryl iodides as coupling partners. However, mono- and diarylated products were obtained unselectively, highlighting the unique properties of the rhodium(III) catalyst system in the C−H activation.

A wide range of triarylboroxines were treated with 1-isopropyl-3,4,5-trimethylpyrazole (1-isopropyl-TMP) (**1g**) to explore the functional group tolerance of this rhodium-catalyzed C(sp^3)−H arylation (Scheme 2). Arylboron reagents (**2**) bearing *para* or *meta* substituents gave the corresponding products in moderate to good yields (53−85%). A wide variety of functional groups, such as MeO, F, Cl, Br, CF_3, and CO_2Me, were well tolerated in this transformation (**3g**−**p**). Multiply substituted arylboron reagents also reacted well, affording the corresponding monoarylated products in good yields (**3q**,**r**,**t**). Importantly, condensed-ring boron reagents also performed

Scheme 2. Scope of Arylboron Reagents in the Rhodium-Catalyzed C(sp^3)−H Arylation*



*Reactions were performed with **1** (0.2 mmol) and **2** (2 equiv) in 1 mL of toluene. [a]$[Cp^*RhCl_2]_2$ (10 mol %). [b]150 °C

well, providing the corresponding products in good yields (**3s**,**u**,**v**).

We next investigated various 1-alkyl-TMPs under the optimal conditions (Scheme 3). The substrates **4a** and **4b** were both selectively arylated at the β-Me position, providing the monoarylated products (**5a**,**b**) in good yields. 1-Ethyl-TMP also reacted smoothly, leading to monoarylated product **5c** in 78% yield. Moreover, 1-cyclobutyl-TMP, 1-cyclopentyl-TMP, and 1-cyclohexyl-TMP all gave the monoarylated products in moderate to good yields, although methylene units are generally less reactive in C−H activation. However, the substrates of *n*-propyltrimethylpyrazole (**4g**) could not be tolerated under standard reaction conditions, and only starting material was recovered. The product of **5c**, which contained β-secondary benzylic C−H bonds, was treated with triarylboroxine **2a**, but it failed to give any β-arylated product. The substrate **4h** was unreactive in the reaction, affording the arylated products in less than 10% yield.

In all previously reported rhodium(III)-catalyzed C(sp^3)−H activations, a five-membered Rh−C(alkyl)-cyclic intermediate has been invoked. To the best of our knowledge, a six-membered Rh−C(alkyl)-cyclic intermediate has not hitherto been observed in a Cp*Rh(III)-catalyzed C(sp^3)−H activation reaction. Inspired by palladium-catalyzed C−H activation reactions, in which a six-membered Pd−C(alkyl)-cycle is readily formed when the C−H activation step proceeds by a CMD pathway, we speculated that the modified pyrazole-directed rhodium-catalyzed C(sp^3)−H activation may also facilitate γ-C(sp^3)−H arylation. Thus, 2,2-dimethylpropane-TMP was examined under the standard conditions. As expected, the monoarylation reaction proceeded well with different triarylboroxine reagents (**6a**,**b**). For example, both

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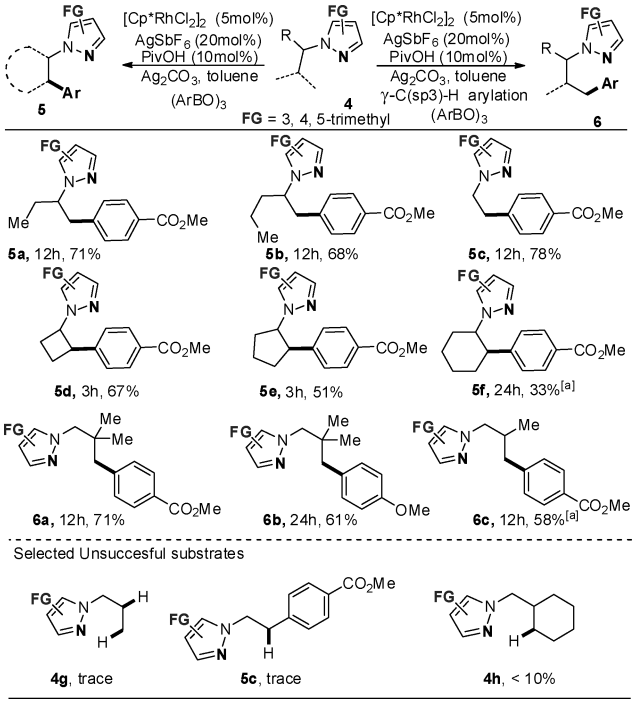
Scheme 3. Scope of Arylboron Reagents in Rhodium-Catalyzed C(sp^3)−H Arylation Reactions*

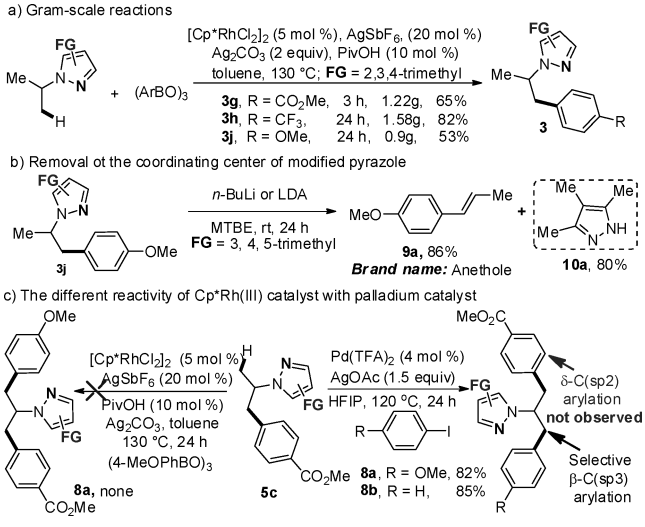


*Reactions were performed with **4** and $(ArBO)_3$ (2 equiv) in 1 mL of toluene. [a]$[Cp^*RhCl_2]_2$ (10 mol %), 150 °C.

electron-rich and electron-deficient substituted triarylboroxine reagents were tolerated in the transformation, indicating the potentially wide scope of these reagents. Isopentyl-TMP gave monoarylted **6c** in 58% yield.

Gram-scale reactions were easily performed with a range of triarylboroxine reagents under the standard reaction conditions (Scheme 4a). More importantly, we demonstrated that the trimethylpyrazole coordinating center could be easily removed from product **3j** under basic conditions at room temperature, affording the important product anethole, which is widely used as a flavoring agent (Scheme 4b). This result implied that not only can various pyrazole derivatives be prepared from simple alkyl halides but also a facile approach to alkenes from alkyl halides via a transitive directing center has also been developed.

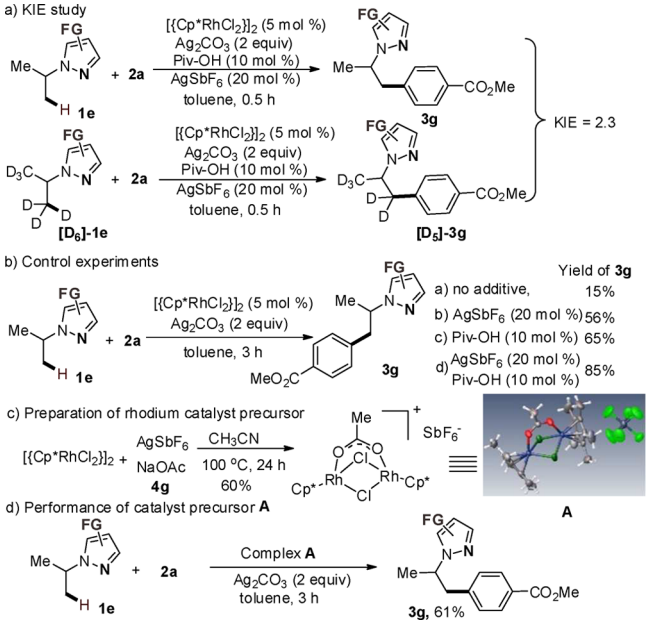
Scheme 4. Further Study on This Rhodium-Catalyzed C(sp^3)−H Arylation Reaction



Because mono- and diarylated products were inevitably obtained when we treated **1g** with aryl iodides in the presence of a palladium catalyst, the product **5c** was further treated with the aryl iodide using the palladium catalyst to form the heterodiarylated product. To our delight, the arylation occurred selectively at the β-C(sp^3)−H position rather than at the δ-C(sp^2)−H position, indicating that a five-membered Pd−C(alkyl) intermediate is more stable than a seven-membered Pd−C(arene) intermediate. We also treated **5c** with triarylboroxine **2a** under the optimal reaction conditions, but it proved to be completely unreactive, which explains why the diarylate could not be observed in the Cp*Rh-catalyzed C(sp^3)−H arylation and is a clear reason why a diarylated product was not obtained under the Rh(III)-catalyzed conditions. We proposed that the rhodium(III) complex might have interacted weakly with the arenes, which prevented secondary C−H activation. In addition, steric effects might also be a reason for the absence of a secondary arylation.

Several experiments were performed to gain more insight into the mechanism. Hydrogen−deuterium-exchange experiments were explored with the rhodium catalyst or palladium acetate. A deuterated product was never observed, indicating that C(sp^3)−H bond activation is irreversible (see the SI). Intermolecular kinetic isotope effect (KIE) experiments were carried out (Scheme 5a), which gave a consistent KIE of 2.3.

Scheme 5. Preliminary Mechanism Study



Control experiments revealed that the additives $AgSbF_6$ and PivOH both had a promoting effect (Scheme 5b). To understand the role of these additives, a catalyst precursor was prepared by the reaction of $[Cp^*RhCl_2]_2$, $AgSbF_6$, and NaOAc in acetonitrile, affording a complex in the form of deep-red prisms. Its structure was confirmed by single-crystal X-ray diffraction analysis (Scheme 5c). Complex A was further utilized as the catalyst instead of $[Cp^*RhCl_2]_2$, $AgSbF_6$, and PivOH, and the desired product **3g** was obtained in 61% yield

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(Scheme 5d). This result implied that complex A is an active species in the catalytic cycle.

In conclusion, we have developed a rhodium-catalyzed site-selective monoarylation of both methyl and methylene at either the β or γ position by employing a modified pyrazole as a transitive coordinating center. Preliminary mechanistic studies have revealed that a CMD pathway might be involved in the C−H activation step. This may pave the way for a comprehensive understanding of the mechanism of rhodium-(III)-promoted C(sp^3)−H activation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03522.

Experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds (PDF)

X-ray data for rhodium catalyst precursor (CIF)

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Notes

The authors declare no competing financial interest.

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