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RESEARCH ARTICLE

View Article Online
View Journal

Cite this: DOI: 10.1039/d2qo00667g

Rh(III)-Catalyzed C–C coupling of unactivated $C(sp^3)$–H bonds with iodonium ylides for accessing all-carbon quaternary centers†

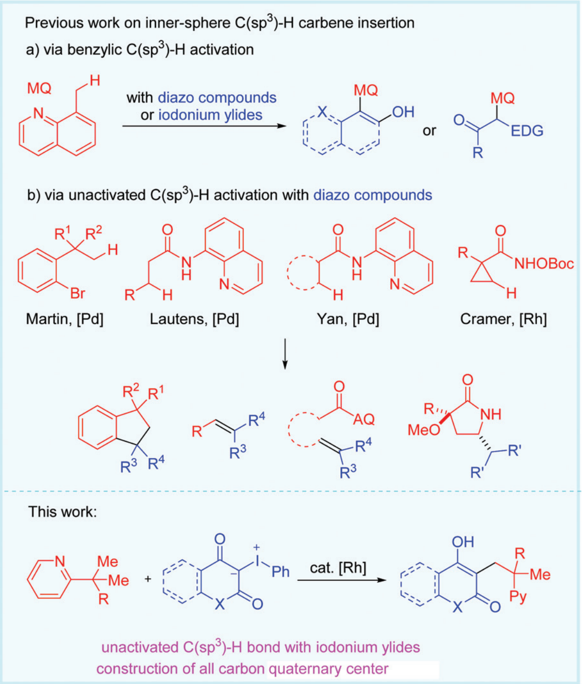
Pengfei Xie, Huixing Gao, Xingwei Li, Yuqin Jiang* and Bingxian Liu *

Received 25th April 2022,
Accepted 1st June 2022
DOI: 10.1039/d2qo00667g
rsc.li/frontiers-organic

Rhodium-catalyzed inert $C(sp^3)$–H activation/carbene insertion, which enables the construction of all-carbon quaternary centers, has been realized. Iodonium ylides are used as C1 synthons for efficient C–C bond formation with PhI being the only by-product. A rhodacycle has been synthesized and proved to be the active intermediate.

Strategies that achieve C–C bond formation from inert C–H bonds are favored by organic chemists due to their advantages of atom- and step-economy, wide source of substrates, accessibility of complex molecules and convenient late-stage functionalization. With the development of transition metal-catalyzed C–H functionalization, the coupling reaction of C–H bonds with carbon synthons to form C–C bonds has been widely applied in the total synthesis of natural products, late-stage functionalization of drug-related frameworks and synthesis of material molecules.[1] Among the carbon synthon coupling components, carbene precursors have been extensively studied, which can undergo C–H bond carbenoid insertion.[2] Compared to the C–C coupling of $C(sp^2)$–H bonds with carbenes by transition metal catalysis, the studies of $C(sp^3)$–H bond carbene insertion are still limited to the outer-sphere pathway.[2,3] Only a few examples of inner-sphere $C(sp^3)$–H bond carbene insertion reactions have been reported (Scheme 1). For example, the C–C couplings of a benzylic C–H bond with diazo compounds or iodonium ylides have been developed by Zhou,[4] Shi,[5] Samanta[6] and our group.[7] Martin's group realized oxidative addition-initiated $C(sp^3)$–H carbene insertion/reductive elimination to access all-carbon quaternary centers.[8] Lautens's group[9] and Yan's group[10] independently reported $C(sp^3)$–H carbene insertion/C–C cleavage to access alkenes. Cramer's group achieved the ring expansion of cyclopropanes using diazo compounds as carbene precursors.[11] Despite the advances, the inner-sphere coupling of an unactivated $C(sp^3)$–H bond with non-diazo carbene precursors remains a challenge.

Iodonium ylide is a widely studied carbene precursor,[2f,12] and has been applied to Rh^{III}-catalyzed C–H functionalization by our group.[7] It acted as a highly active coupling partner in $C(sp^2)$–H carbene insertion/annulation reactions.[13] We reasoned that the high reactivity of iodonium ylide might be matched by the challenging inert $C(sp^3)$–H activation. Thus, we herein report an unactivated methyl C–H activation/



Scheme 1 C–C bond formation *via* inner-sphere $C(sp^3)$–H bond carbene insertion.

NMPA Key Laboratory for Research and Evaluation of Innovative Drug, Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, China. E-mail: liubingxian@htu.edu.cn

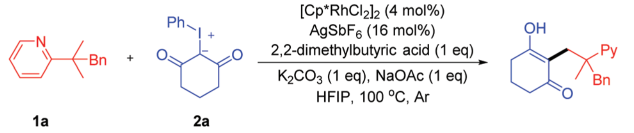
† Electronic supplementary information (ESI) available: Detailed experimental procedures, analytical data and NMR spectra. See DOI: **https://doi.org/10.1039/d2qo00667g**

carbene insertion reaction, leading to the construction of all-carbon quaternary centers.[14]

By treating a pyridine derivative containing *gem*-dimethyl groups (**1a**) with iodonium ylide **2a** in the presence of a rhodium(III) catalyst at 100 °C in HFIP, the C–C bond coupling product with an all-carbon quaternary center was obtained in a good yield (Table 1, entry 1, 88%). The fluctuation of the reaction temperature slightly affected the reaction efficiency and products were obtained in 78% and 79% yields (entries 2 and 3). The changes of the silver salt from $AgSbF_6$ to AgOAc, $AgPF_6$, or $AgBF_4$ all gave negative results (entries 4–6). Other carboxylic acid additives such as AdCOOH and PivOH were applicable with slightly lower reaction efficiency (entries 7 and 8, 80% and 78% yields). DCE or MeOH was not the optimal solvent for the reaction (entries 9 and 10). Control experiments revealed that both $[Cp^*RhCl_2]_2$ and $AgSbF_6$ are necessary for the reaction system (entries 11 and 12). The desired product was isolated with decreased yields in the absence of NaOAc or K_2CO_3 (entries 13 and 14). The *in situ* generated **2a** only gave traces of the product under the standard conditions (entry 15). Addition of K_3PO_4 enhanced the reaction efficiency and afforded the product in a moderate yield (entry 16). No product was detected when the corresponding diazo compound[15] was used instead of iodonium ylide, indicating the high reactivity of iodonium ylide in the coupling system (entry 17).

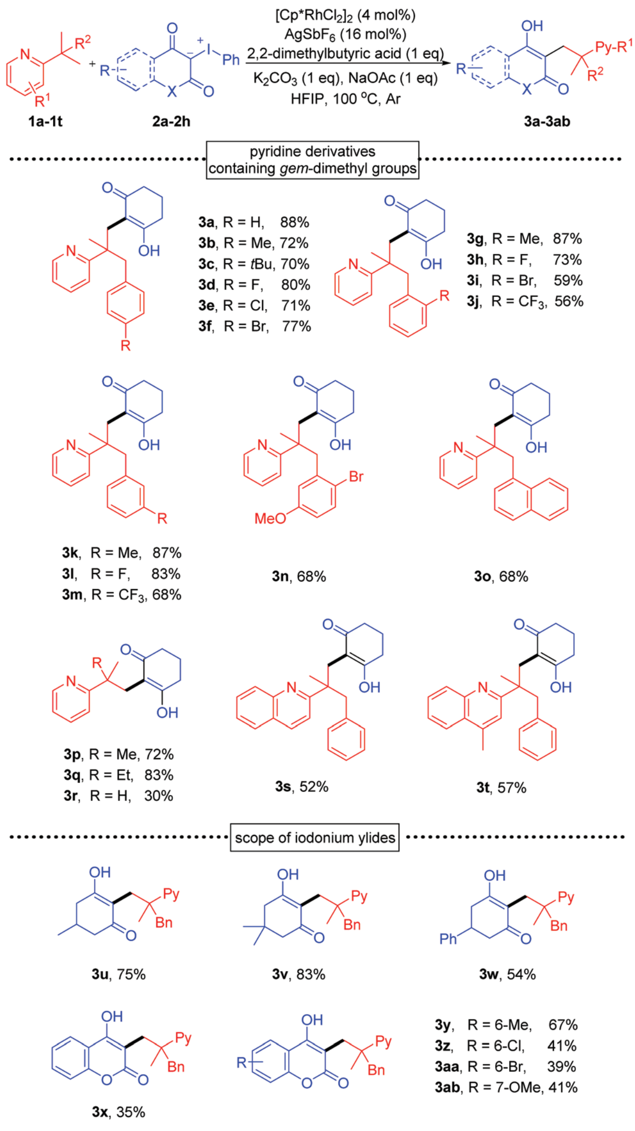
With the standard conditions in hand, the scope of pyridine derivatives containing *gem*-dimethyl groups was screened (Scheme 2). Substitutions at the 4-position of the phenyl ring had little effect on the reaction efficiency (**3b–3f**, 70–80%). The substrates bearing halogen, alkyl, trifluoromethyl and other functional groups all reacted with iodonium ylide **2a** smoothly, giving the products in moderate to high yields (**3g–3m**, 56–87%). The occupation of the *ortho*-position of the phenyl ring by a Br or CF_3 group led to the desired product with lower yields, which may be caused by the steric effects (**3i** and **3j**). The substrates containing a naphthyl ring or disubstituted phenyl ring gave the product with moderate yields (**3n** and **3o**, 68%). 2-*tert*-Amylpyridine, 2-*tert*-butylpyridine and 2-isopropylpyridine were all applicable to the reaction system affording the corresponding products (**3p–3r**, 30–83%). The reaction could also occur when quinoline was used as the directing group (**3s** and **3t**). The scope of iodonium ylides was then investigated, where cyclic iodonium ylides were found to be

Table 1 Optimization of the reaction conditions



Entry	Verifications of the optimal conditions[a]	Yield/%
1	No changes	88
2	80 °C	78
3	110 °C	79
4	AgOAc instead of $AgSbF_6$	48
5	$AgPF_6$ instead of $AgSbF_6$	49
6	$AgBF_4$ instead of $AgSbF_6$	Trace
7	AdCOOH instead of 2,2-dimethylbutyric acid	80
8	PivOH instead of 2,2-dimethylbutyric acid	78
9	DCE	Trace
10	MeOH	n.d.
11	Without $[Cp^*RhCl_2]_2$	n.d.
12	Without $AgSbF_6$	n.d.
13	Without NaOAc	47
14	Without K_2CO_3	46
15[b]	*In situ* generated **2a** was used	Trace
16[b,c]	K_3PO_4 (0.15 mmol) was added	58
17	2-Diazocyclohexane-1,3-dione instead of **2a**	n.d.

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%), NaOAc (0.1 mmol), 2,2-dimethylbutyric acid (0.1 mmol), K_2CO_3 (0.1 mmol), HFIP (0.5 mL), 100 °C, 12 h, under Ar, n.d. = not detected, HFIP = hexafluoroisopropanol. [b] 1,3-Cyclohexanedione (0.15 mmol) and $PhI(OAc)_2$ (0.15 mmol) instead of **2a**. [c] *In situ* generated **2a**, K_3PO_4 (0.15 mmol).

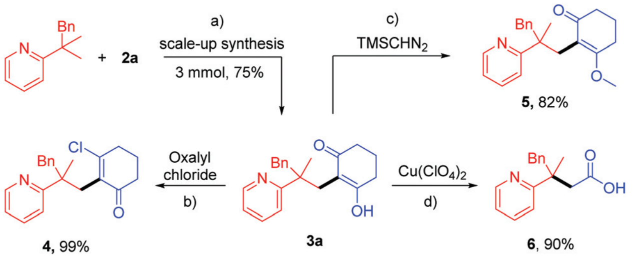


Scheme 2 Scopes of the substrates. Standard conditions, isolated yields.

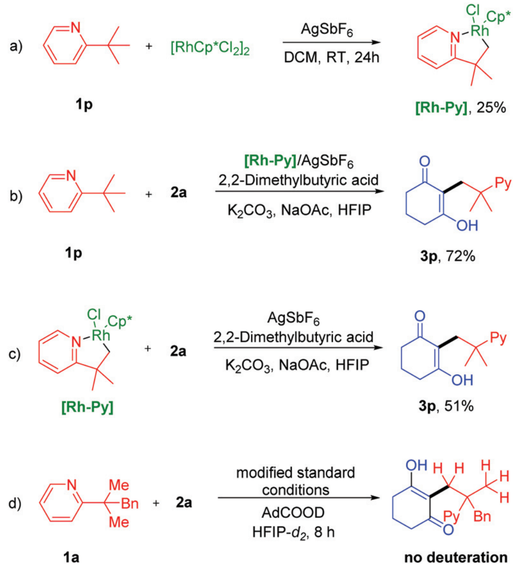
tolerated (Scheme 2). Noncyclic iodonium ylides from dicarbonyl compounds all gave negative results. Cyclohexa-2,5-dienone iodonium ylides with a methyl or phenyl group provided the products with good yields (**3u**–**3w**). Iodonium ylides from 4-hydroxycoumarin were found to be tolerated, affording coumarin derivatives with moderate yields (**3x**–**3ab**, 35–67%).

The scale-up synthesis and derivatization of product **3a** were conducted to showcase the practicability of the C–C coupling reaction. The product was isolated with a slightly decreased yield at the 3 mmol scale (Scheme 3a). The chlorination reaction with oxalyl chloride gave compound **4** quantitatively (Scheme 3b). The hydroxyl group can be transformed into a methoxy group when compound **3a** was treated with $TMSCHN_2$ (Scheme 3c). Oxidation of compound **3a** by $Cu(ClO_4)_2$ and O_2 led to product **6** by the cleavage of C–C bonds (Scheme 3d).

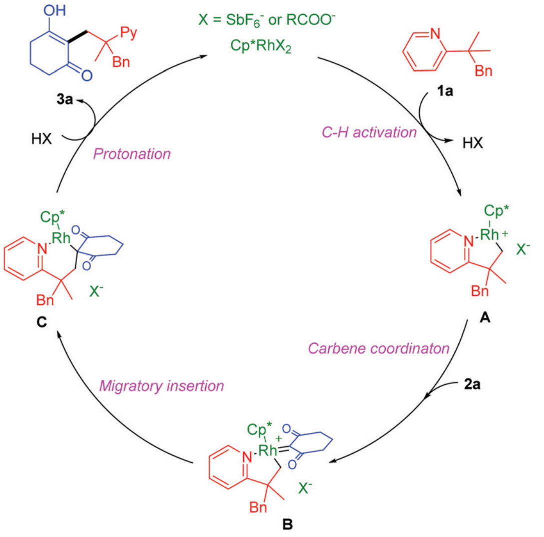
To gain insight into the mechanism of the catalytic system, a rhodacycle from **1p** and $[Cp^*RhCl_2]_2$ was synthesized according to the literature report (Scheme 4a).[16] When the **[Rh-Py]** complex was used as the catalyst, **1p** reacted with **2a** to afford the corresponding product with 72% yield (Scheme 4b). The stoichiometric reaction of the rhodacycle with **2a** also led to product **3p** with a moderate yield (Scheme 4c). The results revealed that the rhodacycle may be one of the key intermediates of the cyclic process. Using HFIP-d_2 as the reaction solvent, H/D exchange at the methyl groups with adamantoic acid-d_1 was conducted. No deuteration was detected at either the methyl or methylene position in the corresponding product **3a**, indicating the irreversibility of the methyl C–H activation process (Scheme 4d).



Scheme 3 Scale-up synthesis and derivatization of product **3a**.



Scheme 4 Mechanism studies.



Scheme 5 Proposed catalytic cycle.

According to the results and literature report,[4,7,13] a catalytic cycle was proposed as shown in Scheme 5. Pyridine-assisted methyl C–H activation by the active rhodium catalyst gives rhodacycle **A**, which can react with **2a** to lead to intermediate **B** by leaving of PhI. Intermediate **B** can undergo migratory insertion to afford the six-membered rhodacycle **C**. Finally, protonation of rhodacycle **C** gives the desired product **3a** with the regeneration of the active rhodium catalyst.

Conclusions

In summary, we have realized the inner-sphere $C(sp^3)$–H carbene insertion reaction, leading to C–C coupling products with all-carbon quaternary centers. A rhodacycle was synthesized and proved to be the active intermediate of the reaction system, revealing the inner-sphere pathway of the carbene insertion process. The cyclic iodonium ylides exhibited high reactivity for the coupling reaction. The reaction can proceed smoothly with wide substrate scopes and the useful derivatization of the product can be easily conducted.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge the financial support for this work from the National Key R&D Program of China (2021YFC0864700), the NSFC (No. 21801066, U1804283 and 82130103), the Central Plains Scholars and Scientists Studio Fund (2018002), the project funded by the Natural Science Foundation of Henan (222300420056), and the China Postdoctoral Science Foundation (2020M682307 and 2021T140183).

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