

Palladium(0)-Catalyzed Methylcyclopropanation of Norbornenes with Vinyl Bromides and Mechanism Study

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Supporting Information

ABSTRACT: An unusual methylcyclopropanation from [2 + 1] cycloadditions of vinyl bromides to norbornenes catalyzed by Pd(OAc)₂/PPh₃ in the presence of CH₃ONa and CH₃OH has been established. A methylcyclopropane subunit was installed by a 3-fold domino procedure involving a key protonation course. Preliminary deuterium-labeling studies revealed that the proton came from methyl of CH₃OH and also exposed an additional hydrogen/deuterium exchange process. These two proton-concerned reactions were fully chemoselective.

s a significant structural motif, the cyclopropane skeleton is **A** found in numerous biomolecules and pharmaceutical drugs, such as pyrethrum,¹ FR-900848,² lactobacillic acid,³ and tranylcypromine.⁴ Cyclopropanation is always a highly active area of organic chemistry for both theoretical and practical purposes⁵ and has attracted tremendously attention from organic chemists. Among the myriad methods available for constructing the cyclopropane scaffold, ^{5,6} transition-metal-catalyzed C-H or C-C bond activation is undoubtedly a fascinating methodology,⁷ except for carbene/carbenoid cycloaddition,⁸ Simmons-Smith reaction,⁹ Michael-initiated ring closure (MIRC),¹⁰ and cycloisomerization.¹¹ The cyclopropanation via the coupling of norbornenes with organoboron reagents or alkynes has been reported.¹² The intermolecular cyclopropanation of halohydrocarbon generally underwent a carbone intermediate.^{8a,b} However, transition-metal-catalyzed cyclopropanation of halohydrocarbon with alkenes via a noncarbene mechanism remains underdeveloped.¹³ Herein, we report the first example of Pd(OAc)₂/PPh₃-catalyzed methylcyclopropanation of bromostyrenes with norbornenes via [2 + 1] cycloaddition involving a methylene protonation and an additional H/D exchange with CD_3OD (Scheme 1).

In a few cases, the protonation reaction was accompanied by transition-metal-catalyzed coupling reactions. The proton sources may be materials such as alcohol and water, etc.¹⁴ The alkoxy group of alcohol can afford a proton via coordination with transition metal,¹⁵ and hydroxyl can also initiate an H/D exchange by transition-metal-catalyzed C–H activation.¹⁶ However, to the best of our knowledge, transition-metal-catalyzed coupling reactions involving both protonation and H/D exchange reactions have not been reported.

The Pd(0)-catalyzed methylenecyclopropanation and bismethenylcyclobutanation of bromostyrenes with norbornenes were



Scheme 1. Protonation and H/D Exchange in Transition-Metal-Catalyzed Coupling Reaction

Ref 14b, The protonation of D₂O in the Rh-catalyzed cyclopropanation



carried out successfully using K_2CO_3 and Cs_2CO_3 as base, respectively, in our laboratory.^{13a,17} While further studying the selectivity of the above reactions, we found methylcyclopropane product in the presence of CH₃ONa as base. The preliminary evaluation on this result revealed that the norbornenylpalladium imtermediate grabbed a proton from the reaction system. However, subsequent reaction mechanism research demonstrated that the methylcyclopropanation process underwent a protonation and an additional H/D exchange with CD₃OD. Two kinds of deuterium atoms from CD₃OD were all embedded chemoselectively in the different positions of norbornene-fused methylcyclopropane derivatives (Scheme 1).

The interesting domino [2 + 1] cycloaddition reaction prompted us to investigate the reaction parameters. (Z)-1-(2-Bromovinyl)-4-methoxybenzene 1a and *endo-N*-(*p*-tolyl)norbornenesuccinimide 2a were employed as model substrates to optimize the reaction conditions. The results are summarized in the Supporting Information (Table SI1). Previous studies

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showed that base was a key reaction parameter, so different bases such as K_2CO_3 , Cs_2CO_3 , CsOAc, C_2H_5ONa , and CH_3ONa were reviewed first. It affected both product yields and product categories. When 2.0 and 3.0 equiv of Cs_2CO_3 was used as base and 0.2 mL of CH_3OH was added, the desired product **3aa** was isolated, respectively, in 31% and 78% yields (see Table SI1, entries 2 and 3). When K_2CO_3 was employed as base, the reaction gave **4aa** as product but not **3aa** (92% yield, Table SI1, entry 1).^{13a} Even if 4.0 or 6.0 equiv of CsOAc was used as base, **4aa** was still the main product (72% and 75% yield, Table SI1, entries 4 and 5). C_2H_5ONa afforded 85% yield product **3aa**. The [2 + 1] cycloaddition afforded methylcyclopropane **3aa** with the best yield in the presence of 3.0 equiv of CH₃ONa (96% yield, entry 10).

After CH₃ONa was identified as the best base, other reaction parameters were optimized using it. Several Pd precatalysts were screened (Table SI1, entries 10-13). Using Pd(dppf)Cl₂ as the precatalyst, 3aa was obtained in 83% yield (Table SI1, entry 13), while $PdCl_2$ and $Pd(PPh_3)_4$ delivered the desired products in 52% and 74% yields, respectively (Table SI1, entries 11 and 12). Then the ligands dppe, BINAP, TMOPP, and TCHP were screened and afforded 3aa in 74%, 70%, 91%, and 68% yields, respectively (Table SI1, entries 6-9). The effects of solvent and additive were also investigated. The reaction could be conducted successfully in methanol (63% yield, Table SI1, entry 18). Other solvents, such as CH₃CN, dioxane, DMSO, and DMF, were also suitable for the reaction but only afforded 3aa in low or moderate yields (43%-66% yield, Table SI1, entries 14-17). Subsequently, additives such as C2H5OH, PhCH2OH, and Cl-(CH₂)₂OH were also surveyed; methylcyclopropane 3aa was obtained in 42%, 61%, and 72% yields, respectively, in the presence of Cs_2CO_3 due to the different pK₂ and steric hindrance of the alcohols (Table SI1, entries 21-23). The loading of 1.0 mL of CH₃OH reduced the yield of **3aa** to 75% (Table SI1, entry 20). When the reaction was carried out in the absence of CH₃OH, the result was not ideal and only afforded a trace of the desired product (Table SI1, entry 19). The best reaction temperature is at 110 °C (96% yield, Table SI1, entry 10). The yields decreased to 91% and 66%, respectively, when the reactions were carried out at 120 and 90 °C (Table SI1, entries 24 and 25). The best yield of methylcyclopropane 3aa was obtained when the model reaction was catalyzed by $Pd(OAc)_2/PPh_3$, 3.0 equiv of CH₃ONa was employed as base, and 0.2 mL of CH₃OH was used as the additive in toluene (96% yield, Table SI1, entry 10).

With the optimized reaction conditions in hand, some representative substrates were employed to investigate the scope and generality of the [2 + 1] cycloaddition domino reaction, as shown in Scheme 2. (Z)-2-Bromovinylarenes bearing electron-donating (3-Me, 4-Me, and 4-MeO) groups on the benzene core afforded the corresponding methylcyclopropane derivatives 3 in excellent yields (Scheme 2, 3aa, 3ca-da, 3db, **3ac**, **3cc**-**dc**, **3ad**, **3cd**-**dd**), while (Z)-2-bromovinylarenes bear-ing electron-withdrawing groups (2-Cl, 3-Cl, 4-Cl, and 4-F) on the benzene ring provided products 3 in good to high yields (Scheme 2, 3ea-ha, 3fb, 3hb, 3hc, 3hd). The para-substituted vinylarenes provided methylcyclopropane products 3ca, 3ea, 3cc, and 3cd in higher yield (Scheme 2, 95%, 89%, 85% and 83% yield) owing to much smaller steric hindrance compared with the corresponding meta-substituted vinylarenes (3da, 3fa, 3dc, and 3dd; 91%, 82%, 82%, and 81% yield). The reaction scope was further extended to aliphatic (Z)-1-bromoalkenes 1i successfully,

Scheme 2. Substrate Scope of Pd-Catalyzed

Methylcyclopropanation of Norbornenes with (Z)-Vinyl Bromides a



^aReaction conditions unless otherwise noted: 1 (0.55 mmol), 2 (0.5 mmol), Pd(OAc)₂ (0.05 mmol), PPh₃ (0.11 mmol), CH₃ONa (1.5 mmol), toluene (2.0 mL), CH₃OH (0.2 mL), 110 $^{\circ}$ C, 12 h in sealed tube. Isolated yields are shown. ^bCH₃ONa (1.0 mmol). ^cReaction conditions: 1 (0.5 mmol), 2 (0.6 mmol), Pd(OAc)₂ (0.05 mmol), PPh₃ (0.11 mmol), CH₃ONa (2.0 mmol), toluene (2.0 mL).

and afforded methylcyclopropanation products **3ia** and **3ib** in 71% and 76% yields, respectively.

After the scope of the (Z)-2-bromovinylarenes was screened, another coupling partner, norbornene derivatives, was investigated. endo-N-IsobutyInorbornenesuccinimide 2b was coupled smoothly with (Z)-vinyl bromides to give corresponding products 3db, 3fb, and 3hb-ib in good to high yields under the optimized reaction conditions. Norbornene itself 2c also provided the desired methylcyclopropanes with good yields in the presence of 4.0 equiv of CH₃ONa (Scheme 2, 3ac, 3cc-dc, 3hc). Functionalized norbornene derivatives such as (1R,4S)-1,4-dihydro-1,4-methanonaphthalene-5,8-diyl diacetate successfully produced the corresponding methylcyclopropanes in good to excellent yields (Scheme 2, 3ad, 3cd, 3dd, 3hd). Cyclohexene was also employed as alkene to carry out the $\begin{bmatrix} 2 + 1 \end{bmatrix}$ cycloaddition reaction, however, the reaction did not proceed smoothly. The structure of products was further confirmed unambiguously by X-ray crystallography of 3da (see the SI, Figure S1). The formed methylcyclopropane subunit took the exo-face of norbornane.

Subsequently, (E)-2-bromovinylarene substrates (E)-1 were investigated, and the corresponding methylcyclopropane prod-

ucts 3aa, 3ba, 3ea, 3ha, 3hb, and 3bd were obtained under the same reaction conditions (Scheme 3, 71%, 63%, 52%, 56%, 51%,

Scheme 3. Substrate Scope of Pd-Catalyzed Methylcyclopropanation of Norbornenes with (E)-Vinyl Bromides^a



^aReaction conditions unless otherwise noted: (*E*)-1 (0.55 mmol), 2 (0.5 mmol), Pd(OAc)₂ (0.05 mmol), PPh₃ (0.11 mmol), CH₃ONa (1.5 mmol), toluene (2.0 mL), CH₃OH (0.2 mL), 110 °C, 12 h in sealed tube. Isolated yields are shown. ^bReaction conditions: 1 (0.5 mmol), 2 (0.6 mmol), Pd(OAc)₂ (0.05 mmol), PPh₃ (0.11 mmol), CH₃ONa (2.0 mmol), toluene (2.0 mL), CH₃OH (0.2 mL).

and 59% yields). Obviously, the (*Z*)-2-bromovinylarene substrates provided better yields than that of (*E*)-ones. It may be that the benzene ring of (*Z*)-2-bromovinylarene stabilizes the norbornenylpalladium intermediate via favorable interaction between the π system of benzene ring and Pd center.¹⁸ However, (*E*)-2-bromovinylarene cannot exert the same stabilizing role because it lacks such space advantage.

Where did the additional hydrogen atom came from? In order to answer the question, deuterium-labeling experiments were carried out using (*Z*)-(2-bromovinyl)benzene **1b** and *endo-N*-(pmethoxy)phenylnorbornenesuccinimide **2e** as model substrates (Scheme 4).¹⁹ First, when toluene- d_8 was used as solvent and

Scheme 4. Deuterium-Labeling Studies



CH₃OH was employed as additive, nondeuterated methylcyclopropane **3A** was obtained in 73% yield (Scheme 4, eq 1). Second, when CD₃OH was employed as the additive and toluene was used as solvent, benzyl methylene-deuterated methylcyclopropane **3B** was successfully isolated in 55% yield (Scheme 4, eq 2). Subsequently, the reaction was investigated again using CH₃OD as additive and toluene as solvent, methylcyclopropane **3C** of α deuterium of one carbonyl was obtained in 62% yield (Scheme 4, eq 3). Finally, when the reaction was carried out in toluene using CD₃OD as additive, another methylcyclopropane **3D** with both an α -deuterium of one carbonyl and a methylene-deuterated of benzyl was produced successfully in 45% yield (Scheme 4, eq 4).

The α -H of carbonyl tended to undergo hydrogen/deuterium exchange with CH₃OD or CD₃OD in the presence of base owing to its relatively small pK_a . In order to see whether the H/D exchange is caused by its acidity, deuterium-labeling experiments of the **2e** and **3A** were carried out, respectively, in the absence of Pd(OAc)₂ and PPh₃, only using Cs₂CO₃ as base and CH₃OD as additive. However, no product with an α -deuterium of carbonyl was observed. This meant that the H/D exchange of the α -position of carbonyl is not because of its acidity, but the catalytic cycle may have a key influence on the H/D exchange.

On the basis of the current experimental results and related precedents, $^{13-16,20}$ a postulated mechanism was proposed (Figure 1). The oxidative addition of palladium(0) species to



Figure 1. Proposed reaction mechanism for the palladium-catalyzed methylcyclopropanation.

(Z)-bromostyrene derivative 1 produced (Z)-styrylpalladium-(II) bromide I. Subsequently, the syn addition of I to norbornene 2 at the exo-face generated norbornenyl palladium complex II. Palladium complexes might exist in an equilibrium between neutral and cationic species.²¹ The polar solvent could stabilize the cationic species and the polarity of solvent toluene would be increased in the presence of CD₃OD, thus rendering a cationic palladium species III as the major intermediate, which was called the outer form.²² Subsequently, "bridging" palladium complex IV was generated.²³ Thus, the corresponding norbornene fragment became more positively charged to prompt the α -H/D exchange in the presence of base, while CD_3OD coordinated to the Pd(II) and provided a D from OD group. The olefin of the intermediate VI coordinated to the Pd center, which was followed by an insertion reaction to produce cyclopropanepalladium intermediate VII. The selective β -H elimination of VII yielded Pd-D complex VIII and released methanal.²⁴ Reductive elimination of complex VIII produced methylcyclopropane derivatives 3 and regenerated Pd(0).

In conclusion, we have developed a novel $Pd(OAc)_2/PPh_3$ catalyzed [2 + 1] cycloaddition domino reaction of vinyl bromides to norbornene derivatives involving a protonation process and an additional H/D exchange from CD₃OD. By this protocol, a methylcyclopropane subunit was installed via the 3fold domino reaction including Heck-type reaction/C–C bond activation/protonation. Preliminary deuterium-labeling studies demonstrated where the proton came from. This method is unusual, but practical, which complemented the classic methods for the fast synthesis of multiple substituted methylcyclopropane derivatives. Further investigation of the reaction mechanism is underway.

Organic Letters

ASSOCIATED CONTENT

S Supporting Information

Experimental details, characterization data, full spectroscopic data for all new compounds, and X-ray crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01603.

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Notes

The authors declare no competing financial interest.

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