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Palladium(0)-Catalyzed Methylenecyclopropanation of Norbornenes with Vinyl Bromides

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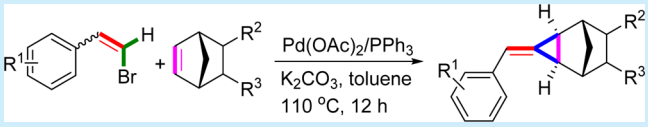
Supporting Information

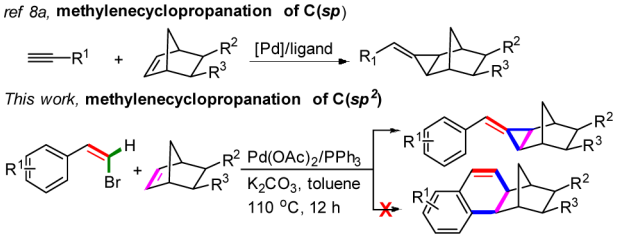
ABSTRACT: Highly strained methylenecyclopropane derivatives have been achieved via a novel and efficient Pd(0)-catalyzed domino reaction. The formal [2 + 1] cycloaddition reaction of vinyl bromides to norbornenes involves a Heck-type coupling and a C(sp^2)−H bond activation.



Methylenecyclopropane (MCP) is the smallest carbocycle with an *exo*-methylene moiety.[1] The construction and transformation of MCP unit has attracted much attention from organic chemists for its sufficient stability, significant strain (40 kcal/mol), and conferring on them an unusually high reactivity.[2] A MCP subunit as a basic skeleton presents in many natural products and biologically active compounds.[3] Numerous efficient and straightforward syntheses of various MCPs have been reported.[4] The [2 + 1] cycloaddition of carbene (or carbenoid) to an unsaturated bond is undoubtedly the most common method for constructing methylene and alkylidenecyclopropane subunit.[5] The elimination reaction of HX, XX, XY Group as well as N_2 from Pyrazolines is also a powerful tool in the synthesis of MCPs.[6] A few peculiar rearrangement reactions of designed compounds for installing MCP units have appeared in the literature since the 1980s.[7]

Recently a few examples of transition metal-catalyzed methylenecyclopropanation via C−H or C−C bond activation have been reported.[8] Buono and co-workers first reported Pd(II)-catalyzed methylenecyclopropanation of terminal alkynes to norbornenes via C(sp)−H bond activation (Scheme 1).[8a] However, to our knowledge, transition metal-catalyzed methylenecyclopropanation of monohalo-molecules via C-(sp^2)−H bond activation has not been reported. Herein, we reported the first example of Pd(0)-catalyzed intermolecular C(sp^2)−H activation methylenecyclopropanation (Scheme 1).

Scheme 1. Transition Metal-Catalyzed Methylenecyclopropanation



Norbornene[9] and cyclopropane-fused norbornene moiety[10] have been discovered in some bioactive compounds such as pharmaceuticals and natural products. Cyclopropane-fused norbornene also served as a significant building block in organic synthesis.[11]

On the basis of our previous studies[12] and our interest in methylenecyclopropanation of norbornenes via Pd(0)-catalyzed C(sp^2)−H bond activation,[13] we evaluated the outcomes of the coupling of (*Z*)-1-(2-bromovinyl)-4-methoxybenzene **1a** with *endo*-*N*-(*p*-tolyl)norbornenesuccinimide **2a** using a Pd(0) catalyst system. To our delight, the desired methylenecyclopropanation compound **3a** was obtained as the final products instead of benzene-fused norbornene compounds (Scheme 1). Therefore, the reaction conditions were screened to achieve the best yield of MCPs. The results were summarized in Table 1.

First, metal catalysts and ligands were screened in the methylenecyclopropanation reaction. $Pd(OAc)_2$ was better than $PdCl_2$, $Pd(PPh_3)_4$, and $Pd(dppf)Cl_2$ (Table 1, entries 1−4, 97% yield compared with 58−81%). The ligand effect was also examined. In contrast to PPh_3, dppf and BINAP resulted in a lower yield of **3aa** (Table 1, entries 5−6). Base also had a significant effect on product yield. Compared with K_3PO_4 and NaOAc, K_2CO_3 was the best in promoting this reaction (Table 1, entries 7−8). The reaction could proceed successfully in toluene (Table 1, entry 2). Other polar aprotic solvents, such as DMSO, dioxane, and CH_3CN, only gave moderate or low yields (Table 1, entries 9−11).

With the optimized reaction conditions in hand, some representative substrates were selected to explore the scope of the reaction (Scheme 2). Substituted (*Z*)-2-bromovinylarene bearing electron-donating substituents (methyl and methoxy) afforded product **3** in excellent yields (Scheme 2, **3aa**, **3ca**, **3da**, **3cb**−**3db**, **3ac**, **3cc**), while (*Z*)-2-bromovinylarenes bearing electron-withdrawing groups (chloro and fluoro) also provided products **3** in good to high yields (Scheme 2, **3ea**−**3ha**, **3eb**−**3fb**, **3ec**, **3fc**, **3hc**). The *ortho*-chloro vinylarene produced **3ga**

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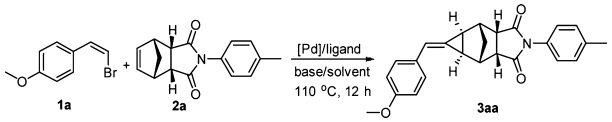
Table 1. Optimization of Reaction Conditions for Methylenecyclopropanation[a]



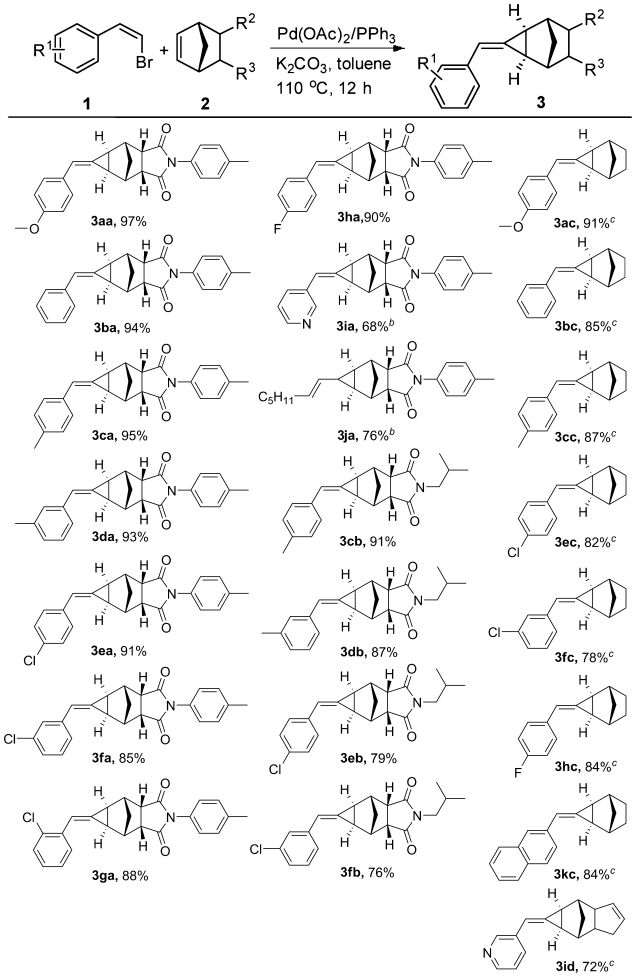
entry	[Pd]	ligand	base	solvent	yield[b] (%)
1	$PdCl_2$	PPh_3	K_2CO_3	toluene	58
2	$Pd(OAc)_2$	PPh_3	K_2CO_3	toluene	97
3	$Pd(PPh_3)_4$	PPh_3	K_2CO_3	toluene	73
4	$Pd(dppf)Cl_2$	PPh_3	K_2CO_3	toluene	81
5	$Pd(OAc)_2$	dppf	K_2CO_3	toluene	46
6	$Pd(OAc)_2$	BINAP	K_2CO_3	toluene	14
7	$Pd(OAc)_2$	PPh_3	K_3PO_4	toluene	53
8	$Pd(OAc)_2$	PPh_3	NaOAc	toluene	62
9	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMSO	42
10	$Pd(OAc)_2$	PPh_3	K_2CO_3	dioxane	65
11	$Pd(OAc)_2$	PPh_3	K_2CO_3	CH_3CN	52

[a]Reaction conditions unless otherwise noted: **1a** (0.55 mmol), **2a** (0.5 mmol), catalyst (0.05 mmol), ligand (0.11 mmol), base (0.25 mmol), solvent (3.0 mL), 110 °C, 12 h in sealed tube. [b]Isolated yields.

in 88% yield due to weaker electron-withdrawing effect compared with *meta*- one (**3fa** 85% yield) and stronger steric hindrance effect compared with *para*- one (**3ea** 91% yield). Heterocyclic and aliphatic vinyl bromides were also employed as substrates to enlarge this process. (*Z*)-1-Bromooct-1-ene yielded vinylidenecyclopropane as product (Scheme 2, **3ja**, 76% yield) because of the regioselective β-H elimination, while (*Z*)-3-(2-bromovinyl)pyridine produced methylenecyclopropane compound **3ia** in 68% yield. Subsequently, (*E*)-2-bromovinylarene substrates **4** were tested, and the corresponding products **3aa**, **3ba**, **3ha**, **3ea**, **3bc** (Scheme 3, 56, 50, 42, 31, and 54% yield) were obtained under the same reaction condition. Obviously the (*Z*)-2-bromovinyl substrates were more active than (*E*)-ones. Maybe the aromatic ring of (*Z*)-2-bromovinylarene stabilized the intermediate of norbornenylpalladium via favorable interaction of the aromatic π system with the Pd center.[14] However, (*E*)-2-bromovinyl-arenes have no such a space advantage to exert the same stabilizing role. The isomerization of (*Z*)- and (*E*)-alkenes is still quite dubious now under the reaction condition. Obviously, The isomerization of (*E*)-alkenes to (*Z*)- ones generally needs a higher activation energy and is difficult to achieve.[15]

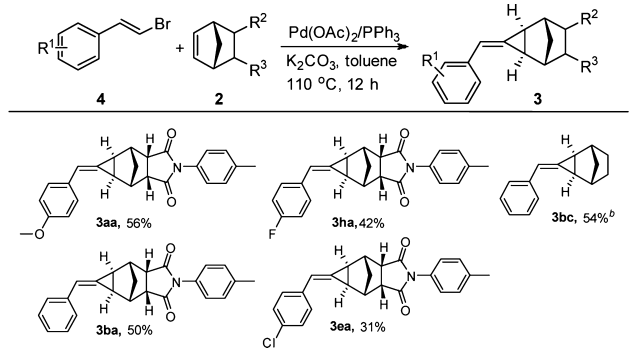
After investigating the scope of the (*Z*)-2-bromovinylarenes, another coupling partner of norbornene was examined. *endo*-*N*-(Isobutyl) norbornenesuccinimide **2b** was smoothly reacted with (*Z*)-vinyl bromides to afford corresponding products **3cb**−**3fb** in good to high yields under the above optimized reaction conditions. Norbornene itself **2c** showed lower reactivity. However, by doubling the base dosage, the corresponding methylenecyclopropane products were obtained in good to high yields (Scheme 2, **3ac**−**3cc**, **3ec**−**3fc**, **3hc**−**3ic**). Dicyclopentadiene **2d** provided product **3id** in 72% yield. Cyclohexene was also employed as the alkene to undergo this cycloaddition; however, the reaction did not proceed successfully. The structure of **3da** is further unambiguously elucidated by X-ray crystallography (see the Supporting Information, Figure S1), the formed methylenecyclopropane moiety took the *exo*-face of norbomene. On the basis of the chemical shifts and coupling constants (*J*) of all the products, it can be ascertained that the stereochemistry of all the

Scheme 2. Substrate Scope of Pd-Catalyzed Methylenecyclopropanation[a]



[a]Reaction conditions unless otherwise noted: **1** (0.55 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.11 mmol), K_2CO_3 (0.25 mmol), toluene (3.0 mL), 110 °C, 12 h in sealed tube. Isolated yields are shown. [b]Reaction conditions: K_2CO_3 (0.5 mmol), toluene (2.0 mL). [c]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), K_2CO_3 (0.5 mmol), toluene (2.0 mL).

Scheme 3. Methylenecyclopropanation of (*E*)-2-Bromovinylarene[a]



[a]Reaction conditions unless otherwise noted: **4** (0.55 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.11 mmol), K_2CO_3 (0.25 mmol), toluene (3.0 mL), 110 °C, 12 h in sealed tube. Isolated yields are shown. [b]Reaction conditions: K_2CO_3 (0.5 mmol), toluene (2.0 mL).

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compounds is the same with that of **3da**.[12] In addition, a sole diastereomer was obtained in all cases.

On the basis of the experiment results and earlier precedents,[12,16] a putative mechanism was proposed (Figure 1). The oxidative addition of palladium(0) species to (*Z*)-vinyl

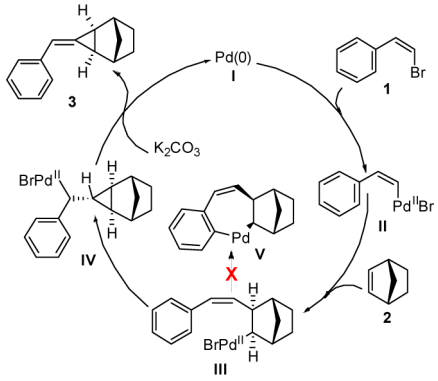

Figure 1. Proposed reaction mechanism for the Pd(0)-catalyzed methylenecyclopropanation.

bromides generated a vinylpalladium(II) species **II**. Subsequent Heck-type carbopalladation at the *exo*-face of the norbornene gave norbornenylpalladium complexes **III**, which underwent selective C−C double bond activation on the (*Z*)-vinyl bromides, rather than C−H bond activation on benzene ring and generated an intermedate **IV** consisting of cyclopropane. The selectivity might result from the energy advantage of transition states **IV** compared with **V**[12] and, following reductive elimination of intermedate **IV**, generated the *exo*-methylene, afforded the desired methylenecyclopropane compounds **3**, and regenerated Pd(0) **I**.

In conclusion, a novel and highly efficient Pd(0)-catalyzed [2 + 1] cycloaddition of vinyl bromides to norbornene derivatives to prepare multisubstituted methylenecyclopropane derivatives has been established. The domino reaction involves a Heck-type reaction and a C(sp^2)−H bond activation. By this protocol, a methylenecyclopropane subunit was constructed in a single operation via successive two carbon−carbon bond formations. Vinyl bromide was added to norbornene via a Pd(0)-catalyzed [2 + 1] cycloaddition reaction. This method is simple, practical, and unusual, which enriched the synthesis methodologies of methylenecyclopropane for the rapid construction of multiple substituted cyclopropane derivatives.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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