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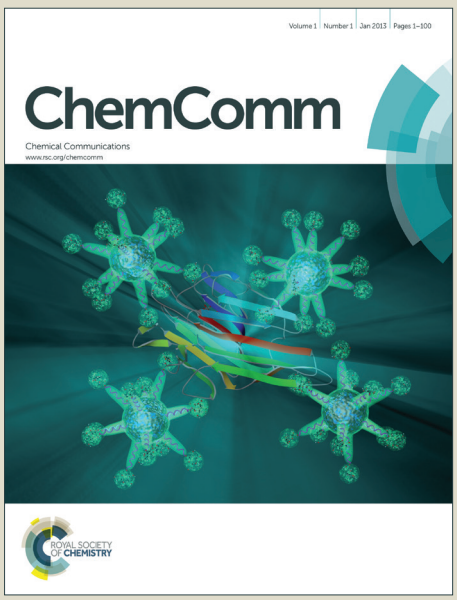

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ARTICLE TYPE

Palladium-Catalyzed [2+1+1] Annulation of Norbornenes with (*Z*)-Bromostyrenes: Synthesis of Bismethylenecyclobutanes *via* Twofold C(sp^2)-H Bond Activation

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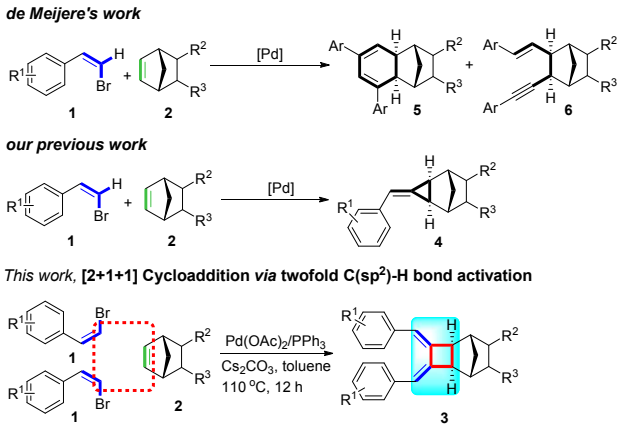
The first Pd-catalyzed intermolecular [2+1+1] annulation reaction of (*Z*)-bromostyrene derivatives and norbornenes has been realized. Bismethylenecyclobutane derivatives were obtained with high yields. The domino coupling reaction involves in double Heck-type coupling process, twofold C(sp^2)–H bond activation and three carbon-carbon bonds formation.

Synthesis of small cycloalkanes such as cyclobutanes has captivated organic chemists for several decades, for both theoretical and practical purposes.[1] Cyclobutanes represent an important structural motif frequently found in biological active natural products,[2] pharmaceuticals,[3] and organic synthesis.[4] Its synthesis has greatly attracted the interest of chemists and many effective methodologies have been developed. The most straightforward synthetic routes to cyclobutanes are photochemically initiated [2+2] pericyclic reactions[5] and other ionic or free radical stepwise cycloaddition strategies.[6] The ring expansion of cyclopropylcarbinyl precursors,[7] intramolecular 1,4-cyclization of acyclic substrates,[8] intermolecular [3+1] cycloaddition[9] and transition metal catalyzed C-H bond activation were also used to construct cyclobutane derivatives.[10] However, to our knowledge, no [2+1+1] annulation reaction has been reported yet.

Prospect of devising catalytic processes to convert selectively simple substrates into two or more products in a controlled fashion is always a fascinating challenge to organic chemists,[11] due to its fundamental scientific interest and potential usage in organic synthesis. Selectivity (chemo-, regio-, stereo- and enantio-) strategy as a versatile handle can afford diverse and industrially important chemicals.[11,12] de Meijere and co-workers reported a domino coupling of bromostyrene derivatives with norbornenes in 1994, which gave a mixture of compounds **5** and **6,** or produce **6** (26% yield) as exclusive product by changing reaction conditions, but only one example[13] (Scheme 1). Recently we found that Pd(0)-catalyzed C−H bond activation reactions of bromostyrene derivatives and benzyl bromides with norbornenes could provide cyclopropane derivatives **4** via [2+1] cycloaddition processes (Scheme 1).[14] In the experiment we found the synthesis of cyclobutanes **3** via [2+1+1] annulation of (*Z*)-bromostyrene derivatives with norbornenes was possible if suitable reaction conditions were sought.

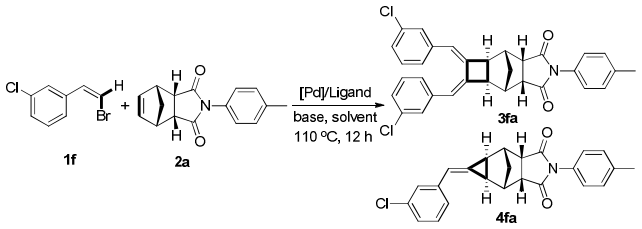


Scheme 1. Selective synthesis of small cycloalkanes.

To reach the best results, (*Z*)-1-(2-bromovinyl)-3-chlorobenzene **1f** was initially employed to react with endo-*N*-(*p*-tolyl)norbornenesuccinimide **2a** using palladium catalyst system under various conditions (Table 1). The desired bismethenylcyclobutane derivative **3fa** was obtained selectively as the final products instead of compounds **4**, **5** or **6** (Scheme 1). Then, the reaction conditions were screened to achieve the best selectivity and yield of bismethenylcyclobutane **3fa**. The results were summarized in Table 1.

At the outset, metal catalysts were screened in the [2+1+1] cycloaddition reactions. $Pd(OAc)_2$ was better than $PdCl_2$, $Pd(PPh_3)_4$ and $Pd(dppf)Cl_2$ (Table 1, entries 1-4, 91% yield compared with 66%-84%). The effect of ligand was then investigated, and PPh_3 was found to be the optimal, affording **3fa** in 91% yield. Other screened ligands (dppf, dppe, TMOPP, DCHPP and TCHP) could also promote the reaction with decreased yields, possibly due to either steric or electronic effects (65%-89%, entries 5-9). Varying the types and load of the bases (K_2CO_3, KOAc, CsOAc, *t*BuOK and Cs_2CO_3) influenced the outcome considerably (Table 1, entries 10-17). The basicity had a significant effect on reaction selectivity and product yield. The usage of *t*BuOK yielded bismethylenecyclobutane **3fa** (79%, entry 17), while K_2CO_3, KOAc and CsOAc gave methylenecyclopropane derivatives **4fa** in good to high yields

Table 1. Optimization of reaction conditions and chemoselectivity under various conditions.[a]



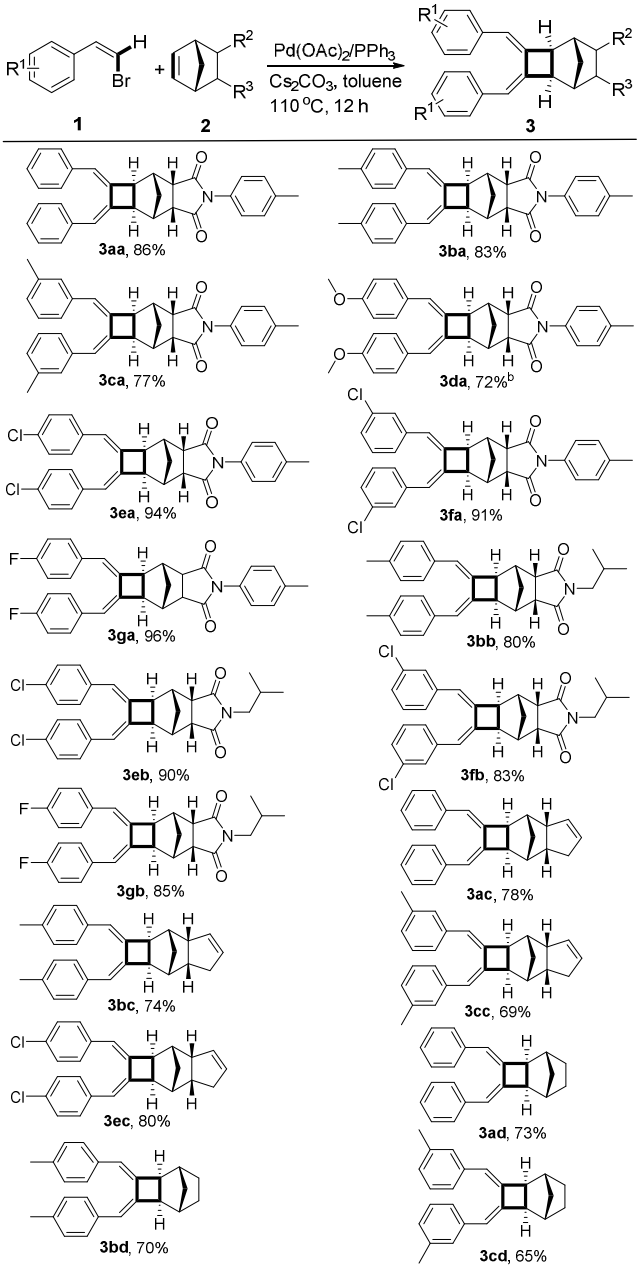
Entry	[Pd]	Ligand	Base(mmol)	Solvent	**3fa** or **4fa** Yield [%][b]
1	$PdCl_2$	PPh_3	Cs_2CO_3	toluene	**3fa** (84)
2	$Pd(PPh_3)_4$	PPh_3	Cs_2CO_3	toluene	**3fa** (82)
3	$Pd(OAc)_2$	PPh_3	Cs_2CO_3(1.5)	toluene	**3fa** (91)
4	$Pd(dppf)Cl_2$	PPh_3	Cs_2CO_3	toluene	**3fa** (66)
5	$Pd(OAc)_2$	dppe	Cs_2CO_3	toluene	**3fa** (67)
6	$Pd(OAc)_2$	dppf	Cs_2CO_3	toluene	**3fa** (63)
7	$Pd(OAc)_2$	TMOPP	Cs_2CO_3	toluene	**3fa** (86)
8	$Pd(OAc)_2$	DCHPP	Cs_2CO_3	toluene	**3fa** (89)
9	$Pd(OAc)_2$	TCHP	Cs_2CO_3	toluene	**3fa** (65)
10	$Pd(OAc)_2$	PPh_3	K_2CO_3(1.5)	toluene	**4fa** (86)
11	$Pd(OAc)_2$	PPh_3	KOAc(3.0)	toluene	**4fa** (72)
12	$Pd(OAc)_2$	PPh_3	CsOAc(1.0)	toluene	**4fa** (80)
13	$Pd(OAc)_2$	PPh_3	CsOAc(2.0)	toluene	**4fa** (77)
14	$Pd(OAc)_2$	PPh_3	CsOAc(3.0)	toluene	**4fa** (81)
15	$Pd(OAc)_2$	PPh_3	Cs_2CO_3(0.5)	toluene	**4fa** (84)
16[c]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3(1.0)	toluene	**3fa** (31)/ **4fa** (56)
17	$Pd(OAc)_2$	PPh_3	*t*BuOK(1.5)	toluene	**3fa** (79)
18	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	dioxane	**3fa** (78)[d]
19	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DEDM	**3fa** (81)

[a] Reaction conditions unless otherwise noted: **1a** (0.55 mmol), **2a** (0.5 mmol)，catalyst (0.05 mmol), ligand (0.11 mmol), base (1.5 mmol), solvent (2.0 mL), 110 °C, 12 h in sealed tube. [b] Yield of isolated product. [c] The ratio of **3** and **4** was determined by ^{1}H NMR analysis. [d] 100 °C. dppe = 1,2-Bis(diphenyl phosphino)ethane. dppf = 1,1'-Bis(diphenylphosphino) ferrocene. TMOPP = tris(4-methoxylphenyl)phosphine. DCHPP = dicyclohexylphenyl phosphine. TCHP = tricyclohexyl phosphine. DEDM = diethylene glycol dimethyl ether.

(72%-86%, entries 10-14). Compared with *t*BuOK, Cs_2CO_3 (3.0 equiv) was the best in promoting this reaction (91%, Table 1, entry 3). The varying load of Cs_2CO_3 (0.5mmol, 1.0 mmol and 1.5mmol) controlled successfully the chemoselectivity of the domino cycloaddition processes, and thus yielded exclusively [2+1] or [2+1+1] cycloaddition products (entries 3, 15-16). However, intrinsic detailed mechanism of the selectivity is still quite dubious at the moment.[13,15] Next, the effect of solvent was also examined. The reaction in toluene gave the best result, affording **3fa** in 91% yield (entry 3). Other polar aprotic solvents (dioxane, DEDM) also gave good yields (Table 1, entries 18-19).

Under the optimized reaction conditions with the palladium (0) catalyst, formed in situ from $Pd(OAc)_2$ and PPh_3, various (*Z*)-bromostyrene derivatives were tested to investigate the generality of the [2+1+1] cycloaddition reaction, as shown in Scheme 2. (*Z*)-2-bromovinylarene substrates bearing electron-withdrawing group (3-Cl, 4-Cl, 4-F) on the benzene ring led to the corresponding bismethenylcyclobutane derivatives **3** in excellent yields (Scheme 2, **3ea-3ga, 3eb-3gb, 3ec**), while substrates bearing electron-donating (3-Me, 4-Me, 4-MeO) group on the benzene core also afforded the desired bismethenylcyclobutanation products **3** in good to high yields (Scheme 2, **3ba-3da**, **3bb**, **3bc, 3cc**, **3bd**, **3cd**). The difference of

Scheme 2. Substrate scope of Pd(0)-catalyzed bismethylenecyclobutanation.[a]



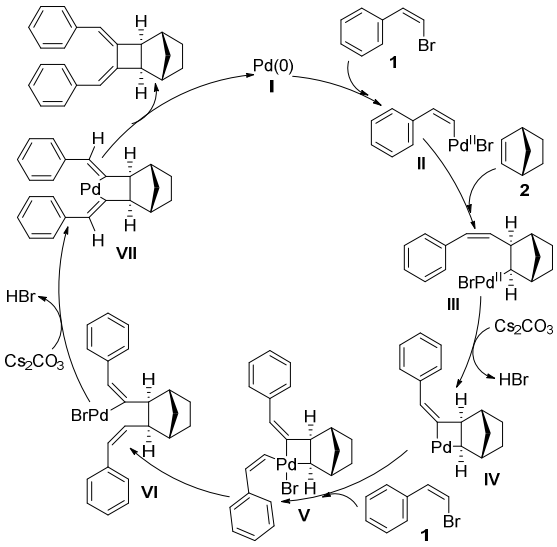
Reaction conditions unless otherwise noted: **1a** (1.1 mmol), **2a** (0.5 mmol)，catalyst (0.05 mmol), ligand (0.11 mmol), base (1.5 mmol), solvent (2.0 mL), 110 °C, 12 h in sealed tube. [a] The yield is that of the isolated product. [b] **1a** (1.0 mmol), **2a** (0.6 mmol).

yields may root in electronic effect of the substituents. The *para*-substituted vinylarenes produced annulation products **3ba**, **3ea**, **3eb** and **3bc** in higher yield (83%, 94%, 90% and 70% yield) due to much smaller steric hindrance compared with the corresponding *meta*-ones (**3ca, 3fa**, **3fb** and **3cc**; 77%, 91%, 83% and 67% yield). O*rtho*-substituted products can not be isolated because of its strong steric hindrance and the corresponding low yield. We extended the method to (*E*)-(2-bromovinyl)benzene and (*E*)-1-(2-bromovinyl)-4-fluorobenzene to prepare bismethenylcyclobutane compounds under the same reaction

condition. Unfortunately, no desired corresponding product was obtained. Maybe the aromatic ring of (*Z*)-2-bromovinylarene stabilized the intermediate of norbornenyl palladium *via* favorable remote coordination of the aromatic π system with the Palladium center.[14a,16] However, the spatial configuration of (*E*)-2-bromovinylarenes is difficult to exert the same stabilizing function. Heterocyclic and aliphatic bromostyrene derivatives such as (*Z*)-3-(2-bromovinyl)pyridine and (*Z*)-(2-bromovinyl)cyclohexane were also employed to examine the scope of substrates, but only very low yield products were discovered and couldn't be isolated.

The optimized [2+1+1] cycloaddition procedure was subsequently applied to a range of norbornene derivatives. *Endo*-*N*-(*p*-tolyl)norbornenesuccinimide **2a** and *endo*-*N*-(isobutyl) norbornenesuccinimide **2b** underwent the bismethenylcyclobutanation reaction smoothly with (*Z*)-bromostyrene derivatives to provide the corresponding products **3aa**−**3ga**, **3bb** and **3eb**-**3fb** in good to excellent yields. Dicyclopentadiene **2d** also yielded desired annulation products **3ac**, **3bc**, **3cc** and **3ec** in 78%, 74%, 69% and 80% yields respectively. Only one of the carbon-carbon double bonds of dicyclopentadiene was selectively cyclized by (*Z*)-bromostyrene derivatives. Norbornene itself **2d** showed lower reactivity and gave the corresponding products in moderate yields (**3ad**, **3bd** and **3cd**; 73%, 70% and 65%). For norbornene substrates, the electronic effect influenced the yields more than its steric hindrance. Non-rigid alkene, such as cyclohexene, was also tested to carry out the [2+1+1] cycloaddition procedure, however, the reaction did not proceed smoothly. The structure of the product was further confirmed unambiguously by an X-ray crystallographic analysis of a single crystal of **3ba** (see the Supporting Information, Figure S1). The formed bismethenylcyclobutane moiety took the *exo*-face of norbomene. The stereochemistry of all the compounds is the same as that of **3ba** based on the analysis of the chemical shifts and coupling constants (*J*) of their NMR.[14] In addition, only one diastereomer was isolated in all cases.

Based on the current experiment results and related precedents,[14,17] a postulated mechanism was proposed (Scheme 3). The oxidative addition of palladium (0) species to (*Z*)-bromostyrene derivative **1** produced a (*Z*)-styrylpalladium (II) bromide **II**. Subsequently the *syn* addition of **II** to norbornene **2** generated norbornenylpalladium complexe **III** at the *exo*-face of **2**, which underwent a selective C(sp^2)−H bond activation on the (*Z*)-bromostyrene derivative, rather than C(sp^2)−H bond on benzene ring and gave a regioselective four-membered palladacycle **IV** in the presence of Cs_2CO_3. The selectivity might result from the energy advantage of intermediate **IV**,[14] which could undergo oxidative addition to another equivalent of **1** again and generated the intermediate **V** with octahedrally coordinated palladium(IV).[17a,18] The selective reductive elimination of the intermediate **V** produced another (*Z*)-styrylpalladium (II) bromide intermediate **VI**,[19] which underwent once again C(sp^2)−H bond activation and afforded palladacyclopentadiene complex **VII** in the presence of Cs_2CO_3. Following reductive elimination of the intermediate **VII**, the desired bismethenylcyclobutane compound **3** was produced and the Pd(0) **I** was regenerated.



Scheme 3. Proposed reaction mechanism for the Pd(0)-catalyzed bismethenylcyclobutanation.

In summary, a new methodology for the synthesis of cyclobutane is developed. The Pd-catalyzed selective [2+1+1] annulation of (*Z*)-bromostyrene derivatives with norbornene derivatives is realized under extremely concise reaction condition. Highly functionalized bismethenylcyclobutane deirvatives were obtained selectively in good to excellent yields in the presence of Cs_2CO_3. The annulation is an one-pot, mutiple-step domino reaction, which involves a double Heck-type coupling, twofold C(sp^2)–H bond activation and three carbon-carbon bonds formation. The reaction is interesting both for theoretical and organic synthetic chemistry.

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† Electronic Supplementary Information (ESI) available: Experimental procedures, NMR spectra and characterizations for all new compounds. See DOI: 10.1039/b000000x/

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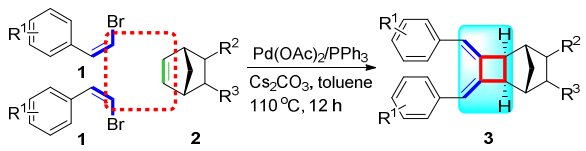
TOC



A Pd(0)-catalyzed domino bismethylenecyclobutanation reaction was established. The [2+1+1] cycloaddition involves twofold C(sp^2)–H bond activation and three carbon-carbon bonds formation.