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Z-Selective Synthesis of γ,δ-Unsaturated Ketones via Pd-Catalyzed Ring Opening of 2-Alkylenecyclobutanones with Arylboronic Acids

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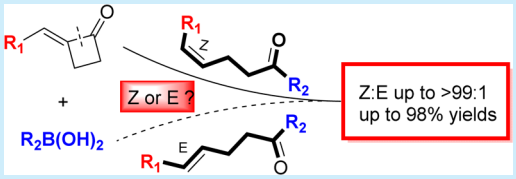
Supporting Information

ABSTRACT: Pd-catalyzed 1,2-addition (instead of 1,4-addition) of arylboronic acids to 2-alkylenecyclobutanones followed by β-carbon elimination from the resulting palladium cyclobutanolates to afford γ,δ-unsaturated ketones was developed. The desired γ,δ-unsaturated ketones were obtained in good to excellent yields with *Z*/*E* selectivities of up to >99:1 and a broad spectrum of functional group tolerability.



Organoboron compounds are nontoxic and widely used in transition-metal-catalyzed carbon−carbon bond formation reactions.[1] Among the precedent transformations, transition-metal-catalyzed addition of arylboronic acids and their analogues to α,β-unsaturated compounds catches our attention, since there are two types of functional groups on α,β-unsaturated compounds, namely, olefin and carbonyl groups, which might bring forth a selectivity issue in the addition reaction. To date, 1,4-addition rather than 1,2-addition of arylboronic acids to α,β-unsaturated compounds has been dominant on most occasions (Figure 1).[2,3] To our knowledge,

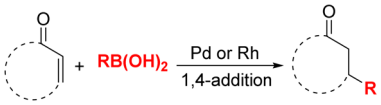
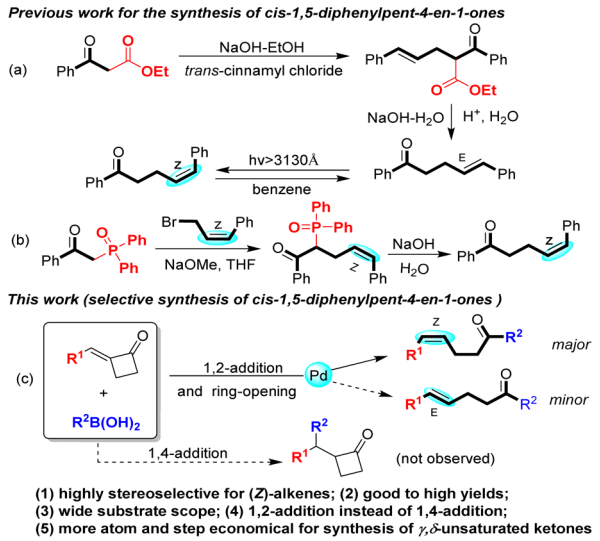


Figure 1. Transition-metal-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated compounds.

there are very few publications[4] in which efficient 1,2-addition of arylboronic acids to α,β-unsaturated compounds has been reported. The inherent strain in cyclobutanone derivatives bestows them with reactivity that cannot be observed in other less-strained, larger cyclic analogues. Myriad reports have described the use of cyclobutanone derivatives as versatile substrates, leading to a variety of structurally diverse synthetic transformations.[5−9] For instance, Murakami reported some elegant transformations based on C−C bond cleavage reactions of 3-phenylcyclobutanones.[6] Recently, Dong also developed a number of rhodium-catalyzed C−C activations of benzocyclobutenones.[7] As a special α,β-unsaturated compound, the seminal study of 2-alkylenecyclobutanones in a $(PhSe)_2$-catalyzed Baeyer−Villiger oxidation reaction was reported by Yu and co-workers.[8] Very recently, Wu also found tandem reactions of 2-(2-bromobenzylidene)cyclobutanone with 2-alkynylphenol or 2-alkynylbenzenesulfonamides.[9] Among transition-metal-catalyzed activation of C−C bonds in cyclobutanones,[5−9] rhodium has emerged as a valid and frequently used catalyst, and a limited number of examples of using palladium for C−C bond activation in cyclobutanones have been reported.[6e,f,9] As part of our ongoing interest in transition-metal-catalyzed carbon−carbon activation reactions,[10] we herein report C−C bond cleavage of 2-alkylenecyclobutanones via an unusual palladium-catalyzed 1,2-addition of arylboronic acids.

In 1971, Cowan disclosed the synthesis of (*Z*)-1,5-diphenylpent-4-en-1-ones through *E*-to-*Z* isomerization via intramolecular triplet energy transfer (Scheme 1a).[11] In 2004, Warren's group developed a general two-step method to synthesize ketones via alkylation and dephosphinoylation of β-

Scheme 1. Syntheses of (*Z*)-1,5-Diphenylpent-4-en-1-ones



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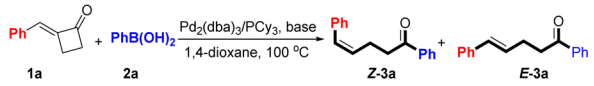
keto diphenylphosphine oxides.[12] The ketones were obtained almost exclusively in the *E* configuration. In only one example was obtained the *Z* form, when (*Z*)-PhCH=CHCH$_2$Br was used as the electrophile (Scheme 1b). To date, there have been no reports of a direct and effective approach to (*Z*)-1,5-diphenylpent-4-en-1-ones in one step. (*Z*)-Alkenes are highly valuable and abundant feedstocks for bioactive molecules, flavors, and natural products,[13] and therefore, an efficient and facile method to obtain these thermodynamically less stable (*Z*)-alkenes would be highly desirable. Herein we describe a Pd-catalyzed ring opening of 2-alkylenecyclobutanones with arylboronic acids leading to (*Z*)-1,5-diphenylpent-4-en-1-ones in good to excellent yields with high stereoselectivity and wide substrate scope (Scheme 1c).

We commenced our study by using (*E*)-2-benzylidenecyclobutanone (**1a**) and phenylboronic acid (**2a**) as model substrates for optimization of the reaction. The initial attempt was performed in the presence of Pd$_2$(dba)$_3$ (5 mol %) and tricyclohexylphosphine (10 mol %) in 1,4-dioxane at 100 °C using KOAc as the base (Table 1, entry 1). A 74% yield of 1,5-diphenylpent-4-en-1-one (**3a**) was obtained as a mixture of (*E*)-**3a** and (*Z*)-**3a**. Although the product **3a** was obtained in 63% yield when the reaction was performed in the absence of base, both the conversion of the starting material and the *Z*/*E* selectivity decreased (Table 1, entry 2). When the model reaction was performed in the absence of ligand, no product **3a** was detected (Table 1, entry 3). In view of the importance of the ligand, we attempted to change the ligand to enhance the reactivity and selectivity. Disappointingly, only marginal inprovements were gained when other ligands, such as dba, P(*t*-Bu)$_3$, PPh$_3$, DPPE, Xantphos, Ruphos, X-phos, and BINAP, were used in place of PCy$_3$ (see Table S1 for details). Subsequently, the model reaction was submitted to various bases to examine the effect of the bases (Table S2, entries 1−13). Strong inorganic bases such as KOH and Cs$_2$CO$_3$ improved the *Z*/*E* selectivity but gave the product **3a** in much lower yields (Table 1, entries 4 and 5). To our delight, both the selectivity and the yield were significantly increased when K$_2$CO$_3$ was employed as the base and the reaction time was 22 h (Table 1, entry 8), leading to compound **3a** in 95% yield with a *Z*/*E* selectivity of 20:1. The reason for the preference for the thermodynamically less stable (*Z*)-alkene still remained unclear. We also screened the palladium catalysts and it turned out that Pd$_2$(dba)$_3$ was the optimal one (Table S2, entries 14−18).

Table 1. Screening of Conditions[a]



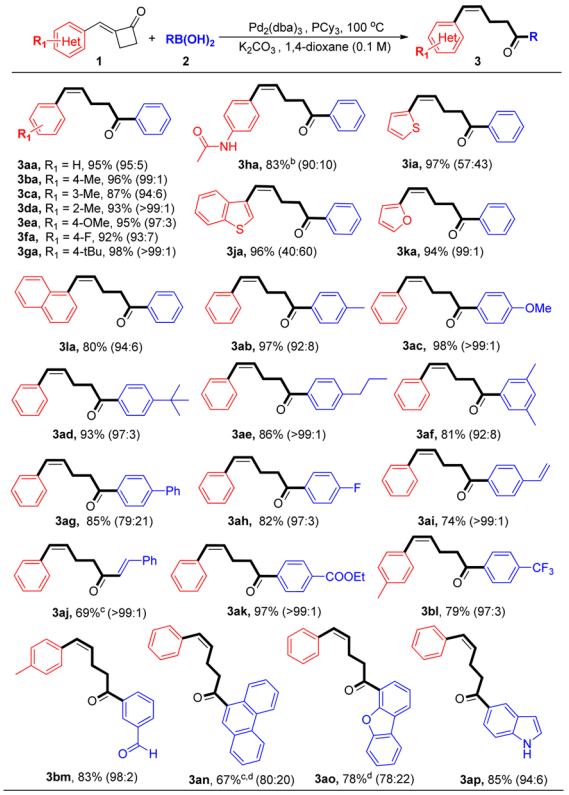
entry	catalyst	base	ligand	yield (%)[b]	*Z*:*E*[c]
1	Pd$_2$(dba)$_3$	KOAc	PCy$_3$	74	2.23:1
2	Pd$_2$(dba)$_3$	–	PCy$_3$	63	1.19:1
3	Pd$_2$(dba)$_3$	KOAc	–	N.D.	–
4	Pd$_2$(dba)$_3$	KOH	PCy$_3$	28	8.36:1
5	Pd$_2$(dba)$_3$	Cs$_2$CO$_3$	PCy$_3$	32	>30:1
6	Pd$_2$(dba)$_3$	Na$_2$CO$_3$	PCy$_3$	98	1.29:1
7	Pd$_2$(dba)$_3$	K$_2$CO$_3$	PCy$_3$	98 (93[d])	8.2:1
8[e]	Pd$_2$(dba)$_3$	K$_2$CO$_3$	PCy$_3$	>99 (95[d])	20:1

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Pd catalyst (5 mol %), base (1 equiv), and PCy$_3$ (10 mol %) under N$_2$ at 100 °C for 18 h. [b]GC yields. [c]Detected by GC. [d]Isolated yield. [e]22 h.

With the optimized reaction conditions in hand, the scope of this Pd-catalyzed ring opening of 2-alkylenecyclobutanones with arylboronic acids was assessed (Scheme 2). A number of functionalized 2-alkylenecyclobutanone derivatives were inspected initially. Interestingly, *ortho*-, *meta*-, and *para*-substituted groups on the aromatic rings of the 2-alkylenecyclobutanones had no influence on the selectivity and gave the desired products **3ba**−**da** in excellent yields. Moreover, electronic effects of the substituents on the aromatic rings of the 2-alkylenecyclobutanones had no significant influence on the selectivity, and the corresponding products were obtained in good yields (**3ea**−**ha**). Heteroaromatic cyclobutanones such as **1i**−**k** were also good candidates in this transformation, rendering the products **3ia**−**ka** in 97%, 96% and 94% yield, respectively. Compared to 2-(furan-2-ylmethylene)cyclobutanone (**1k**), lower *Z*/*E* selectivities of the products (**3ia** and **3ja**) were observed when a thiophene group was installed in the 2-alkylenecyclobutanone. When sterically demanding (*E*)-2-(naphthalen-2-ylmethylene)cyclobutanone (**1l**) was employed under the standard conditions, the ring-opening product **3la** was obtained in 79% yield with a *Z*/*E* selectivity of 94:6.

Next we focused on the scope of arylboronic acids. To our delight, a variety of arylboronic acid derivatives having different

Scheme 2. Substrate Scope



[a]Unless otherwise noted, the reactions were run with **1** (0.2 mmol), **2** (0.3 mmol), Pd$_2$(dba)$_3$ (5 mol %), K$_2$CO$_3$ (0.2 mmol), and PCy$_3$ (10 mol %) under N$_2$ at 100 °C for 22 h. The values in parentheses are the *Z*:*E* ratios detected by ^{1}H NMR spectroscopy. [b]The reaction was performed with 0.1 mmol of **1**. [c]2 equiv of **2** was used. [d]The reaction time was 24 h.

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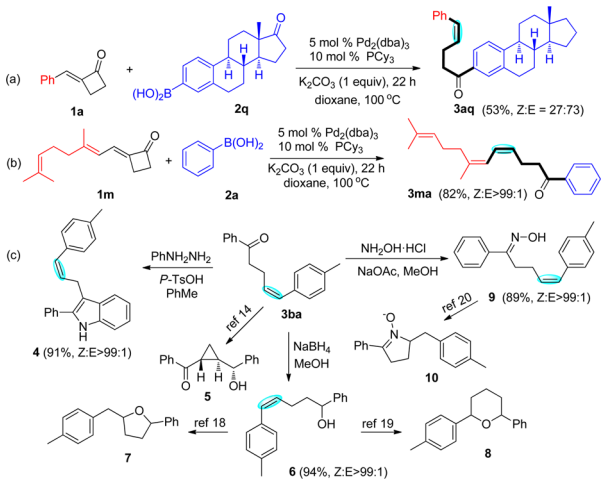
electronic properties were well-tolerated, giving the desired products in good to excellent yields with good Z/E selectivities (**3ab**–**ah**). Moreover, boronic acid derivatives bearing vinyl groups, such as **2i** and **2j**, were very compatible with this transformation as well, delivering the corresponding products **3ai** and **3aj** in good yields with high Z/E selectivities of up to >99:1. When the reactions were performed with larger arenes, such as **2n** and **2o**, the corresponding products **3an** and **3ao** were obtained with a slightly lower selectivity for the Z configuration in good yields as a result of steric hindrance. (1*H*-indol-4-yl)boronic acid (**2p**) was also amenable to this transformation, generating an 85% yield of **3ap** with a Z/E selectivity of 94:6. Notably, the Z/E selectivity of the product (**3aa**) was preserved after several weeks of storage at room temperature. Moreover, when current protocol was scaled up 5 times, the γ,δ-unsaturated ketone **3ba** was reduced without affecting either the yield or the selectivity.

The utility of this method is illustrated by its application to decoration of natural products. Estrone boronic acid **2q** was applicable to the transformation and gave estrone derivative **3aq** in moderate yield (Scheme 3a). Moreover, 2-alkylenecyclobutanone **1m**, prepared from geranialdehyde and cyclobutanone, delivered the product **3ma** in 82% yield (Scheme 3b). Some other conversions of the (*Z*)-1,5-diphenylpent-4-en-1-ones were also performed (Scheme 3c). 2,3-Bis-substituted unprotected indole **4** was obtained via Fischer indole synthesis of **3ba** with phenylhydrazine. Asymmetric cyclopropane (1*R*,2*R*,1′*R*)-**5**, which appears in a range of natural products and medicinally active molecules, could be obtained from **3ba** on the basis of previous work.[14] Cyclic ethers such as tetrahydropyrans and tetrahydrofurans are prevalent scaffolds in a great variety of natural products[15] and bioactive compounds,[16] and they are also widely used in cosmetic formulations and flavors.[17] Cyclic ethers **7**[18] and **8**[19] were readily obtained via intramolecular hydroalkoxylation of olefins from unsaturated alcohol **6**, the reduction product of compound **3ba**. Cyclic nitrones **10**[20] could also be synthesized via a two-step transformation initiating from **3ba**. When the reaction was extended to **11** and **12**, no corresponding desired products were obtained (eq 1), suggesting that the strain of the four-membered ring is requisite for this ring-opening reaction.

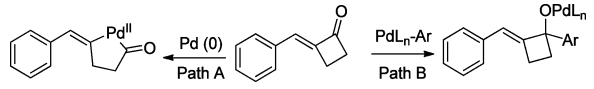
Subsequently, we turned our attention to the reaction mechanism. Both 1,2-addition to the 2-alkylenecyclobutanone with arylpalladium and Pd(0) insertion into the cyclobutanone[21] could release the strain of the four-membered ring (Scheme 4). To determine which pathway is the inceptive step, deuterium experiments were performed. When the reaction was performed in 3 equiv of D_2O without phenylboronic acid (**2a**), 60% deuteration was detected at the sp^3 carbon adjacent to the carbonyl group of **1a** (eq 2). However, when **1a** and **2a** were reacted in 3 equiv of D_2O under the standard conditions, deuterium was incorporated at both the α- and γ-positions of the produced (*Z*)-1,5-diphenylpent-4-en-1-one (eq 3). Furthermore, we were able to detect the homocoupling product of the excess arylboronic acid by GC–MS, implying the existence of arylpalladium in this transformation. The homocoupling product along with the deuterium experiments verified that path B in Scheme 4 was a possible pathway.

On the basis of all of the experimental results mentioned above, a plausible mechanism is described in Scheme 5. The catalytic cycle involves (1) 1,2-addition of arylpalladium species **I** to 2-alkylenecyclobutanone **1**, leading to Pd(II) cyclobutanolate intermediate **II**; (2) β-carbon elimination from intermediate **II**[22] via C_{sp^3}–C_{sp^2} bond cleavage, generating vinylpalladium species **III**; and (3) protonolysis and transmetalation with $ArB(OH)_2$, producing the corresponding ring-opening product **3** and arylpalladium species **I**. Enol–keto tautomerism of 2-alkylenecyclobutanone **1** could occur under

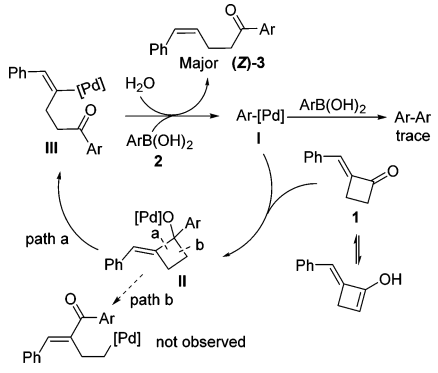
Scheme 3. Synthetic Applications and Transformations



Scheme 4. Two Possible Pathways To Release the Strain in 1a



Scheme 5. Plausible Reaction Mechanism



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basic conditions, which could explain the results of deuterium experiments in eqs 2 and 3. In addition, probably because of the exocyclic C=C bond and inherent ring strain of the carbonyl group, 1,2-addition of arylpalladium species **I** to 2-alkylenecyclobutanone **1** is more preferable than the 1,4-addition. The desired γ,δ-unsaturated ketone products are obtained with favorable *Z* selectivity, possibly on account of the *E* configuration of the 2-alkylenecyclobutanones.

In conclusion, we have disclosed a new method for the *Z*-selective synthesis of γ,δ-unsaturated ketones via Pd-catalyzed ring opening of 2-alkylenecyclobutanones with arylboronic acids. The γ,δ-unsaturated ketones were obtained in good to high yields with high *Z* stereoselectivity and a broad spectrum of functional group tolerance. Further mechanistic studies and synthetic applications of this novel protocol are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01816.

General experimental procedures and spectroscopic data for the corresponding products (PDF)

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Notes

The authors declare no competing financial interest.

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