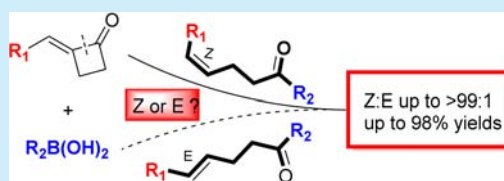


Z-Selective Synthesis of γ,δ -Unsaturated Ketones via Pd-Catalyzed Ring Opening of 2-Alkylencyclobutanones with Arylboronic AcidsYao Zhou,[†] Changqing Rao,[†] and Qiuling Song^{*,†,‡}[†]Institute of Next Generation Matter Transformation, College of Chemical Engineering, College of Materials Science & Engineering at Huaqiao University, 668 Jimei Boulevard, Xiamen, Fujian 361021, P. R. China[‡]National Laboratory for Molecular Sciences, Institute of Chemistry, Beijing 100190, P. R. China

Supporting Information

ABSTRACT: Pd-catalyzed 1,2-addition (instead of 1,4-addition) of arylboronic acids to 2-alkylencyclobutanones 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,

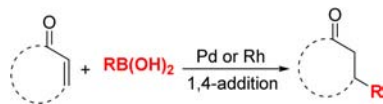


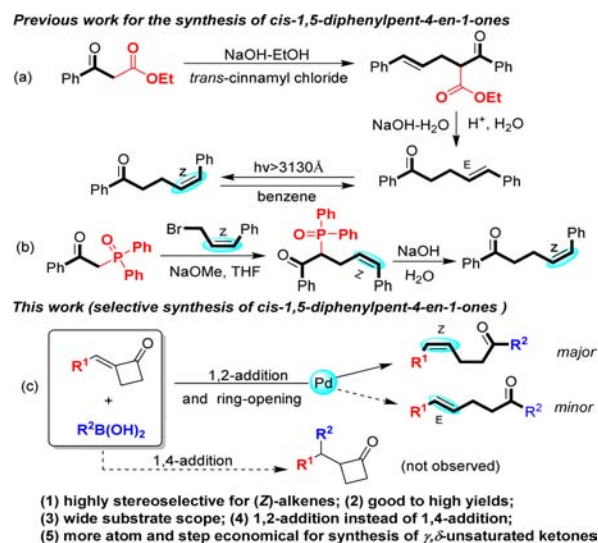
Figure 1. Transition-metal-catalyzed 1,4-addition of arylboronic acids to α,β -unsaturated compounds.

there are very few publications⁴ 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-alkylencyclobutanones 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 cyclo-

butanones,^{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-alkylencyclobutanones 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



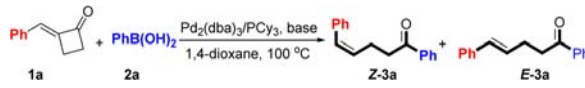
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keto diphenylphosphine oxides.¹² The ketones were obtained almost exclusively in the *E* configuration. In only one example was obtained the *Z* form, when (Z)-PhCH=CHCH₂Br was used as the electrophile (Scheme 1b). To date, there have been no reports 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 Pd₂(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-

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

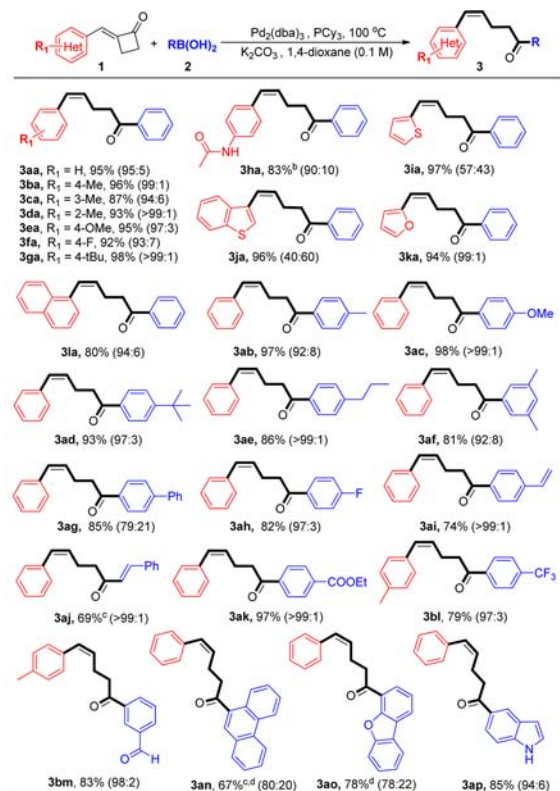
^aReaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Pd catalyst (5 mol %), base (1 equiv), and PCy₃ (10 mol %) under N₂ at 100 °C for 18 h. ^bGC yields. ^cDetected by GC. ^dIsolated yield. ^e22 h.

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 improvements were gained when other ligands, such as dba, P(*t*-Bu)₃, PPh₃, DPPE, Xantphos, Ruphos, X-phos, and BINAP, were used in place of PCy₃ (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 Cs₂CO₃ 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 K₂CO₃ 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 Pd₂(dba)₃ was the optimal one (Table S2, entries 14–18).

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

Scheme 2. Substrate Scope



^aUnless otherwise noted, the reactions were run with **1** (0.2 mmol), **2** (0.3 mmol), Pd₂(dba)₃ (5 mol %), K₂CO₃ (0.2 mmol), and PCy₃ (10 mol %) under N₂ at 100 °C for 22 h. The values in parentheses are the Z:E ratios detected by ¹H NMR spectroscopy. ^bThe reaction was performed with 0.1 mmol of **1**. ^c2 equiv of **2** was used. ^dThe reaction time was 24 h.

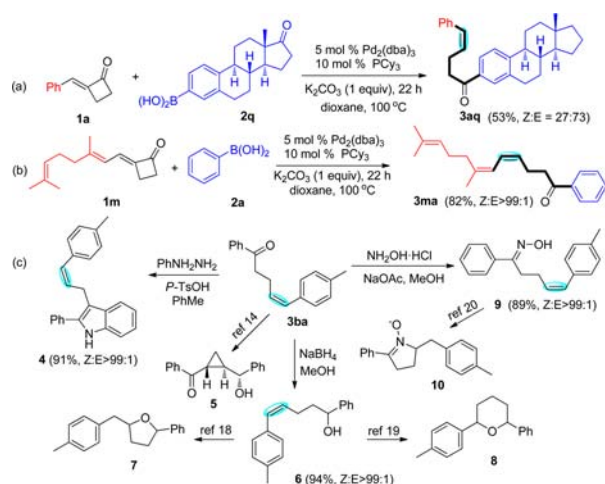
functionalized 2-alkylenecyclobutanone derivatives were inspected initially. Interestingly, *ortho*-, *meta*-, and *para*-substituted groups on the aromatic rings of the 2-alkylenecyclobutanones had no influence on the selectivity and gave the desired products **3ba–da** in excellent yields. Moreover, 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

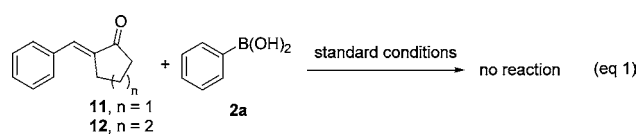
electronic properties were well-tolerated, giving the desired products in good to excellent yields with good *Z/E* selectivities (3ab–ah). Moreover, boronic acid derivatives bearing vinyl groups, such as 2i and 2j, were very compatible with this transformation as well, delivering the corresponding products 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 products¹⁵ and bioactive compounds,¹⁶ and they are also widely used in cosmetic formulations and flavors.¹⁷ Cyclic ethers 7¹⁸ and 8¹⁹ were readily obtained via intramolecular hydroalkoxylation of olefins from unsaturated alcohol 6, the reduction product of compound 3ba. Cyclic nitrones 10²⁰ 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.

Scheme 3. Synthetic Applications and Transformations

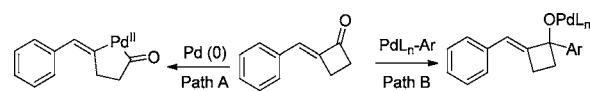


Subsequently, we turned our attention to the reaction mechanism. Both 1,2-addition to the 2-alkylenecyclobutanone

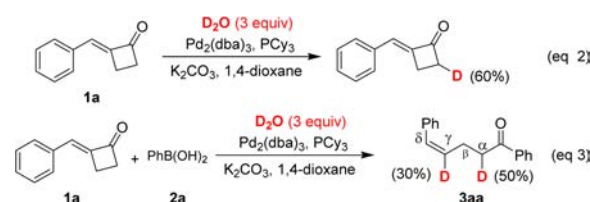


with arylpalladium and Pd(0) insertion into the cyclobutanone²¹ could release the strain of the four-membered ring (Scheme 4). To determine which pathway is the inceptive

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



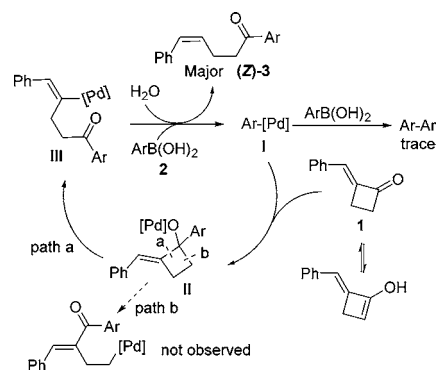
step, deuterium experiments were performed. When the reaction was performed in 3 equiv of D₂O without phenylboronic acid (2a), 60% deuteration was detected at the sp³ carbon adjacent to the carbonyl group of 1a (eq 2). However,



when 1a and 2a were reacted in 3 equiv of D₂O 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

Scheme 5. Plausible Reaction Mechanism



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 II²² 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

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 **1** 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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