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Stereoselective Access to Alkylidenecyclobutanes through γ-Selective Cross-Coupling Strategies

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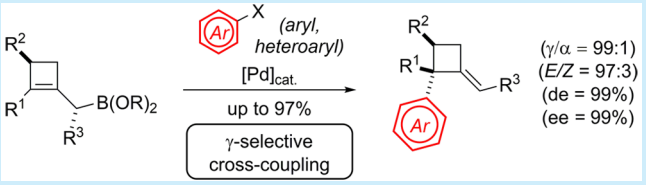
Supporting Information

ABSTRACT: Alkylidenecyclobutanes (ACBs) containing all-carbon quaternary stereocenters were simply and efficiently synthesized by combining boron-homologation and γ-selective cross-coupling strategies. This unique sequence led to excellent regio- and diastereoselectivities in the generation of targeted four-membered rings with up to 99% enantiomeric excess using chiral substrates. In addition to the original synthesis of ACBs, the first asymmetric catalytic formation of quaternary stereocenters based on γ-selective cross-coupling reactions is finally shown.



While the Suzuki−Miyaura cross-coupling is already a well-established method in pharmaceutical sciences,[1] the use of allylic boronic esters therein still remains scarcely described. Pioneering studies by Szabó and Miyaura[2] demonstrated that the reaction of allylboronic ester at the γ-position can be triggered by employing an appropriate palladium precatalyst. Since then, however, this interesting transformation was only examined by a few groups.

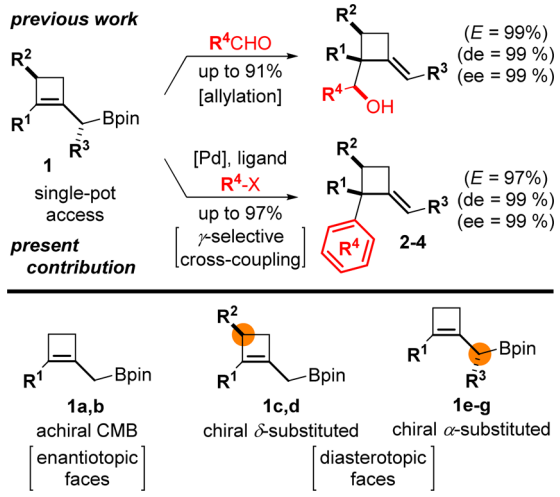
Recently, the groups of Morken, Buchwald, and Organ independently illustrated highly regioselective γ-cross-coupling reactions,[3] while Aggarwal and Crudden described very good stereoselectivities of these transformations when employing substituted allyl- and propargylboronic esters.[4]

We envisioned that combining such a powerful tool with an in situ generation of cyclobutenylmethylboronic esters (CMBs) would result in a straightforward formation of alkylidenecyclobutanes (ACBs). These small architectures have a rather limited accessibility but are encountered in many natural products and biologically active substances.[5] Moreover, the relatively strained nature of ACBs allows for a variety of further transformations.[6] Recently, merging boron homologation of cyclobutenyl metal species and allylboration strategies in a one-pot sequence, we have described a very efficient approach toward stereodefined ACBs.[7]

In this communication, we present a unique combination of boron homologation with a highly γ-selective Suzuki−Miyaura cross-coupling for the diastereo- and enantioselective construction of ACBs containing a quaternary stereocenter (Scheme 1) starting from achiral CMBs (**1a,b**) and chiral α- or δ-substituted CMBs (**1c−g**).

Negishi π-cyclization[8] of readily available 4-bromobutynes followed by a Matteson homologation led to CMBs **1**. Morken's conditions were initially employed for optimizing our reaction conditions when 4-iodotoluene was used as the cross-coupling partner.[3d] After a short screening, reactions performed in THF with KOH introduced from a stock solution proved to give the best results (Table 1, entry 3) in only 1 h.

Scheme 1. Approach to ACBs Containing a Quaternary Stereocenter through γ-Selective Cross-Coupling



Similar conversions were observed when replacing THF by MTBE or ethyl acetate (Table 1, entries 8 and 9), nonetheless requiring 14 h to reach completion. Attempts to replace potassium hydroxide as the base only resulted in decreasing either conversion or regioselectivity levels (Table 1, entries 4 and 5).

With optimal conditions in hand, a set of various aryl halides were engaged in the presence of **1a,b** (Scheme 2). With an exception for aldehydes (that would lead to a fast allylboration) and alcohols, a wide range of functional groups were tolerated.

Not only aryl iodides or bromides but also aryl chlorides were successfully engaged, although with lower yield (**2f**: 57% compared to 91% for the corresponding aryl bromide). The

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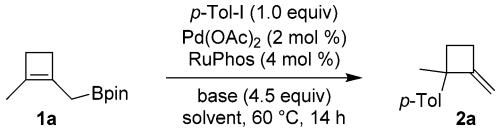
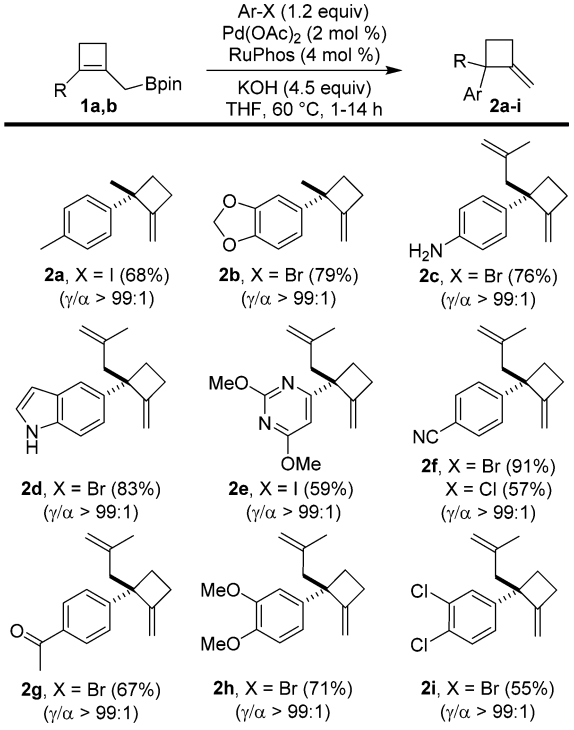
Table 1. Survey of Base and Solvent in γ-Cross-Coupling Reactions



entry	solvent	base	conv (%)[a]	γ/α[a]
1	THF	KOH	72	>99:1
2	THF/H_2O (1:1)	KOH	80	>99:1
3	**THF**	**$KOH_{(aq)}$**[b]	**>99**[c]	**>99:1**
4	THF	TBAF	74	86:14
5	THF	CsF	65	>99:1
6	dioxane	$KOH_{(aq)}$[b]	91	>99:1
7	acetonitrile	KOH	94	72:28
8	MTBE	KOH	>99	>99:1
9	ethyl acetate	KOH	>99	>99:1

[a]Determined by GC. [b]8.0 M solution. [c]After 1 h.

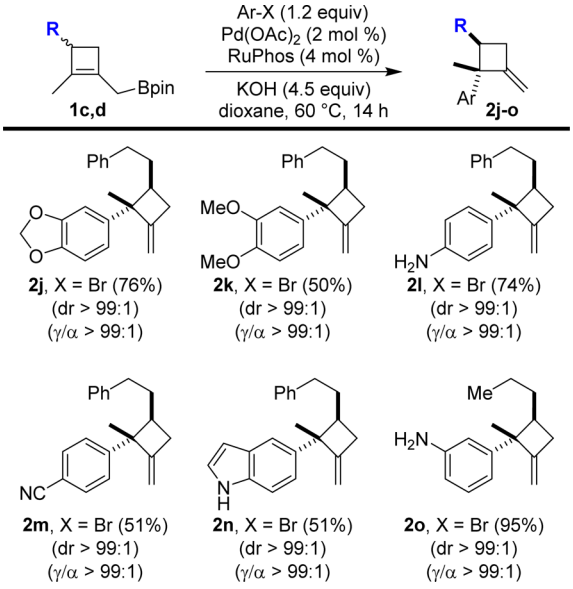
Scheme 2. Electrophilic Scope of γ-Selective Cross-Coupling



lower reaction rate of aryl chloride was exploited in the chemoselective synthesis of **2i**, accounting for only negligible side reactions. Electron-donating (**2a,b** and **2h**) as well as electron-withdrawing groups (**2f,g**) led to good yields up to 91%, while heterocyclic products were isolated in up to 83% yield (**2d** and **2e**). Interestingly, free amines led to a complete conversion of the starting material, giving the expected cross-coupled compound in 76% yield. In all cases the γ-selective cross-coupling products were exclusively detected, probably enhanced by a strain release when shifting the π-system outside of the ring structure.[9]

Having established an efficient route toward alkylidenecyclobutanes, we took a step further by employing chiral cyclobutenylmethylboronic esters (**1c,d**) (Scheme 3) possessing a lateral chain R. Performing reactions in dioxane showed slightly better diastereoselectivities in this case, and aromatic- as

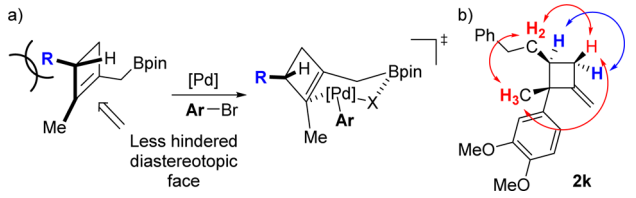
Scheme 3. γ-Selective Cross-Coupling of Chiral Substrates 1c and 1d



well as heteroaromatic-substituted methylenecyclobutanes **2j–o** were obtained with high yields up to 95% and with a full control over the diastereochemical outcome of the transformation (dr >99:1).

As postulated by Buchwald et al. (Scheme 4), we propose to explain the high diastereoselectivity by a ZT transition state in which the transmetalation step would follow a chair model.[10]

Scheme 4. (a) Proposed ZT Model and (b) Observed NOEs Supporting the Proposed Configuration



In this case, the palladium complex preferably approaches from the less hindered diastereotopic face of the double bond—opposite side of the R chain—leading selectively to the described isomer. The 2D-NMR assignments of **2k** supported the above-mentioned hypothesis, placing the aromatic moiety *anti* to the preinstalled R chain (Scheme 4).

To further expand the scope toward more elaborated structures and to open the possibility of synthesizing enantioenriched ACBs, we chose to study the reactivity of α-chiral boronic esters in γ-selective cross-coupling reactions. First experiments using previously described catalytic systems led to expected compounds but without control over *E*/*Z* ratios (50:50). Screening of diverse conditions showed the best results when PCy_3 or dppb (1,4-bis(diphenylphosphino)-butane) was employed as ligands in the presence of $Pd(OAc)_2$ or $Pd(PPh_3)_2Cl_2$, respectively (Table 2, entries 1 and 12). However, when full conversion was to be observed, other conditions only led to worse *E*/*Z* ratios. In most cases bidentate ligands gave better *E*/*Z* ratios, a trend that could be attributed to a favorable shielding of the pseudoaxial position toward the formation of the *E*-product. Presenting similar stereoselectiv-

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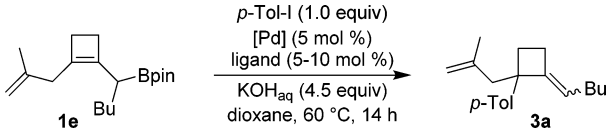
Table 2. Survey of Conditions for Synthesis of Alkylidenecyclobutanes



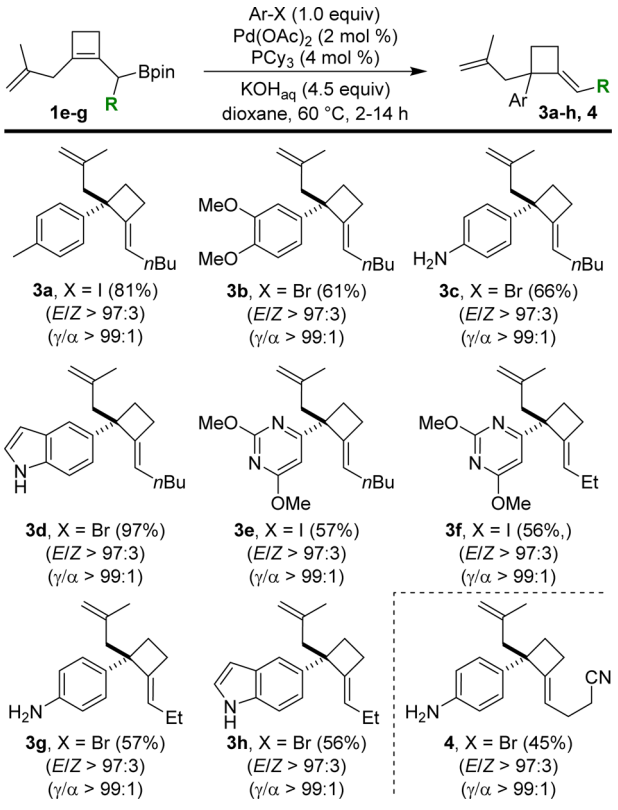
entry	Pd species	ligand[a]	E/Z[b]
1	**$Pd(OAc)_2$**	**PCy_3**	**95:5**
2	$Pd(OAc)_2$	XPhos	87:13
3	$Pd(OAc)_2$	DavePhos	66:34
4	$Pd(OAc)_2$	RuPhos	49:51
5	$Pd(OAc)_2$	Tetraphos-Li	89:11
6	$Pd(OAc)_2$	dppBz	88:12
7	$Pd(OAc)_2$	dppb	92:8
8	$Pd(OAc)_2$	dppp	92:8
9	$Pd(OAc)_2$	PPh_3	50:50
10	$Pd(PPh_3)_2Cl_2$	PCy_3	91:9
11	$Pd(PPh_3)_2Cl_2$	dppp	92:8
12	**$Pd(PPh_3)_2Cl_2$**	**dppb**	**94:6**
13	$Pd(PPh_3)_4$	PCy_3	91:9
14	$[Allyl\text{-}PdCl]_2$	PCy_3	93:7

[a]10 mol % of monodentate, 5 mol % of bidentate ligands. [b]Determined by GC.

ities, the $Pd(OAc)_2/PCy_3$ (Table 2, entry 1) system was preferentially employed for economic reasons.

$Pd(OAc)_2$ was thus chosen as precatalyst, and the transformation was exemplified with a range of coupling partners (Scheme 5). Boronic esters **1e,f** were readily prepared by a double boron homologation in order to introduce α-substituents and subsequently cross-coupled with different halides, achieving overall good to excellent yields (up to 97%). None of the reactions showed α-cross-coupling, and *E*-**3a–h** were obtained in more than 97% of stereochemical purity. In the case of **4**, a 2-cyanoethyl substituent was introduced through the double-homologation sequence, pointing out the functional group tolerance of the transformation. Worthy of note, the starting cyclobutenylmethylboronic ester bearing the 2-cyanoethyl chain was engaged in the γ-cross-coupling after simple filtration of residual salts, avoiding fastidious purification steps and furnishing **4** in 45% yield. 2D NMR experiments on **3f** supported the favored formation of *E*-isomers.

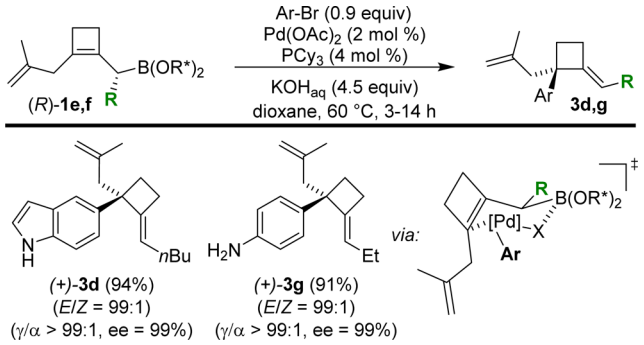
Scheme 5. Synthesis of Alkylidenecyclobutanes from 1e and 1g



Taking advantage of a substituent present at the α-position—that can easily be introduced in a stereoselective way—we took on the challenge of relaying the chiral information from the boronic ester moiety to the quaternary stereocenter.

A preinstalled enantiomerically pure ligand on the boron atom led to enantiomerically enriched cyclobutene derivatives ((*R*)-**1e** and (*R*)-**1f**) via successively diastereoselective and diastereospecific boron-homologation sequences. 5-Bromoindole and 4-bromoaniline were chosen for the γ-selective cross-coupling, and corresponding ACBs were obtained in very good yields up to 94% and with a perfect control of the stereochemistry (99% *E* and 99% ee) (Scheme 6). High stereoselectivities observed in this reaction can be attributed to a sterically favored *pseudo*-equatorial positioning of the α-substituent R in the ZT transition state.

Scheme 6. Diastereoselective Access to Enantioenriched ACBs 3d and 3g



The next step toward enantioenriched ACBs was designed through asymmetric catalysis, employing chiral palladium ligands in the presence of achiral substrates **1b**.

To the best of our knowledge, intermolecular enantioselective formation of a quaternary stereocenter through γ-selective cross-coupling remains unexplored. While TADDOL-$PNMe_2$[11] failed our expectations, the first positive results were observed when employing (*R*)-BINAP as the chiral ligand (er = 64:36) (Table 3, entry 2). Changing the ligand to the JosiPhos series (entries 3–8) could improve the enantiomeric ratio to 81:19 with **L1** at 60 °C. Performing the reaction at room temperature gave the best enantioselectivities (er = 85:15). Adjustments on the ligand structure (**L2–5**) did not lead to any amelioration on the stereoselectivity of the reaction. Finally, methylenecyclobutanes (−)-**2c** and (−)-**2g** were—for the first time—generated from corresponding allylboron species through stereoselective γ-cross-coupling in up to 77% yield and moderate enantiomeric ratios (up to 85:15 er).

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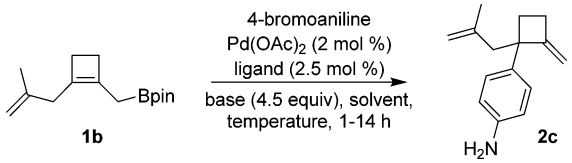
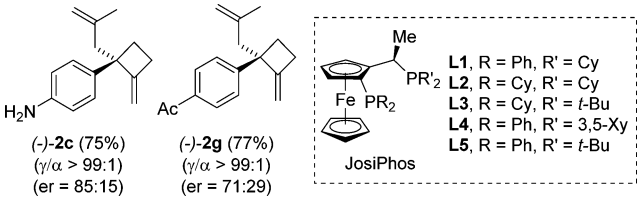
Table 3. Survey of Conditions for Enantioselective Synthesis of MCBs



entry	ligand	base	solvent	temp (°C)	er[a]
1	TADDOL-PNMe$_2$[b]	CsF[c]	THF	60	-[d]
2	(*R*)-BINAP	KOH$_{aq}$	dioxane	60	64:36
3	L1	KOH$_{aq}$	dioxane	60	81:19
4	**L1**	**KOH$_{aq}$**	**dioxane**	**rt**	**85:15**
5	L2	KOH$_{aq}$	dioxane	60	50:50
6	L3	KOH$_{aq}$	dioxane	60	-[d]
7	L4	KOH$_{aq}$	dioxane	60	74:26
8	L5	KOH$_{aq}$	dioxane	60	-[d]

[a]Determined by HPLC utilizing a chiral stationary phase. [b]7 mol %. [c]3.0 equiv. [d]No conversion.



In conclusion, we have reported a new strategy to easily synthesize alkylidenecyclobutanes containing a quaternary stereocenter in very good yields by combining boron-homologation sequences with γ-selective Suzuki–Miyaura cross-coupling reactions. Excellent regio- and diastereocontrol was established in this unique transformation, and the first—yet moderate—enantioselective intermolecular couplings of allylboronic esters were undertaken for the generation of quaternary stereocenter-containing ACBs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01803.

Contains all experimental procedures and characterization (IR, HRMS, and ^{1}H and ^{13}C NMR data) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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