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Boronic acid-mediated ring-opening and Ni-catalyzed arylation of 1-arylcyclopropyl tosylates†

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Herein, we describe a protocol for the ring-opening arylation of 1-arylcyclopropyl tosylates, in which boronic acids promote ring-opening and a Ni catalyst facilitates arylation in high regioselectivity. A number of 2-arylated allyl derivatives are synthesized, which are relevant motifs found in biologically active molecules.

Cyclopropanols are well established synthetic intermediates that serve as three-carbon units for accessing a number of valuable products.[1] A unique cyclopropanol-derived reagent is the cyclopropyl tosylate (Fig. 1a), which is readily accessed from an ester using Kulinkovich chemistry (retrosynthesis arrow), or from the corresponding ketone using Simmons–Smith chemistry.[1] These intermediates are labile at the C–O bond, and can be activated with a Brønsted or Lewis acid in the presence of a nucleophile (Nu) to give the ring-opened, allyl product. An early example of this type of ring-opening functionalization is the solvolysis of cyclopropyl tosylates with acetic acid reported by DePuy and coworkers in 1965, which yields the allyl acetate.[2,3] Since then, there have been a number of reports employing cyclopropyl tosylates,[1,4,5] including studies of the mechanism of ring-opening,[6] and metal-catalyzed substitution reactions.[7] A different use of the ring-opening reactivity of cyclopropyl tosylates was reported by Kulinkovich and coworkers, who discovered that these intermediates can be converted to the 2-substituted allyl bromide in the presence of $MgBr_2$.[8] Other Lewis acids like $MgCl_2$, $TiCl_4$, and $AlCl_3$ can also achieve ring-opening to generate the corresponding allyl halide.[8] More recently, Cha and coworkers found that 1-alkenylcyclopropyl tosylates are amenable to ring-opening functionalization with nucleophiles such as amines in the presence of catalytic Pd.[9] However, the scope of this transformation is limited to 1-alkenyl-substituted cyclopropyl tosylates.

Herein, we report the ring-opening functionalization of 1-arylcyclopropyl tosylates. This process was discovered while we were exploring related chemistry for the use of cyclopropanols as C–O electrophiles in a Ni-catalyzed Negishi cross-coupling.[10] For this reaction, the ring-opening is mediated by arylboronic acid ($Ar^2B(OH)_2$), which generates the allyl cation (Fig. 1b). The allyl cation then undergoes Ni-catalyzed cross-coupling with the arylboronic acid, giving the arylated product.[11] Together, this reactivity is a simple and straightforward way of accessing allyl derivatives bearing a variety of aryl substituents at the 2-position, which are valuable synthetic intermediates.[12,13] While other methods for the metal-catalyzed arylation of 2-aryl-substituted allyl electrophiles exist,[14] rapid access to allyl coupling partners is not always trivial, since they are often synthesized in multiple steps from esters, ketones, or other oxidized derivatives. Since cyclopropyl tosylates are directly synthesized from esters or ketones,[1] our strategy offers complementary access to 2-substituted allyl products.

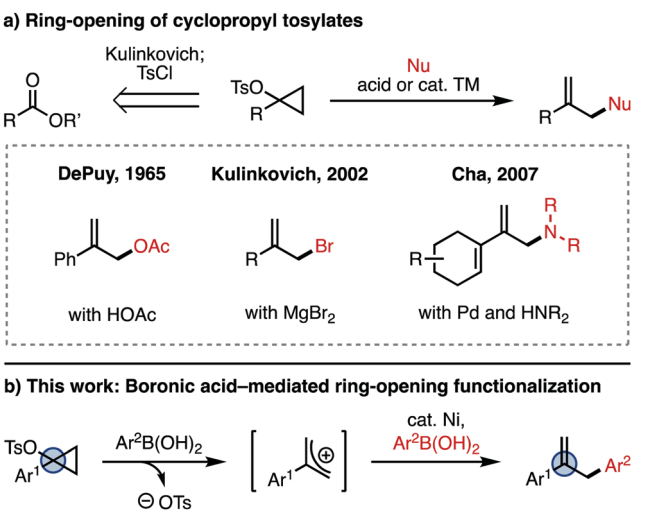

Fig. 1 The 2-substituted allyl motif and synthetic approaches for its preparation.

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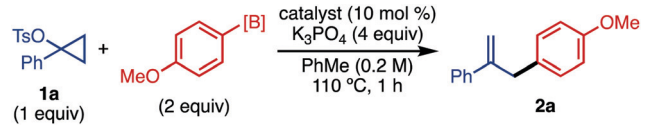
Table 1 Optimization of the reaction[a]



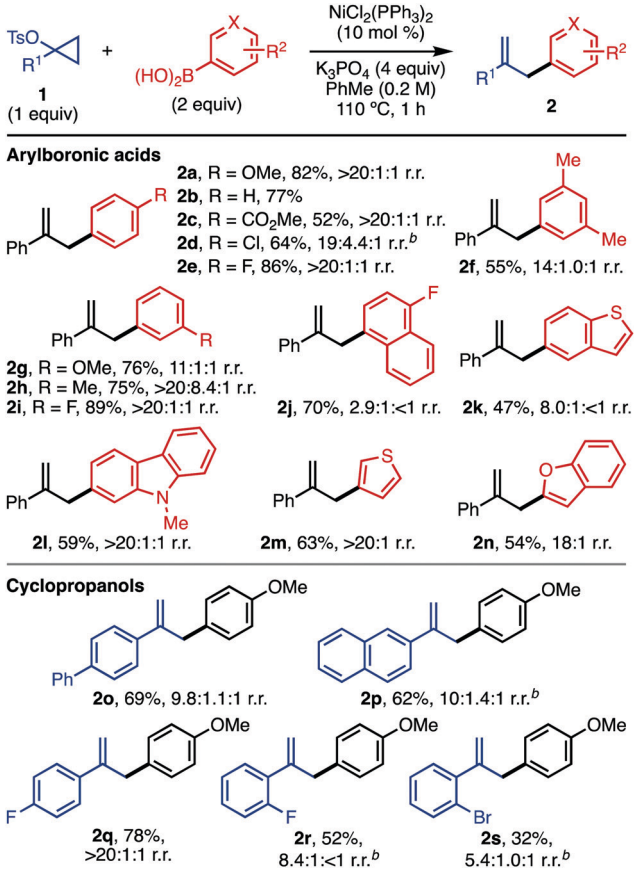
Entry	Catalyst	[B]	Yield 2a[b] (%)	*para* : *ortho*
1	$PdCl_2(PPh_3)_2$	$B(OH)_2$	22	—
2	$NiCl_2(PPh_3)_2$	$B(OH)_2$	96 (82)[c]	>20 : 1
3	$NiCl_2(PCy_3)_2$	$B(OH)_2$	82	>20 : 1
4	None	$B(OH)_2$	92	8.9 : 1
5	None	$(ArBO)_3$[d]	33	7.6 : 1
6	None	Bnep	<5	—
7	None	BF_3K	<5	—

[a] Reactions performed on 0.10 mmol scale. See ESI for full details. [b] GC-MS yield using *n*-dodecane as internal standard. [c] Isolated yield. [d] 0.67 equiv. nep = neopentylglycol.

Since some 1-substituted cyclopropyl tosylates can be ring-opened and functionalized using catalytic Pd,[9] we began our investigation by exploring Pd catalysis to facilitate this reaction (Table 1). Using 1-phenylcyclopropyl tosylate (**1a**), 4-methoxyphenylboronic acid (2 equiv.), $PdCl_2(PPh_3)_2$ (10 mol%), and K_3PO_4 (4 equiv.), the arylated product (**2a**) was obtained in a modest 22% yield (entry 1). Switching the catalyst to $NiCl_2(PPh_3)_2$ delivered the product in excellent 96% yield (entry 2). Other Ni catalysts like $NiCl_2(PCy_3)_2$ were also competent in this reaction, though performed slightly less efficiently (entry 3) (for other catalysts, see the ESI†). Intriguingly, the reaction was still efficient in the absence of catalyst, giving the product in 92% yield, though with imperfect selectivity for substitution at the *ipso* position (entry 4). Arylboronic acids are known to participate in S_EAr chemistry with imperfect regioselectivity,[15] suggesting that a similar process may be occurring under these catalyst-free conditions. Under catalyst-free conditions, we found that the aryl boroxine (entry 5) was less efficient than the arylboronic acid, affording product **2a** in 33% yield. Arylboronic esters such as ArBnep (entry 6), as well as potassium aryl trifluoroborate salts (entry 7), were ineffective in this transformation. It should also be noted that cyclopropyl tosylate (**1a**) is stable at 110 °C after 1 h, both in the absence and presence of a Ni catalyst. In the presence of arylboronic acid at 110 °C, full conversion of this substrate is achieved after 1 h.

With these optimized conditions, we next explored the scope of this reaction (Table 2). Since some arylation is possible in the absence of a Ni catalyst (Table 1, entry 4), several entries gave mixtures of regioisomers. However, reactions in the presence of Ni are generally more regioselective than those carried out without catalyst. For the structures drawn, the substitution reflects the regioisomer obtained after *ipso* substitution of the boronic acid. The conditions are compatible with a number of arylboronic acids, including electron-rich (**2a**), electron-neutral (**2b**, **2f**), and electron-deficient (**2c–2e**, **2j**) substrates. Arylboronic acids with strong *para* electron-withdrawing groups (4-acetylphenyl, 4-cyanophenyl) gave <20% yield of the desired product. A number of *meta*-substituted arylboronic acids were also viable (**2f–2i**). For substrates with labile halogens like

Table 2 Scope of the reaction[a]



[a] Reactions performed on 0.20–0.40 mmol scale. Yields are isolated and the combination of regioisomers. Regioisomer ratios were determined by GC-MS analysis of the crude reaction mixture. The structures drawn reflect the regioisomer obtained after *ipso* substitution of the arylboronic acid. [b] Reaction performed without $NiCl_2(PPh_3)_2$; for yields with and without Ni, see ESI.

chlorides (**2d**), the reaction performed better in the absence of a Ni catalyst; in the presence of Ni, products resulting from halide functionalization (reduction, arylation) were detected by GC-MS. The compatibility of electron-withdrawing groups (**2c**) is complementary to related Friedel–Crafts chemistry of activated cyclopropanols using electron-rich arenes.[11]

For this Ni-catalyzed process, the regioselectivity with respect to arylboronic acid functionalization with both electron-donating and -withdrawing groups is dictated by the position of the boronic acid and not the inherent reactivity expected for S_EAr chemistry (*e.g.* *ortho* and *para* for **2f–2i**; *meta* for **2c**). Employing electron-deficient substrates (*e.g.* **2c**) in the absence of catalytic Ni gave low yields (<10%). A number of electron-rich heteroaromatic boronic acids are also compatible with the chemistry (**2k–2n**). For heteroaromatic boronic acids with rings that could participate in Friedel–Crafts chemistry (*e.g.*, **2k**, **2l**), substitution was only detected on the boronic acid-containing ring.

A number of 1-arylcyclopropyl tosylates are compatible with the chemistry, including electron-neutral (**2o**, **2p**) and electron-deficient (**2q–2s**) substrates.[16] *ortho*-Substituted 1-arylcyclopropyl

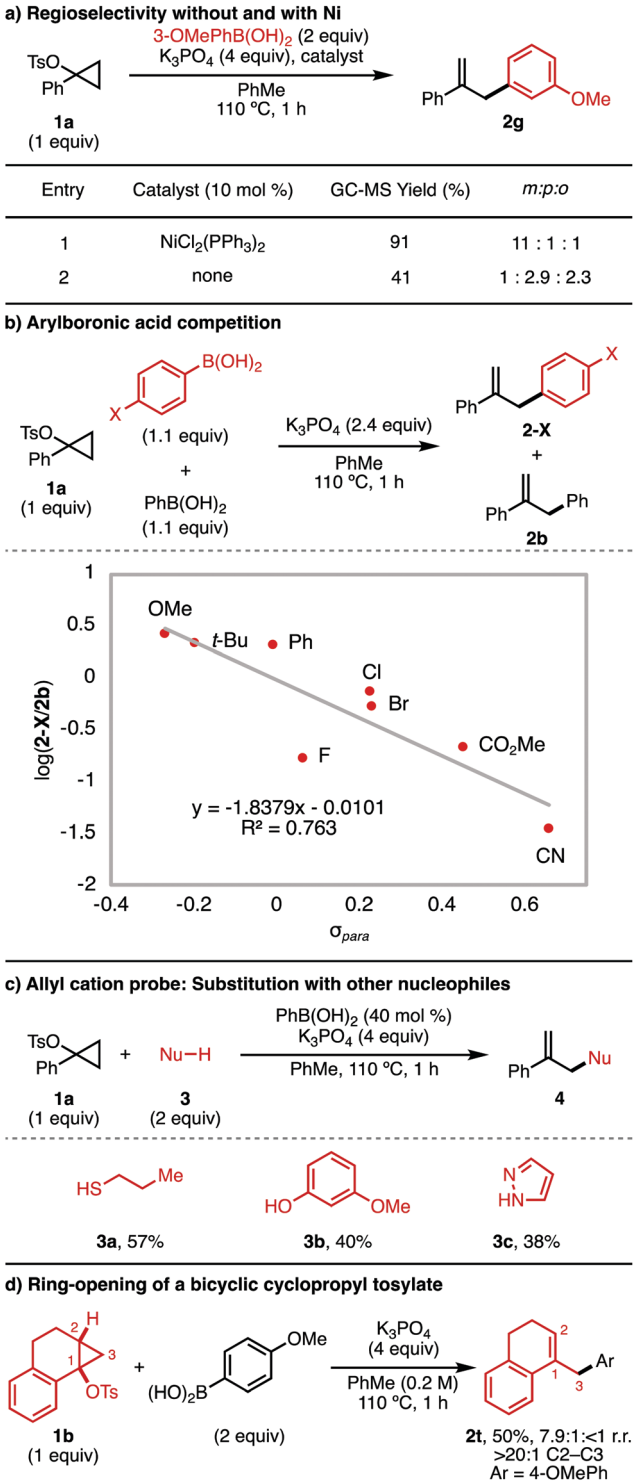


Fig. 2 Mechanistic experiments.

tosylates (**2r**, **2s**) afforded the desired product in higher yield in the absence of Ni catalyst (for yields and selectivity in the presence of catalytic Ni, see the ESI†). Cyclopropyl tosylates without 1-aryl substituents gave very little conversion under standard conditions, both in the presence and absence of $NiCl_2(PPh_3)_2$. The low yields for some substrates may be due to decomposition of the cyclopropyl tosylate (**1**) at the reaction temperature (110 °C).

Next, mechanistic experiments were performed to better understand (i) the mechanism of the background Ni-free arylation reaction and (ii) the role of the boronic acid in this background process (Fig. 2). First, a head-to-head comparison was made for the reaction of 3-methoxyphenylboronic acid with and without a Ni catalyst (Fig. 2a). In the presence of 10 mol% $NiCl_2(PPh_3)_2$ (entry 1), product **2g** was obtained in 91% GC-MS yield and 11 : 1 : 1 selectivity for functionalization at the *ipso* position. The predominant formation of this regioisomer is consistent with transmetallation of 3-methoxyphenylboronic acid to Ni. Alternatively, in the absence of Ni (entry 2), the product was obtained in only 41% GC-MS yield, with the major regioisomers instead being those resulting from substitution *para* and *ortho* to the electron-donating methoxy substituent. This result is consistent with an S_EAr mechanism for the Ni-free background process. It also suggests that the arylboronic acid is likely responsible for cyclopropane ring-opening to generate the allyl cation intermediate.

To better understand the Ni-free background reaction, competition experiments were performed between 4-substituted arylboronic acids (1.1 equiv.) and phenylboronic acid (1.1 equiv.). The product distribution between the 4-substituted aryl product (**2-X**) and the phenyl product (**2b**) was evaluated (Fig. 2b). When the log(**2-X**/**2b**) was taken and plotted according to σ_{para} of **2-X**, a negative linear relationship was obtained, consistent with build-up of positive charge in the product-determining step. This finding is consistent with an S_EAr mechanism to yield the arylated product in the absence of Ni catalyst. It should be noted that in this experiment any electronic effects which promote boronic acid–mediated ring-opening of **1a** cannot be excluded.

To further confirm the role of the arylboronic acid in ring-opening of the cyclopropyl tosylate, we investigated whether other nucleophiles could be used to trap an allyl cation generated from **1a** using $PhB(OH)_2$ (Fig. 2c). In the presence of substoichiometric amounts of phenylboronic acid (40 mol%) and K_3PO_4, 1-phenylcyclopropyl tosylate **1a** underwent trapping with a range of nucleophiles (**3**) to yield the allyl product, **4**. Viable nucleophiles include thiol (**3a**), phenol (**3b**),[17] and pyrazole (**3c**).[18]

Finally, we examined whether the arylboronic acid-mediated cyclopropyl tosylate ring-opening was consistent with known regio- and stereoselectivity for acid-catalyzed ring-openings of cyclopropanol derivatives. Thus, a bicyclic cyclopropyl tosylate (**1b**) was exposed to the reaction conditions in the absence of Ni (Fig. 2d). The product obtained (**2t**) was that resulting from C2–C3 cleavage, with retention of the *cis* relationship between the 1-position and 2-position substituents. This result is consistent with conventional selectivity for S_N1 reactions of cyclopropyl electrophiles, which are known to undergo concerted, disrotatory C2–C3 ring-opening to generate the allyl cation.[5,6,19]

A proposed mechanistic picture for this cyclopropyl tosylate ring-opening arylation is outlined in Fig. 3. Starting with 1-arylcyclopropyl tosylates (**1**), activation of the substrate occurs with arylboronic acid, which likely acts as an H-bond donor (**5**).[20] This intermediate then fragments to release tosylate anion and allyl cation **6**. In the absence of Ni, this cation can

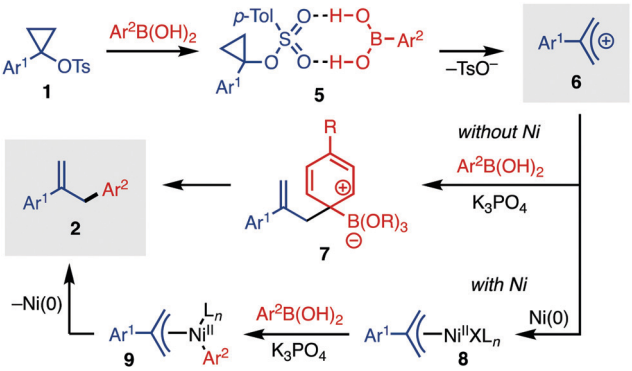


Fig. 3 Proposed mechanisms without and with Ni.

be trapped with an activated arylboronate to yield Wheland intermediate **7**. Elimination of the boronate restores aromaticity, forming arylated product **2**. Alternatively, in the presence of Ni(0), oxidative addition can yield Ni(II) intermediate **8**, which can undergo transmetallation with arylboronic acid to yield intermediate **9**. Finally, reductive elimination releases the allyl arene **2**. In the presence of Ni, it is likely that some of the non-Ni-catalyzed process also occurs, which explains the imperfect regioselectivity for certain entries in Table 2.

In conclusion, we have discovered an arylboronic acid-mediated and Ni-catalyzed process for the ring-opening arylation of 1-arylcyclopropyl tosylates, which are readily accessible from esters *via* the Kulinkovich reaction. The arylboronic acid plays two roles in this reaction: (i) it enables cyclopropane ring-opening and (ii), it participates in a Ni-catalyzed cross-coupling to yield allyl products bearing aryl substituents at the 2 position.

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Conflicts of interest

The authors declare no conflicts of interest.

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