

Achieving Chemo-, Regio-, and Stereoselectivity in Palladium-Catalyzed Reaction of γ -Borylated Allylic Acetates

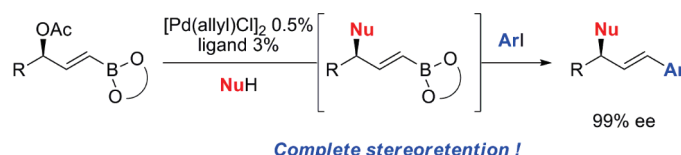
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ABSTRACT



Three-carbon highly functionalized γ -borylated allylic acetates underwent a regio- and stereocontrolled Tsuji–Trost reaction in the presence of palladium complexes. An ipso substitution of the acetate with complete stereoretention of the chiral center was achieved, leading to vinylic boronates with enantiomeric excesses above 99%.

Organometallic catalysis has arisen as a special key tool in modern synthetic methods, especially for pharmaceutical preparation. In many cases, the flexibility of transition metal complexes offers unusual reactivity and complementary methods for synthesis. Indeed, many transformations are catalyzed by palladium complexes, including Heck reactions, Suzuki–Miyaura and Sonogashira cross coupling, Tsuji–Trost allylic substitution, and Hartwig–Buchwald N-arylations.¹ However, despite a plethora of publications reporting the development of new catalysts for promoting such transformations, the issue of chemoselectivity is usually poorly addressed when substrates bear multiple putative reaction sites.

We sought to contribute to this issue by using γ -borylated allylic acetates as coupling partners. These highly functionalized three-carbon building blocks offer the additional

challenges of engendering regioisomers and displaying a chiral center on both the starting material and the products. The preparation of these compounds is quite straightforward starting from the corresponding propargylic acetates. A one-pot procedure has been optimized, consisting of a hydroboration using diisopinocampheylborane followed by a refunctionalization at the boron atom using acetaldehyde. The resulting diethyl boronates were transesterified in situ by pinacol leading to the stable and easy to handle vinylpinacol boronates. Such compounds can alternatively be prepared following other reported methods. Hydroboration using dicyclohexylborane followed by oxidation with trimethylamine oxide leads to similar yields.² Direct hydroboration with pinacolborane of the TMS protected propargylic alcohol followed by deprotection with citric acid and subsequent acetylation³ turned out equally effective but slightly longer (Scheme 1).

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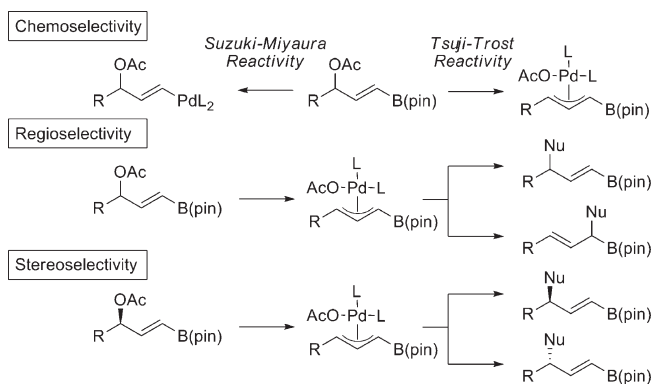
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Scheme 1. Chemo-, Regio-, and Stereoselectivity Issues

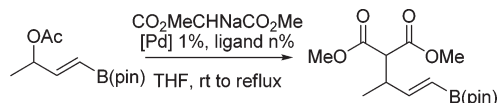


Considering the mechanistic difference between oxidative addition to the carbon–oxygen bond leading to a π -allyl complex and the transmetalation from boron to palladium, we first aimed for a selective allylic substitution.⁴ To our knowledge, only a few examples of allylic substitution on similar substrates are known. Asymmetric allylic substitution using a Grignard reagent can be catalyzed by phosphoramidite–copper complexes, leading to exclusive formation of the S_N2' products with excellent regio- and stereocontrol.⁵ Similarly, iridium–phosphoramidite complexes react on these allylic acetates, leading to the product substituted α to boron with good regio- and stereocontrol.⁶ However, in those cases reported by Hall, chemoselectivity is a lower concern as transmetalation of boron to iridium or copper is relatively sluggish although theoretically possible. In the presence of palladium catalysts, few examples have been reported, but they confirm that good chemoselectivity can be achieved when using highly reactive species. For instance, diazomethane reacts smoothly with γ -borylated allylic acetates to form the corresponding cyclopropylboronates.⁷ Favoring the Suzuki–Miyaura cross coupling is also possible⁸ when *tert*-butyl carbonate and activated aryl iodides are used or when water is used as a solvent.⁹ However, achieving selective palladium-catalyzed allylic substitution with mild nucleophiles is a much greater challenge and leads “to mixtures of regioisomeric deboration products and other unidentified materials” as Hall noticed. Indeed, some cross-coupling between allylic acetates and boronic acids has already been described, showing the wide range of reactions promoted by palladium

complexes.¹⁰ However, Walsh recently showed that, on similar substrates bearing a boron in the β position, a selective nucleophilic substitution could be achieved using carbon- and nitrogen-based nucleophiles.¹¹

We present here our recent studies related to the chemo-, regio-, and nucleophilic substitution on γ -borylated allylic acetates. After optimization of reactions conditions, it turned out that 1% $\text{Pd}(\text{OAc})_2/3\%$ PPh_3 in THF was a general catalytic system, leading to selective ipso substitution (Table 1, entry 1).

Table 1. Catalytic System Optimization



entry	[Pd]	ligand (%)	yield ^a (%)
1	$\text{Pd}(\text{OAc})_2$	PPh_3 (3)	77
2	PdCl_2	PPh_3 (3)	72
3	$[\text{Pd}(\text{allyl})\text{Cl}]_2$	PPh_3 (3)	76
4	$\text{Pd}(\text{OAc})_2$		0
5	$\text{Pd}(\text{OAc})_2$	PPh_3 (4)	77
6	$\text{Pd}_2(\text{dba})_3\text{-CHCl}_3$	PPh_3 (2)	70
7	$\text{Pd}(\text{dba})_2$	PPh_3 (2)	70
8	$\text{Pd}(\text{PPh}_3)_4$		75

^a Isolated yield after purification by flash chromatography.

Using $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (Table 1, entry 3) or PdCl_2 (Table 1, entry 2) led to similar activities, albeit somehow slightly less efficient. Phosphine addition was required for good conversion (Table 1, entries 4 and 5) and more than three equivalents did not improve the system (Table 1, entry 5). Other palladium sources were less efficient, especially when introduced under a $\text{Pd}(0)$ oxidation state as in $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3$ or $\text{Pd}(\text{dba})_2$ (entries 6 and 7). Only $\text{Pd}(\text{PPh}_3)_4$ allowed yields similar to those obtained when $\text{Pd}(\text{II})$ was reduced in situ. Among ligands, other phosphines were at least as efficient as triphenylphosphine. NHC-carbenes were unsuccessful, and nitrogen-based ligands failed. Overall, given its simplicity and cost, triphenylphosphine was kept in the optimized catalytic system. Among other solvents, only THF led reproducibly to good conversions.

These mild conditions allowed us to perform Tsuji–Trost reactions with various nucleophiles. We began our studies using enolate-type nucleophiles derived from 1,3-dicarbonyl compounds. Alkyl malonates were efficient regardless of the ester substitution (Table 2, entries 1, 5, and 9); β -ketoesters (Table 2, entries 2, 6, and 10), 1,3-diketones (Table 2, entries 4 and 8), and cyanoacetate (Table 2, entries 3, 7, and 11) reacted equally well. Even when using a sterically hindered nucleophile such as **2e**, quaternary centers were obtained in similar yields (Table 2, entries 13 and 14). In the case of **1d**, the only isolated

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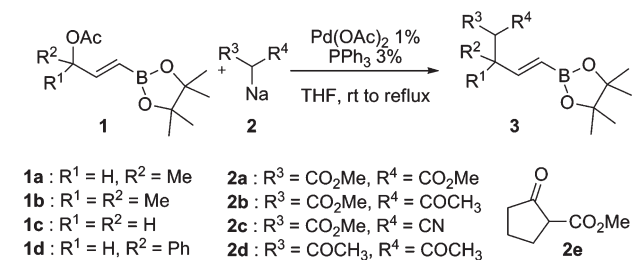
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Table 2. Tsuji–Trost Reaction on γ -Borylated Allylic Acetates

entry	acetate	Nu	product	yield (%)
1	1a	2a	3aa	77
2	1a	2b	3ab	80
3	1a	2c	3ac	80
4	1a	2d	3ad	80
5	1b	2a	3ba	80
6	1b	2b	3bb	83
7	1b	2c	3bc	79
8	1b	2d	3bd	82
9	1c	2a	3ca	74
10	1c	2b	3cb	76
11	1c	2c	3cc	77
12	1d	2a	3da	61
13	1a	2e	3ae	75
14	1c	2e	3ce	79

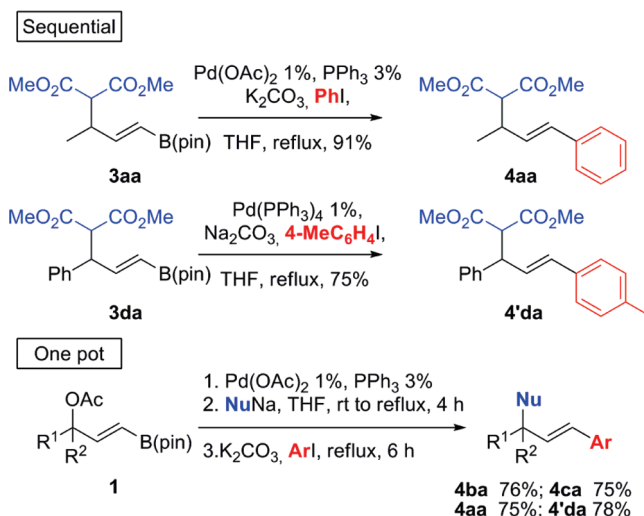
^a Isolated yield after purification by flash chromatography.

boron-containing product is the unconjugated ipso-substituted product, which is unexpected considering the traditional outcome of the Tsuji–Trost reaction in the presence of palladium complexes. However, another product is isolated in 15% yield, which could originate either from direct coupling of the boronate moiety with the malonate or from the S_N2' product protodeboronation during workup. This emphasizes nicely the positive influence of the boron substituent on the regioselectivity of the reaction (Table 2, entry 12, and Scheme 2).

Based on our success in performing selective Tsuji–Trost substitutions, we then pursued our study by using the obtained vinyl boronate in a Suzuki–Miyaura cross coupling. Compound **3aa** led to the styrene derivative in 91% yield in the presence of phenyl iodide and Pd(OAc)₂. In the one-pot sequence beginning with allylic substitution, the residual palladium species efficiently catalyzed the second cross-coupling reaction. We ultimately obtained the double cross-coupled adduct in a slightly better yield than by performing the two steps separately.

In the continuity of controlling the regio- and chemoselectivity of the reaction, we then tackled the stereocontrol issue. Overall, starting from racemic allylic acetate, using DACH-phenyl Trost ligand **L1** in lieu of triphenylphosphine, a 78% ee was observed (Table 3, entry 2). Other chiral ligands from the same family were tested. The simplest ligand turned out to give the best selectivities, as the naphthyl-derived ligand **L2** led to 54% ee (Table 3, entry 3) and the pyridyl ligand **L4** led to 11% ee (Table 3,

entry 5). Modifying the diamine scaffold led to a dramatic ee decrease (30%, Table 3, entry 4) but favored the other enantiomer.

Scheme 2. One-Pot Tsuji–Trost Suzuki–Miyaura Reaction

To our delight, performing the allylic substitution on a chiral substrate (**S**)-**1a** (ee > 99%) led to **3aa** with 88% ee, representing a mere 5% racemization of the substrate (Table 3, entry 6). The size of this memory effect is somehow unprecedented, especially considering the 4 h reaction time, giving to the generated π -allyl complex more than enough time to racemize. Several examples could be found in the literature trying to explain this memory effect. According to Pfaltz and Helmchen,¹² regioselectivity of the reaction is directly related to S_N1 vs S_N2 type mechanism, the latter favoring the linear product. In our case, the complete ipso substitution corroborates a double S_N2 mechanism. This was confirmed by the absolute configuration of the carbon center, which appeared to be formed with a complete stereoretention.¹³ According to several reports,¹⁴ the addition of LiCl often improves this stereoretention effect. In our hands, it led to complete inactivation of the catalytic system. Overall, this reaction is supposed to proceed through a true π -allyl palladium complex bearing a boron substituent.¹⁵

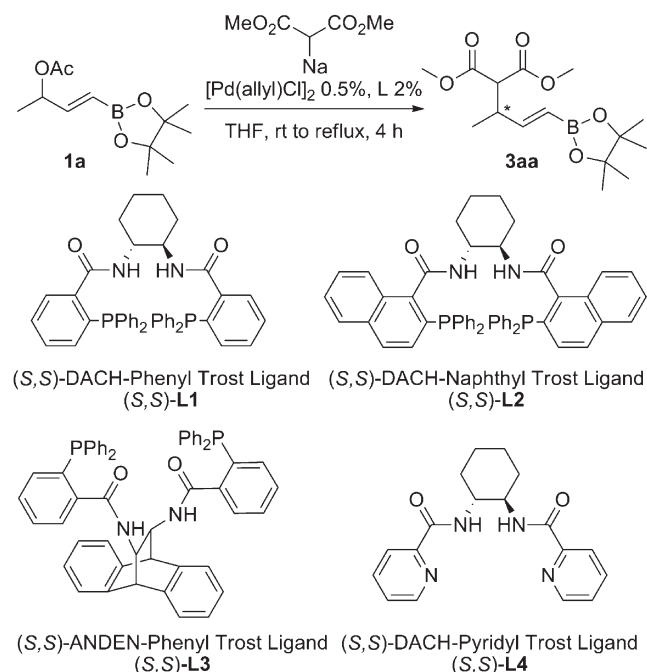
Combining in a matched fashion, (*S,S*)-DACH-phenyl Trost ligand and chiral (*S*)-starting material afforded the boronate with > 99% ee (Table 3, entry 8). More surprising was the 97% ee of the same enantiomer obtained with the mismatched pair (*R,R*)-ligand and (*S*)-boronate,

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Table 3. Tsuji–Trost Reaction on γ -Borylated Allylic Acetates

entry	acetate	L	yield ^a (%)	ee ^b (%)
1	(<i>rac</i>)- 1a	PPh ₃	77 ^c	0
2	(<i>rac</i>)- 1a	(<i>S,S</i>)-L1	80	78 (<i>S</i>)
3	(<i>rac</i>)- 1a	(<i>R,R</i>)-L2	84	54 (<i>R</i>)
4	(<i>rac</i>)- 1a	(<i>R,R</i>)-L3	85	30 (<i>S</i>)
5	(<i>rac</i>)- 1a	(<i>R,R</i>)-L4	25	11 (<i>R</i>)
6	(<i>S</i>)- 1a	PPh ₃	76	88 (<i>S</i>)
7	(<i>S</i>)- 1a	(<i>R,R</i>)-L1	80	97 (<i>S</i>)
8	(<i>S</i>)- 1a	(<i>S,S</i>)-L1	80	99 (<i>S</i>)
9	(<i>S</i>)- 1a	(<i>Rac</i>)-L1	80	99 (<i>S</i>)

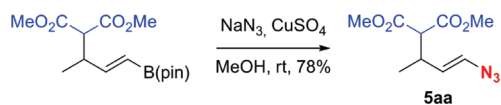
^a Isolated yield after purification by flash chromatography. ^b determined by HPLC using Daicel AS-H column; major enantiomer is noted between parentheses. ^c Pd(OAc)₂ was used instead of [Pd(allyl)Cl]₂.

meaning that the stereochemical outcome of the reaction is mostly driven by the substrate (Table 3, entry 7). This was confirmed when a racemic mixture of the DACH-phenyl Trost ligand was used, leading to a 98.6% ee indicating a complete stereoretention at the acetate center (Table 3,

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entry 9). Using this three-carbon template bearing a boron substituent provides an interesting alternative to the direct Tsuji–Trost reaction owing to the versatility of boron chemistry. For example, in the case of substrate bearing similar aryl groups on both ends of the π -allyl palladium intermediate, it is hard, albeit possible, to control nucleophilic attack.¹⁶ The one-pot procedure provides an interesting alternative for controlling this regioselectivity. The tandem Tsuji–Trost/Suzuki–Miyaura cross coupling between 4-methylphenyl iodide, phenyl-substituted allylic acetate, and dimethyl malonate afforded **4'da** in 78% yield. The one-pot sequence was superior to the stepwise process in improving the overall yield to 78% instead of 45% (Scheme 2). Additionally, if required, the boron substituent could be replaced by a large number of functional groups using more classical transformations such the Chan–Lam–Evans coupling, including the use of sodium azide as a nitrogen counterpart,¹⁷ leading to product **5aa** in 78% yield (Scheme 3).

Overall, we have managed to use a highly functionalized three-carbon building block in a chemo-, regio-, and

Scheme 3. Diversity Enabled by Boron Substituent

stereoselective manner. The resulting products could be used in a large variety of transformations using further reactions of the pinacol boronate moiety. These exciting results have compelled us to investigate the scope and detailed influence of boron in this reaction, and results will be reported in due course.

Note Added after ASAP Publication. A text correction was made in the third paragraph in the version reposted July 12, 2011.

Supporting Information Available. Experimental procedures, characterization data, ¹H, ¹³C, and ¹¹B NMR spectra, and HPLC traces. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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