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Regio- and Enantioselective Cyclobutene Allylations

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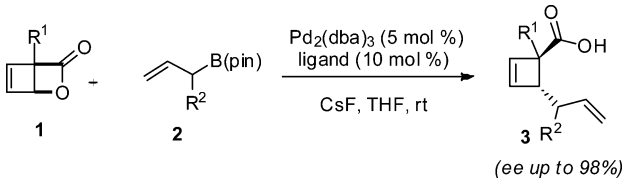
ABSTRACT



Catalytic asymmetric allylation of lactone 1 with allyl boronates leads to functionalized cyclobutenes in high regio- and stereoselectivity.

The palladium-catalyzed asymmetric allylic alkylation (AAA), also known as the Tsuji–Trost reaction, is a powerful synthetic method for the preparation of optically active compounds. Catalytic AAA allows the formation of a variety of bond types including C–H, C–N, C–O, C–S, or C–C linkages depending on the nucleophile employed. The latter are classically categorized as stabilized ("soft") and nonstabilized ("hard") nucleophilic species.[1]

Under palladium catalysis in particular, stabilized nucleophiles dominate the field while their nonstabilized counterparts have received less attention. Nevertheless, a wide range of organometallic reagents have been utilized, especially featuring aryl and alkenyl derivatives of Al, B, Mg, Sn, Zn, and Zr.[2] Most of them have not yet been developed into general systems for palladium-catalyzed AAA.[3] Recently, Morken reported a series of elegant cross-coupling studies between boronates and allylic electrophiles using palladium-catalyzed AAA.[4]

Recent studies in our laboratory have focused on the palladium-catalyzed reactions of bicyclic lactone **1** with stabilized nucleophiles[5] (Scheme 1). This strategy has allowed expeditious access to functionalized cyclobutenes with high and unusual diastero- and enantioselectivities. Inspired by the work of Morken,[4] we were eager to investigate the behavior of our system in the presence of nonstabilized nucleophiles. Herein we report our preliminary results on the catalytic, asymmetric regioselective allylation of lactones **1** with boronates as well as a mechanistic dichotomy that allows those nucleophiles to behave as (enantioselective) reducing agents.

As depicted in Scheme 1, initial experiments showed that the combination of lactone **1a** and the pinacol ester of allylboronic acid (allylB(pin) **2a**), under palladium catalysis, led to a quantitative yield of the *trans*-cyclobutene carboxylic acid **3** as a single diastereoisomer.

To further probe the scope of this transformation, a diverse array of allylboronates were employed in the experiments compiled in Table 1.

Comparing the results obtained with methyl-substituted allyl boronate nucleophiles, where the methyl group occupies either the γ-, β-, or α-position (Table 1, entries 1, 2, and 3 respectively), it quickly became evident that the

(1) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (c) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813–5837. (d) Lu, Z.; Ma, S. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297. (e) Helmchen, G.; Kazmaier, U.; Förster, S. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I., Ed.; John Wiley & Sons, Inc., Hoboken, NJ, USA, 2010; pp 497–641. (f) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427–440.

(2) Negishi, E.; Liu, F. In *Hand book of Organopalladium Chemistry for Organic synthesis*; Nagishi, E., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2002; pp 551–596.

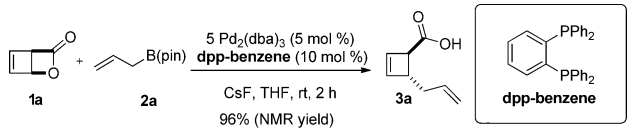
(3) Asymmetric borylation has been achieved under Cu catalysis; see: Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857.

(4) (a) Zhang, P.; A. Brozek, L.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686–10688. (b) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778–16781. (c) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716–9719. (d) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 8770–8773.

(5) (a) Frébault, F.; Luparia, M.; Oliveira, M. T.; Goddard, R.; Maulide, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5672–5676. (b) Luparia, M.; Oliveira, M. T.; Audisio, D.; Frébault, F.; Goddard, R.; Maulide, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 12631–12635.

10.1021/ol401033g

Scheme 1. Initial Experiments on the Allylation of Lactone **1**



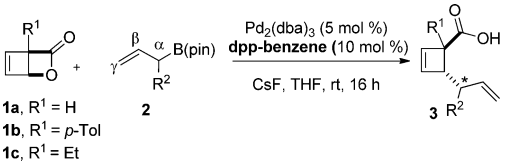
location of the substituent plays a crucial role. Thus, β-substitution (as in methallyl-pinacolborane (Table 1, entry 2) led to no reaction while γ-substitution (*E*-crotyl-pinacolborane, Table 1, entry 1) provided a mixture of the branched and linear products **3b** and **3c** in very low yield. In contrast, when an α-substituted allyl boronate **2d** was used, the branched allylated cyclobutene **3c** was observed as a single regioisomer in 55% yield with moderate diastereoselectivity (Table 1, entry 3).

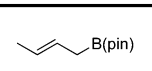
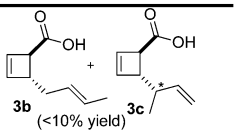
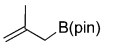
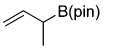
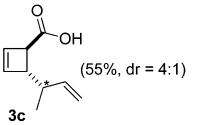
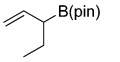
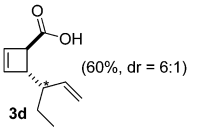
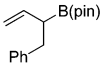
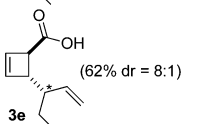
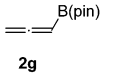
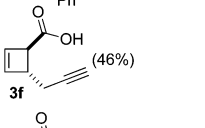
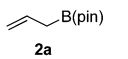
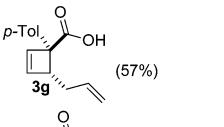
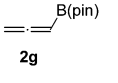
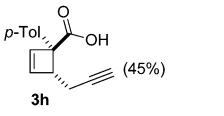
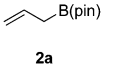
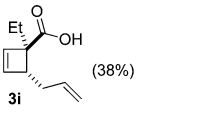
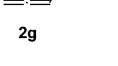
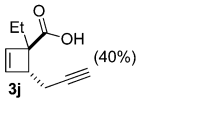
Surprised by this unanticipated selectivity,[4,6] we subjected other α-substituted allylpinacol boranes to the reaction conditions (Table 1, entries 4–5). The regioselectivity remained high in favor of the branched product, accompanied by increased levels of diastereoselectivity. Therefore, allylated cyclobutene **3e** bearing a benzyl branched side chain was obtained in 62% yield and 8:1 d.r. (Table 1, entry 5), suggesting that the diastereoselectivity is positively correlated with the steric bulk of the boronate α-substituent. In addition, allenylpinacol borane was also a viable nucleophile[7] for this transformation (Table 1, entry 6), allowing the preparation of propargylated cyclobutene **3f** in 46% yield.

Targeting the synthesis of cyclobutenes bearing quaternary centers, substituted lactones **1b**–**c** were prepared and evaluated in this allylation protocol.[8] As shown (Table 1, entries 7 and 9), allylated products containing a tolyl- or ethyl-substituted all-carbon quaternary center were generated in moderate to good yields. The propargylated analogues **3h** and **3j** could also be prepared (Table 1, entries 8 and 10).

At this point, we were eager to investigate an asymmetric variant of this transformation that could enable the quantitative deracemization of lactones **1** and the obtention of valuable enantioenriched allylated cyclobutene building blocks. A selection of the chiral ligands that were screened for this purpose is shown in Scheme 2. In the event, only complex mixtures resulted when (*R*,*R*) QuinoxP* (**L1**) was employed, and a low 20% yield (albeit with high enantioselectivity of 90% ee) was obtained upon using

Table 1. Scope of the Pd-Catalyzed Allylation of Lactones **1a**–**c**[a]



entry	lactone **1**	allylborate **2**	product (yield %, dr)[a]
1	**1a**	 **2b**	 **3b** (<10% yield) **3c**
2	**1a**	 **2c**	no reaction
3	**1a**	 **2d**	 (55%, dr = 4:1) **3c**
4	**1a**	 **2e**	 (60%, dr = 6:1) **3d**
5	**1a**	 **2f**	 (62% dr = 8:1) **3e**
6	**1a**	 **2g**	 (46%) **3f**
7[b]	**1b**	 **2a**	 (57%) **3g**
8[b]	**1b**	 **2g**	 (45%) **3h**
9[b]	**1c**	 **2a**	 (38%) **3i**
10[b]	**1c**	 **2g**	 (40%) **3j**

[a] Yields were determined by NMR spectroscopy (internal standard), and products were purified as their amide or ester derivatives. The dr values refer to the center marked with an * and were determined by NMR analysis of the crude reaction mixture. [b] Modified conditions were employed (see Supporting Information for details).

(*R*)-MeO-furyl-biphep (**L2**) as a ligand. Those ligands had afforded the best results in the seminal contributions of Morken.[4] On the other hand, our prior success[5b] with

(6) The selectivity observed is actually opposite to that described by Morken. In those reports, linear (crotyl-like) allylpinacol boranes afforded the branched product. See ref 4.

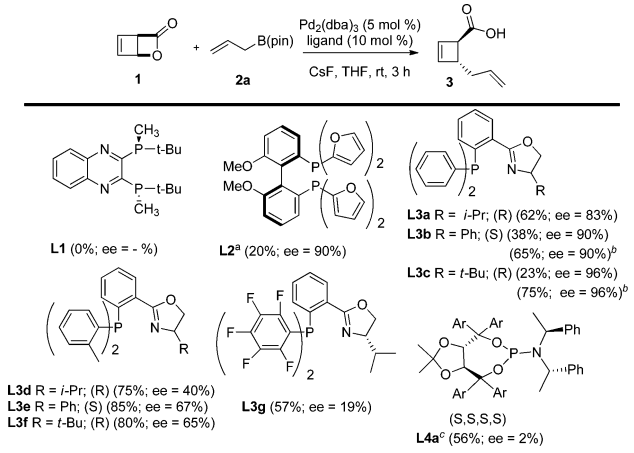
(7) (a) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Johnson, C. S.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 88–91. (b) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T; Tan, Z.; Tang, W.; Capacci, A. G.; Rodriguez, S.; Song, J. J.; Lee, H.; Yee, N. K; Senanayake, C. H. *J. Am. Chem. Soc.* **2010**, *132*, 7600–7601. (c) Fandrick, D. R.; Saha, J.; Fandrick, K. R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschangar, F.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 5616–5619.

(8) Frébault, F.; Oliveira, M. T.; Wöstefeld, E.; Maulide, N. *J. Org. Chem.* **2010**, *75*, 7962–7965. See the Supporting Information for details.

(9) (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1993**, *32*, 566–568. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769–1772.

phosphino-oxazoline (Phox) ligands[9] led us to investigate that class of ligands in the allylation reaction. The substitution pattern both at phosphorus and at the chiral center has a marked influence on the results obtained. For instance, yields and enantioselectivities were directly affected in a contrasting manner by steric bulk at the chiral carbon center (cf. **L3a**, **L3b**, and **L3c**). In addition, replacing the $-PPh_2$ moiety with its bulkier counterpart $-P(o\text{-tolyl})_2$ improved the yields but decreased the enantioselectivity of the reaction (see **L3d**, **L3e**, and **L3f**).

Scheme 2. Ligand Screening for the Catalytic Asymmetric Allylation

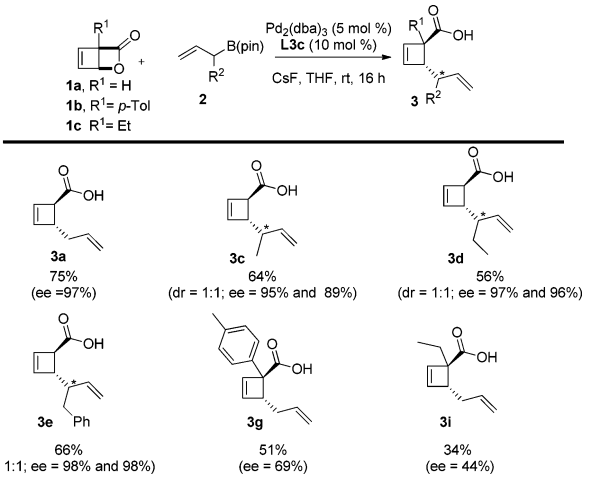


[a] The reaction was carried out over 20 h. [b] Yield after optimization (see Supporting Information for details). [c] Ar = 3,5-di-*tert*-butyl-4-methoxyphenyl. Yields were determined by NMR spectroscopy (internal standard). All ee values were measured on the benzyl ester derivative of **3**. See the Supporting Information for details.

The phosphoramidite **L4a**, which was proven highly *cis*-selective with stabilized nucleophiles in our previous work,[5b] led to *trans*-allylated cyclobutene **1a** with moderate yield but virtually no enantioselectivity along with traces of the *cis*-isomer.[10] Further refinement of the reaction conditions[10] allowed us to obtain good results using ligands **L3b**–**c** (65–75% yield) while retaining high enantioselectivity. The obtention of products with high (≥90%) enantiomeric purity in yields reproducibly higher than 50% is consistent with a dynamic deracemization process.[11]

With suitable conditions in hand, the scope of this catalytic asymmetric allylation was then examined (Scheme 3). As before, high regioselectivity for the branched product was observed upon using α-substituted allylpinacol boronates. However, eroded diastereoselection resulted in those cases (see Scheme 3). Lower levels of selectivity were also observed in the allylation of tolyl- and ethyl-substituted lactone electrophiles **1b** and **1c** respectively.[12]

Scheme 3. Scope of Asymmetric Pd-Catalyzed Allylation of Lactones **1a**–**c**[a]



[a] Yields were determined by NMR spectroscopy (internal standard) and products were purified as their amide or ester derivatives. The dr values refer to the center marked with an * and were determined by NMR analysis of the crude reaction mixture. Ee values were measured on the corresponding benzyl ester (**3a**) or *N*-benzylamide (**3c**–**e**, **3g**, and **3l**) derivatives. See Supporting Information for details. The absolute configuration of the major enantiomers of **3** was not determined.

The combined use of substituted lactone electrophiles **1b**–**1c** and α-substituted allylpinacol boronates led cleanly to new cyclobutene products that did not, however, contain an allylic substituent (Table 2). To our surprise, structural elucidation revealed those products to be the reduced cyclobutenes **4**.

Interestingly, this was the observed outcome regardless of whether Phox or the chiral ligand **L3c** were employed. The reduced cyclobutenes **4a**–**b** could be obtained in high yields and, when **L3c** was used, moderate enantioselectivities.[13] It thus appears that the allylboronate partner can also function as a formal hydride donor.[14] It should be noted that the reduced product **4a** was formed with similar enantioselectivity (Table 2, entries 1–2) when two different, substituted allylpinacol boronates are employed.

From a mechanistic point of view (Scheme 4), oxidative addition of the metal catalyst to lactone **1** should lead to allylmetal complex **5**, onto which transmetalation of the allylpinacol borane fragment may lead to the intermediate **6** (depicted in its η^1-allyl form for simplicity).

(10) The use of the BINOL-derived phosphoramidite akin to **L4a** afforded no reaction. See the Supporting Information for details and further experiments.

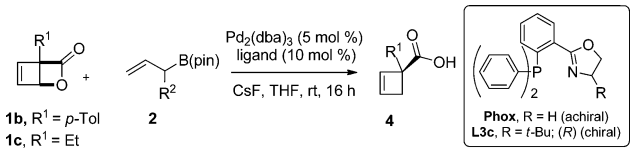
(11) This transformation can be considered an example of DYKAT Type II. See: (a) Stecher, H.; Faber, K. *Synthesis* **1997**, 1–16. (b) Faber, K. *Chem.—Eur. J.* **2001**, *7*, 5004–5010. (c) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J. E. *Chem. Soc. Rev.* **2001**, *30*, 321–331. (d) Steinreiber, J.; Faber, K.; Griengl, H. *Chem.—Eur. J.* **2008**, *14*, 8060–8072.

(12) Asymmetric propargylation of lactone **1** provided the corresponding products in poor yield and enantioselectivity. See the Supporting Information for details.

(13) Masarwa, A.; Fürstner, A.; Marek, I. *Chem. Commun.* **2009**, 5760–5762.

(14) Keinan, E.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151–11152.

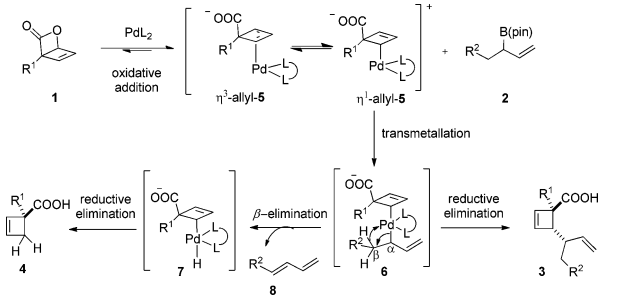
Table 2. Catalytic (Asymmetric) Reduction of Lactones **1b**–**c** Using Allylboronates[a]



entry	lactone, **1**	nucleophile, **2**	product	yield using **Phox**	yield using **L3c**	ee %
1	**1b**	**2d**	**4a**	72%	78%	70
2	**1b**	**2e**	**4a**	74%	75%	70
3	**1c**	**2d**	**4b**	45%	32%	60

[a] Yields were determined by NMR spectroscopy (internal standard), and products were purified as their amide or ester derivatives. All ee values were measured on the *N*-benzylamide derivatives of **4**. See the Supporting Information for details. The absolute configuration of the major enantiomers of **4** was not determined.

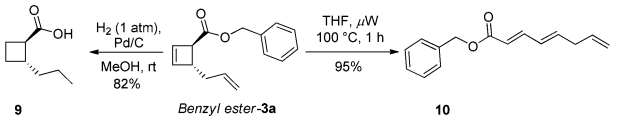
Scheme 4. Proposed Mechanism for the Catalytic Allylation



The obtention of the branched product from α-substituted allyl boronate nucleophiles, in contrast to prior reports,[4] suggests that a normal (rather than a [3,3]-type) reductive elimination is operative in this system, presumably due to steric hindrance. As a corollary, the simultaneous presence of R_1 and R_2 substituents probably leads to conformational changes no longer resulting in reductive elimination[14] but rather leading to β-hydrogen elimination to palladium hydride **7**. Reductive elimination from this intermediate accounts for the formation of reduced cyclobutene products, and also for the observed identical enantioselectivities regardless of the allylating agent employed.[15]

The products obtained are valuable chiral building blocks (Scheme 5). As shown, both olefinic moieties of benzyl ester **9** can be simultaneously hydrogenated leading to the *trans*-cyclobutane carboxylic acid **10** in 82% yield. Additionally, thermolysis induces smooth electrocyclic ring opening to produce the sensitive skipped triene carboxylic ester **11**, with no traces of the fully conjugated isomer.[16]

Scheme 5. Functionalization of the Adducts Obtained



In summary, we have developed a regio- and stereoselective catalytic asymmetric allylation of cyclobutenes using allylpinacol boronates. The reaction displays interesting selectivity in favor of branched allylated products and deposits a versatile allyl substituent, ripe for further synthetic elaboration, into the cyclobutene framework. Furthermore, the allylating agent demonstrated reductive behavior on highly hindered electrophile/nucleophile combinations. Studies aimed at broadening the scope of this and related methodologies as well as applying them to the synthesis of natural products are currently underway.

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Supporting Information Available. Experimental procedures, ancillary experiments, and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) When the benzyl-substituted allylpinacol boronate **2f** was employed, 1-phenylbutadiene (**8** in Scheme 4, R_2 = Ph) was detected by GC-MS and NMR analysis of the crude mixture. See the Supporting Information for details.

(16) Posner, G. H.; Crouch, R. D.; Kinter, C. M.; Carry, J.-C. *J. Org. Chem.* **1991**, *56*, 6981–6987.

The authors declare no competing financial interest.