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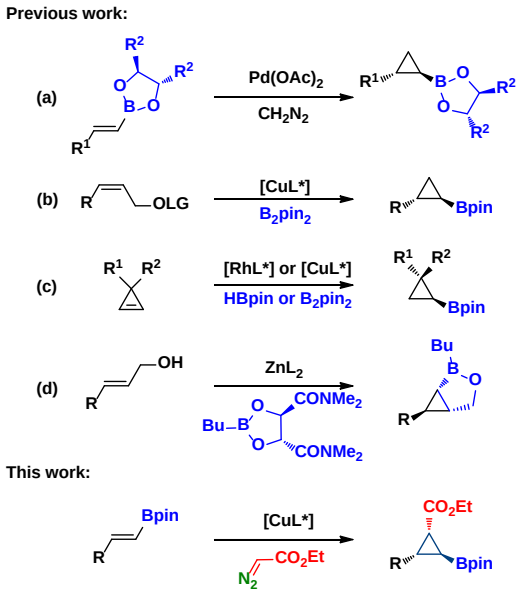
Enantio- and Diastereoselecti ve Cyclopropanation of 1-Alkenylboronates: Synthesis of 1-boryl-2,3-disubstituted Cyclopropanes

Javier Carreras, Ana Caballero,* and Pedro J. Pérez*

Abstract: A novel, highly enantio- and diastereoselective synthesis of 1-boryl-2,3-disubstituted cyclopropanes has been developed by means of the cyclopropanation of alkenylboronates with ethyl diazoacetate in the presence of catalytic amounts of a chiral copper-(I) complex. The products can also be directly accessed from alkynes through an operationally simple sequential hydroboration-cyclopropanation protocol. The resulting enantioenriched 1-boryl-2,3-disubstituted-cyclopropanes are versatile synthetic intermediates through further transformations at the carbon-boron bonds.

Cyclopropane derivatives are present in a wide variety of biologically active natural and synthetic compounds.[1] Natural products bearing the cyclopropane unit have been isolated from plants, fungi and microorganisms, mainly in structural motifs as terpenoids, fatty acid metabolites, pheromones and unusual amino acids. (+)-*trans*-Chrysanthemic acid,[2] which shows insecticide activity or 1-aminocyclopropanecarboxylic acid,[3] a direct precursor of the phytohormone ethylene, are two classical examples of natural products containing the cyclopropane ring. The incorporation of the cyclopropyl ring in the structure of drug candidates started in the 1960s,[4] cyclopropanes being nowadays present in approved drugs or regularly used in different applications.[5]

In spite of the array of synthetic routes described to date toward the synthesis of substituted cyclopropane derivatives (Simmons−Smith type cyclopropanations, metal-catalyzed decomposition of diazo compounds or Michael-initiated ring closure, among others),[6] a straightforward access to building blocks containing enantiopure cyclopropanes yet remains a challenge for synthetic chemist. Among different possibilities, the presence of a boron derivative as one of the substituents is highly desirable, either for the further functionalization of the cyclopropyl moiety, including the introduction of this motif in complex structures. Different approaches have been reported to obtain boryl-substituted cyclopropanes in a diastereoselective manner,[7] with only a few strategies being known for the preparation of optically active cyclopropylboronates. Scheme 1 shows the methodologies developed toward the asymmetric synthesis of borylcyclopropanes: (a) cyclopropanation of chiral alkenylboronates,[8] (b) reaction of allylic carbonates or phosphonates with diboron derivatives,[9] (c) hydroboration of cyclopropenes,[10] and (d) zinco-cyclopropanation of allylic alcohols.[11] These protocols are restricted to the existence of a methylene group in the cyclopropane skeleton, with the exception of the methodology that requires an allylic alcohol as directing group and a chiral stoichiometric boron reagent (Scheme 1d).[11]



Scheme 1. Synthesis of enantioenriched cyclopropylboronates

We have focused on the development of an asymmetric metal-catalyzed protocol, *via* carbene transfer from a diazo-compound, for the conversion of alkenylboronates into chiral 1,2,3-trisubstituted cyclopropanes.[12,13] We herein report the use of a catalytic system, based on a chiral copper-(I)-bisoxazoline complex, [14] for the functionalization of alkenylboronates with ethyl diazoacetate, that provides 1,2,3-trisubstituted cyclopropanes with high enantio- and diastereoselectivity values (Scheme 1).

[*] Dr. J. Carreras, Dr. A. Caballero, Prof. Dr. P. J. Pérez
Laboratorio de Catálisis Homogénea, Unidad Asociada al CSIC
CIQSO-Centro de Investigación en Química Sostenible and Departamento de Química
Universidad de Huelva, 21007-Huelva (Spain)
E-mail: perez@dqcm.uhu.es; ana.caballero@dqcm.uhu.es

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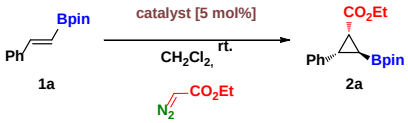
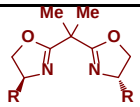
Table 1. Cyclopropanation of alkenylboronate **1a.**[a]



Entry	catalyst	EDA equiv	time (h)	Yield (%)[b]	dr[c]	er[d]
1	$Pd(OAc)_2$	2	14	84	64:36	--
2	[Cu] + **L1**	2	14	41	97:3	97:3
3	[Cu] + **L2**	2	14	41	95:5	97:3
4	[Cu] + **L3**	2	14	56	97:3	96:4
5	[Cu] + **L3**	4	14	79	97:3	96:4
6	[Cu] + **L3**	4	8	91 (85)[e]	97:3	96:4
7[f]	[Cu] + **L3**	4	8	27	97:3	96:4

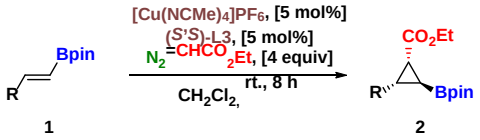


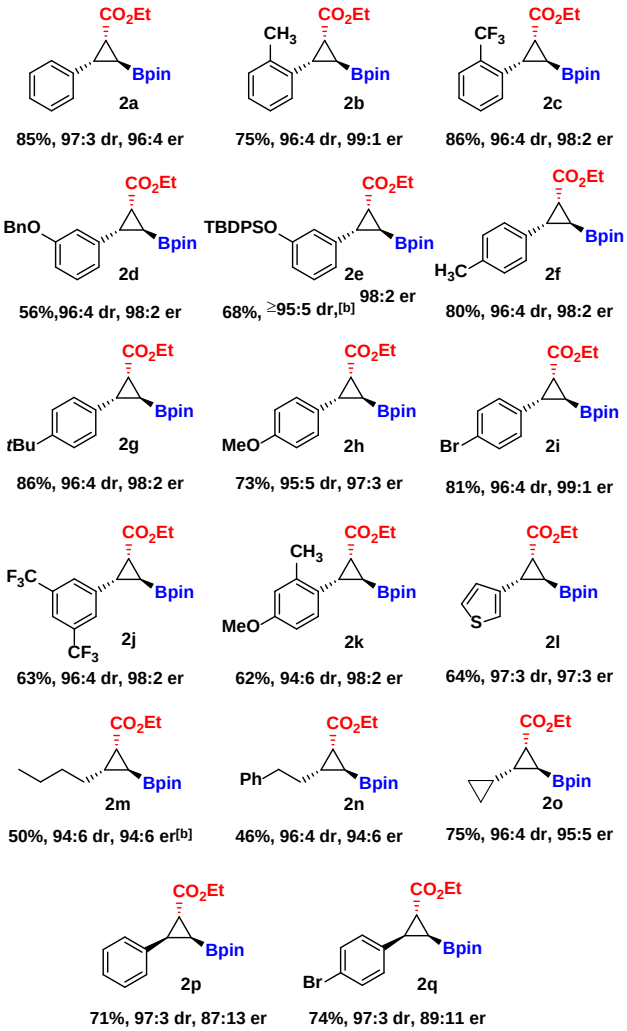
(*S*,*S*)-**L1**; R = *t*-Bu
(*S*,*S*)-**L2**; R = *i*-Pr
(*S*,*S*)-**L3**; R = Ph

[a] Reaction conditions: alkenylboronate **1a** (0.22 mmol), EDA (0.88 mmol), 8 h slow addition, $[Cu(NCMe)_4]PF_6$ (5 mol%), ligand (5 mol%), CH_2Cl_2 (0.07M), inert atmosphere [b] NMR yields based on 1,4-dimethoxybenzene as internal standard. [c] dr determined by ^1H NMR and/or GC. [d] er determined by HPLC. [e] Isolated yield. [f] No inert atmosphere was used.

In a first approach, we investigated the cyclopropanation of (*E*)-styryl pinacolboronate (**1a**) with ethyl diazoacetate (EDA), and an array of different transition metal complexes (Cu,- Au-, Ru-, Pd- or Rh-based) achieving low reactivity was found in all cases.[15] In good agreement with previous reports using diazomethane or substituted diazo derivatives,[16] $Pd(OAc)_2$ provided a good activity (84% yield, Table 1, entry 1), but a low diastereoselectivity (64:36).[17] It is worth mentioning that the concerted nature of the carbene transfer addition to the C=C bond provides the retention of the relative geometry (*E*) of the initial olefin, thus the two diastereomers are defined by the respective positions of the CO_2Et and the Bpin groups. Since the achiral catalysts tested did not induce a noticeable diastereomeric excess, we then moved toward chiral catalysts. We were delighted that a combination of $[Cu(NCMe)_4]PF_6$ and (*S*,*S*)-di*tert*butyl-bisoxazoline (**L1**) provided an excellent control in the diastereoselectivity (entry 2). Other copper sources were screened in the presence of ligand **L1** but the reaction outcome did not improve the above results with $[Cu(NCMe)_4]PF_6$.[15] Upon examining different bisoxazoline ligands, that bearing the less bulky phenyl substituent (**L3**, entry 4) induced some yield improvement, that was optimized upon varying other reaction parameters to finally achieve the complete conversion of the alkenylboronate, leading to a 85% isolated yield (entry 6) with a 97:3 excellent diastereoselectivity. Moreover, a highly satisfactory asymmetric induction was found in this transformation, with an enantiomeric ratio of 96:4 for cyclopropane **2a** being observed.[15] Its relative configuration was confirmed by NMR and X-ray diffraction experiments of the boronic acid derivative.[15,18]

Table 2. Scope of alkenylboronates.[a]





[a] Yield of isolated compounds **2a-2m**. Diastereomeric ratio determined by GC analysis of the reaction crude. Enantiomeric ratio determined by chiral HPLC analysis of the isolated product. [b] Diastereomeric and enantiomeric ratio determined by ^1H NMR. See Supporting Information for more details.

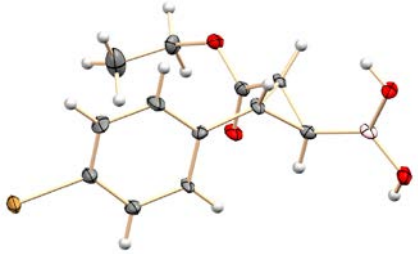
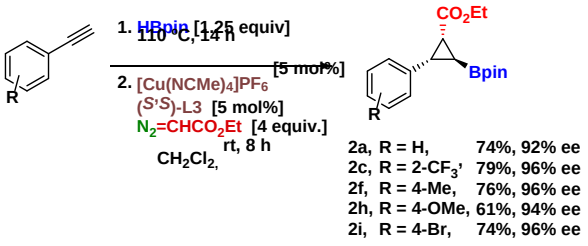


Figure 1. ORTEP diagram (50% thermal ellipsoids) of the molecules of **3i** in the solid state.

With an optimal set of reaction conditions in hand, we next explored the scope of this enantioselective cyclopropanation of alkenylboronates (Table 2). The methodology exhibited good

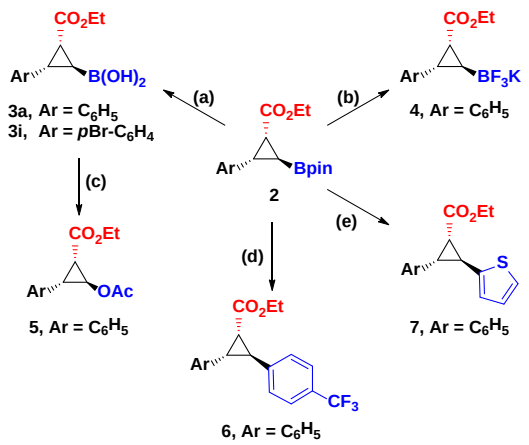
tolerance to different substitution patterns in the aromatic ring. A broad range of *ortho*-, *meta*- and *para*-substituted as well as disubstituted aromatic rings with diverse steric and electronic properties (alkyl, ethers, protected alcohols, trifluoromethyl and bromide) can be readily exploited in this protocol, to afford the 1-borylcyclopropane derivatives (**2a**-**2k**) in good yields (56-86%) and excellent stereoselectivities. In addition to aryl rings, a heterocyclic system such as thiophene (**2l**) or alkyl chains of type butyl (**2m**), 2-phenylethyl (**2n**) or cyclopropyl (**2o**) were suitable substituents for the enantioselective cyclopropanation. Notably, the substitution in the alkenylboronate had no impact on the diastereoselectivity (94:6 to 97:3) and enantioselectivity (94:6 to 99:1) values being within the same range in the whole series. Upon transformation of cyclopropane **2i** into the corresponding boronic acid **3i**, the absolute configuration of the former was determined as (1*R*,2*S*,3*S*) by single crystal X-ray diffraction analysis (**3i**, Figure 1).[18] The use of *Z*-alkenylboronates has also been tested, leading to compounds **2p** and **2q**. Whereas the isolated yields and *dr* values are within the range observed for the *E*-alkenylboronates, the er slightly decreases below 90:10. Overall, we believe that these results support the generality of this procedure for both *Z*- and *E*- isomers. The absolute configuration of **2q** (1*R*,2*R*,3*S*) was determined by X-ray studies of the corresponding boronic acid derivative **3q**.[15,18]

After the above results, we planned a simple and straightforward route to the products using terminal alkynes as starting materials, considering the limited commercial availability of alkenylboronates. Numerous reports of catalytic methodologies are accessible in the literature for the β selective hydroboration of alkynes, leading to (*E*)-alkenylboronates.[19] Nevertheless, we preferred a purely thermal, non-catalytic procedure,[20] aiming to induce a simple and clean hydroboration reaction that would not interfere further in the subsequent enantioselective cyclopropanation step. We found that heating a mixture in 1:1.25 ratio of alkyne:pinacolborane for 14 h provided a synthetically useful sample (89% yield) of the alkenylboronate **1a** (see Supporting Information for optimization experiments).[21] We then examined the sequential hydroboration-cyclopropanation process. Phenylacetylene as well as several derivatives were exposed to the above conditions, the resulting mixture being directly employed in the enantioselective cyclopropanation step (Scheme 2). Cyclopropanes bearing electron-rich or electron-poor aryl substituents were obtained in good overall yields (61-79%) after the two steps (Scheme 2), and with the same very high values of diastereo- and enantioselectivities than those obtained in the experiments shown in Table 2.



Scheme 2. Sequential hydroboration-cyclopropanation process.

The obtained borocyclopropanes are versatile synthetic intermediates, in which the pinacolatoboryl group can be transformed in different functional groups (Scheme 3).[22] With the aim of showing the potential of these precursors, a few derivatizations have been carried out. Boronic acids and trifluoroborate salts were prepared under standard conditions in good yields, using $NaIO_4/HCl_{(aq)}$ and $KHF_{2(aq)}$ in MeOH, respectively (**3a**, **3i**, **4**, Scheme 3). Oxidation of the boronic acid **3a** with Oxone[23] led to acetate **5** after protecting the alcohol, in a reaction where the conditions must be carefully controlled to avoid overoxidation and fragmentation of the cyclopropane ring. Additionally, a Suzuki−Miyaura cross-coupling transformation was accomplished with 1-iodo-4-(trifluoromethyl)benzene, using the $Pd(OAc)_2$/XantPhos catalytic system,[17] to give the diaryl cyclopropane **6** in good yield. In a different transformation, a metal-free sp^2-sp^3 coupling derivatization[24] was carried out with borylcyclopropane **2a** and thiophene, affording the tri-substituted cyclopropane **7**.



Scheme 3. Functionalization of cyclopropylboronate esters. Conditions (a) $NaIO_4$ (1.5 equiv), $HCl_{(aq)}$ (1 equiv), THF/H_2O, 25 °C, 14 h, **3a** (75%), **3i** (72%). (b) KHF_2 (5 equiv) MeOH/H_2O, 25 °C, 8 h, 82%. (c) (i) Oxone, acetone/H_2O, 25 ºC, 10 min (ii) I_2 (0.1 equiv), Ac_2O, 25 ºC, 10 min, 45%. (d) 1-iodo-4-(trifluoromethyl)benzene (1.5 equiv), $Pd(OAc)_2$ (5 mol %), XantPhos (10 mol %), Cs_2CO_3 (3 equiv), *t*BuOH/H_2O, 120 °C, 24 h, 74%. (e) 2-thienyllithium (1.2 equiv), NBS (1.2 equiv), THF, -78 ºC, 2 h, 52%.

In summary, we have developed a highly efficient protocol for the highly diastereo- and enantioselective cyclopropanation of alkenylboronates with ethyl diazoacetate, using copper-(I)-bisoxazoline catalysts. This is the first example of the enantioselective synthesis of 1-boryl-2,3-disubstituted cyclopropanes lacking any directing group. The reaction proceeds in good to excellent yields with high levels of stereocontrol. The protocol can be employed in a sequential manner, starting from terminal alkynes, and avoiding any purification step for the alkenylboronates, leading to the borylcyclopropanes in very good overall yields after the corresponding cyclopropanation reaction. The products are versatile synthetic intermediates for the preparation of polysubstituted cyclopropane derivatives in an enantioselective fashion.

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Keywords: borylcyclopropanes •alkenylboronates • asymmetric cyclopropanation • copper catalysis • alkyne hydroboration

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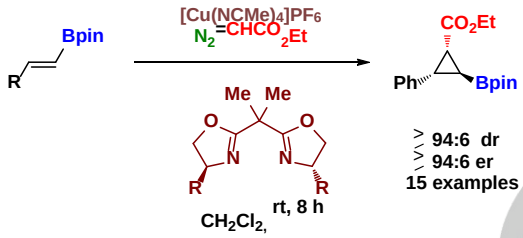
Borylcyclopropanes

1-Boryl-2,3-disubstituted-cyclopropanes can be prepared in high yield and high diastereo- and enantioselectivity from alkenylboronates and ethyl diazoacetate, in the presence of catalytic amounts of Cu(I)-bioxazoline species.



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