Catalytic Stereoselective Borylative Transannular Reactions

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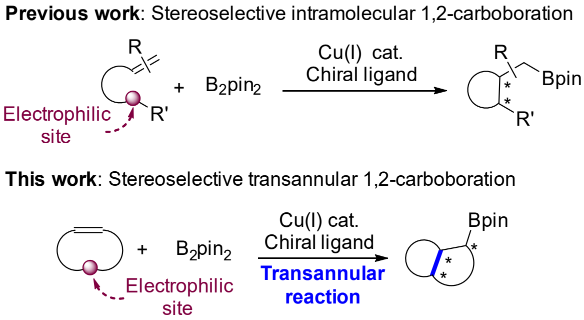
Dedication ((optional))

Abstract: Medium-sized carbocycles containing an α,β-unsaturated ketone moiety as Michael acceptor site and a ketone moiety as internal electrophilic site are ideal substrates to conduct Cu(I)-catalyzed conjugated borylation followed by electrophilic intramolecular trapping that results into a pioneer transannular borylative ring closing reaction. The relative configuration of three adjacent stereocenters is controlled, giving access to a single diastereoisomer for a wide range of substrates tested. Moreover, when a chiral ligand is incorporated, the reaction provides enantioenriched polycyclic products up to 99% e.e.

Generating molecular complexity from simple starting materials is intrinsically associated to the task of organic synthesis. Often, these are a combination of several cyclic structures and, in this sense, chemists typically face the generation of such cyclic molecular scaffolds by using either cyclization or cycloaddition processes. As an alternative, transannular reactions in which the two reacting centers are tethered together as part of a macrocyclic starting material show up as an appealing alternative for the fast and reliable construction of complex polycyclic molecular scaffolds.[1] In fact, several research groups have demonstrated that transannular reactions can be an excellent strategic decision when designing the synthesis of complex natural products.[2] However, in almost all cases, the reported examples make use of chiral starting materials, therefore relying on substrate control during the diastereoselective generation of new stereocentres. On the other hand, catalytic and enantioselective variants of transannular reactions are limited to a handful of examples. In particular, and after the seminal report by Jacobsen dealing with an elegant example of a transannular Diels-Alder reaction under chiral oxazaborolidine catalysis,[3] only four additional transformations have been reported up to date. Jacobsen himself described an enantioselective transannular ketone-ene reaction using a salen-Cr(III) Lewis acid catalyst[4] and Hierseman has reported the use of Cu(II)-bis-oxazoline compexes as catalysts in a transannular Claisen rearrangement.[5] Alternatively, enamine catalysis has been used by List in a transannular aldol reaction,[6] and some of us have also very recently reported one example of a catalytic and enantioselective transannular Morita-Baylis-Hillman reaction under chiral phosphine catalysis.[7]

On the other hand, borylative ring closing of functionalized alkenes bearing internal electrophilic sites appears as a very efficient strategy for the strategic construction of carbocycles. There are many literature examples involving borylative cyclization of enynes, endiynes, allenynes and enallenes under Pd, Au, Rh or Ni catalysis that show the excellent performance of this approach.[8] On the contrary, copper-catalyzed borylative ring closing reactions that take place through C-B bond formation with concomitant C-C coupling based on the 1,2-carboboration concept has been more scarcely studied (Scheme 1, top). Most of the reactions reported involve borylcupration of the alkene followed by intramolecular nucleophilic substitution,[9] together with some limited examples in which the internal electrophile reacting with the alkylcuprate intermediate is a carbonyl-based functionality[10] or an imine.[11] There are also some examples in which chiral ligands are incorporated to achieve enantiocontrol.[12] On the contrary, examples of borylative ring closing reactions that involve an initial conjugated borylation process that generates a copper enolate intermediate that is subsequently trapped by the internal electrophile is restricted to just three limited examples in the literature.[13]

In view of these precedents, we envisaged the possibility of developing transannular reactions initiated by a copper catalyzed borylation/ring closing process on a macrocyclic substrate containing an α,β-unsaturated ketone as suitable moiety for the initial conjugated borylation reaction and a ketone as internal electrophilic site to promote the transannular process (see Scheme 1, bottom). The addition of a chiral ligand at the Cu(I) catalyst would also provide an opportunity to control the stereochemical outcome of the concomitant C-B and C-C bond forming steps, enabling an overall enantioselective transannular reaction, which would significantly expand the toolbox of chemical synthesis through different manipulations of the stereogenic alkyl boronate.[14]


Previous work: Stereoselective intramolecular 1,2-carboboration

This work: Stereoselective transannular 1,2-carboboration

Scheme 1. Catalytic enantioselective borylative ring closing reactions.

We first started our work by evaluating the viability of the envisaged domino conjugated borylation/transannular aldol reaction using (*Z*)-cyclodec-2-ene-1,6-dione (**1**) as a suitable

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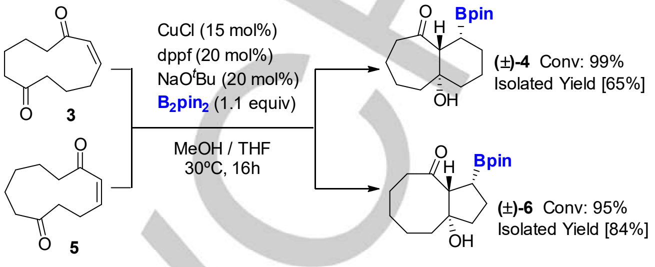
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate)) model compound that would lead to the formation of adduct **2** showing an octahydroazulene-type architecture, which is a general motif present in a variety of natural products and bioactive compounds.[15] We decided to use the catalytic system based on CuCl/base to promote the activation of B$_2$pin$_2$, via σ-bond metathesis step.[16] As it can be seen in Table 1, the projected transannular reaction took place smoothly with NaO^{t}Bu or KO^{t}Bu as bases (entries 1-2), providing the borylated bicyclo[5.3.0]decane adduct (±)-**2** as a single diastereoisomer generating three consecutive stereocenters. Interestingly, no reactivity was observed when NaOMe was the base of choice (entry 3). Since NaO^{t}Bu resulted the most efficient base, we next explored the influence of several mono- and diphosphines in the reaction outcome. It was found that PPh$_3$, P(^{n}Bu)$_3$, dppe and dppf were convenient ligands to achieve high conversions and isolated yields, keeping the formation of the bycyclic product as a single diastereoisomer (entries 4-8). Under optimized reaction conditions, other copper (I) sources were employed without any significant improvement (entries 9-10), whereas no product formation was detected using a Cu(II) salt or in the absence of copper catalysts (entries 11-12). Interestingly, in all the examples, the reaction was fully regioselective, in line with our initial hypothesis that expected an initial β-boration of the enone to generate a copper enolate intermediate.

Table 1. Cu-catalyzed diastereoselective borylative transannular reaction of model substrate **1**.[a]

Entry	Cu catalyst	base	ligand	Conv (%)[b] IY [%][c]
1	CuCl	NaO^{t}Bu	---	92
2	CuCl	KO^{t}Bu	---	63
3	CuCl	NaOMe	---	0
4	CuCl	NaO^{t}Bu	PPh$_3$	99
5	CuCl	NaO^{t}Bu	PCy$_3$	82
6	CuCl	NaO^{t}Bu	P(^{n}Bu)$_3$[d]	99 [91]
7	CuCl	NaO^{t}Bu	dppe	99
8	CuCl	NaO^{t}Bu	dppf	99 [86]
9	CuI	NaO^{t}Bu	dppf	45
10	[Cu(CH$_3$CN)$_4$]OTf	NaO^{t}Bu	dppf	91
11	CuO	NaO^{t}Bu	dppf	0
12	-	NaO^{t}Bu	dppf	0

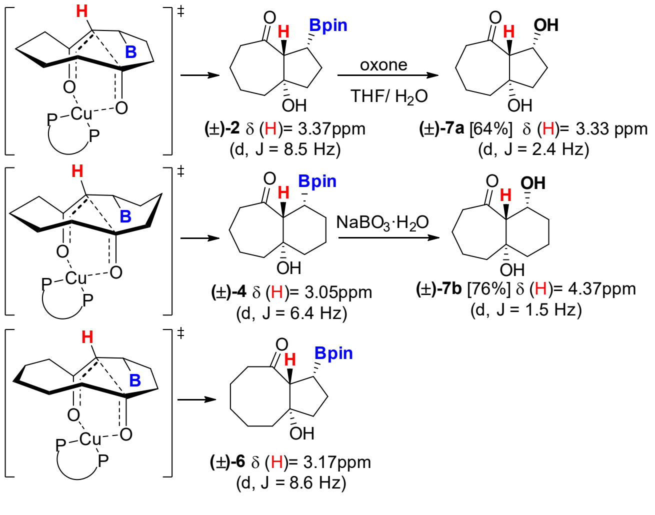
[a] Reactions were performed at 0.1 mmol of substrate, with Cu catalyst (15 mol%), base (20 mol%), ligand (20 mol%), B$_2$pin$_2$ (1.1 equiv), THF (6 mL), MeOH (2 equiv), 30ºC, 16h. [b] Conversion calculated by NMR using naphthalene as internal standard, [c] IY: isolated yields of pure product after column chromatography, [d] 15 mol% of ligand was used.

The precise arrangement of the relative possition of the functional groups in undecane macrocyclic architectures also allowed to convert substrate (Z)-cycloundec-7-ene-1,6-dione (**3**) and (Z)-cycloundec-2-ene-1,6-dione (**5**) into the corresponding adducts with the bicyclo[5.4.0]undecane structure (±)-**4** and bicyclo[6.3.0]undecane core (±)-**6**, respectively, in both cases as single diastereoisomers (Scheme 2).



Scheme 2. Cu-catalyzed diastereoselective borylative transannular reaction of substrates **3** and **5**.

The highly diastereoselective aldol reaction might be explained by the preferred formation of a chelated (Z)-configured cyclic copper enolate intermediate (Scheme 3). The relative stereochemistry has been assigned by comparison of the ^{1}H NMR spectra of the three new products. The bicyclo[5.3.0]decane adduct (±)-**2** has a characteristic doublet at 3.37 ppm for H$_\alpha$ with a coupling constant value (J=8.5 Hz) indicative of this proton being *cis*-axial/equatorial to and the adjacent proton (confirmed by the X-ray structure of a derivative compound, see SI). Similarly, the ^{1}H NMR spectrum for (±)-**4** and (±)-**6** shows a doublet for H$_\alpha$ at 3.05 ppm and 3.17 ppm, respectively, with similar coupling constant values (J=6.4 Hz and J=8.6 Hz) (Scheme 3). These values are in contrast to the typical *trans*-diaxial coupling constants for similar products.[17] When adducts (±)-**2** and (±)-**4** were oxidized, the corresponding diols (±)-**7a** and (±)-**7b** show doublets for H$_\alpha$ at 3.33 ppm and 4.37 ppm respectively, and coupling constants values about J=2.4 Hz and J=1.5 Hz, suggesting a quasi-coplanar disposition of the two adjacent protons probably due to the repulsion of the cis diol moieties.



Scheme 3. Proposed stereochemical models and conversion of borylated adducts into diols

In order to establish the general behavior of the diastereoselective conjugated borylation / transannular aldol reaction, we first focused on macrocycles with cyclodec-2-en-1,6-dione architectures that contain fused aromatic systems with diverse substitution patterns. All these substrates were efficiently converted into the corresponding borylated tricyclic products under optimized conditions as single diastereoisomers (Table 2).

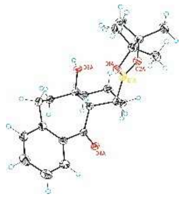
Table 2. Scope of the diastereoselective Cu/dppf diastereoselective borylative transannular reaction.[a]

Entry	Substrate	Product	Conversion (%)[b] Isolated Yield [%][c]
1			99 [86]
2			90 [31]
3			96 [47]
4			99[46]
5			95 [60]
6			99 [71]
7			99 [58]

[a] Reactions were performed at 0.2 mmol of substrate, with Cu catalyst (15 mol%), NaOtBu (20 mol%), dppf (20 mol%), B_2pin_2 (1.1 equiv), THF (6 mL), MeOH (2 equiv), 30ºC, 16h. [b] Conversion calculated by NMR using naphthalene as internal standard, [c] IY: isolated yields of pure product.

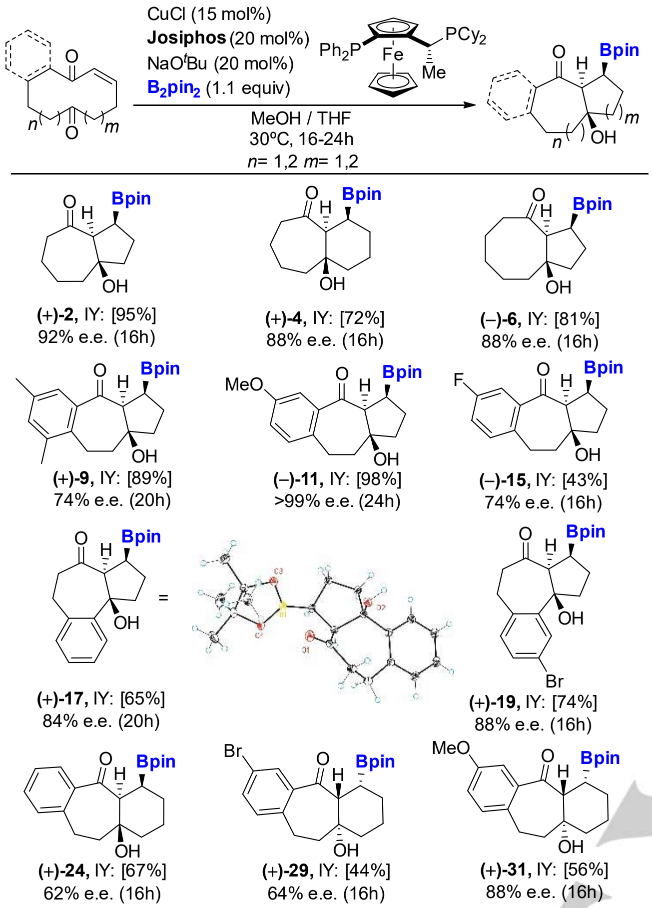
For those substrates with a fused arene at the enone moiety the isolated yield of the bicyclic adduct was strongly dependent on the nature of the substituents at the aryl core, although in all cases the reaction proceeded cleanly towards full conversion towards the corresponding borylated transannular product as NMR analysis indicates (entries 1-4). When this fused aromatic ring was located next to the ketone group, that plays the role of the internal electrophilic site, the expected borylated adducts were obtained with higher isolated yields possibly due to the higher estabilization of the products (entries 5-6). On the other hand the presence of two fused arene moieties next to both the enone and to the ketone in **20**, provided tetracyclic product (±)-**21** with only one stereocenter (entry 7), presumably as a consequence of a dehydration process favoured by the highly conjugated nature of this final product.

With a view to complete the substrate scope, we conducted the Cu/dppf catalyzed borylative transannular reaction of cycloundec-2-en-1,7-dione macrocyclic substrates toward the diastereoselective formation of bicyclo[5,4,0]undecane scaffolds (Scheme 4). These substrates also contain a fused aromatic group adjacent to the enone moiety with different substitution patterns. The control on the diastereoselectivity was complete for all substrates explored when dppf was used as ligand, despite the fact that, as it was observed before, isolated yields were dependent on the nature of the substituents at the arene moiety. In the case of substrate **23**, when $P(^nBu)_3$ was used as ligand, the expected product (±)-**24** was formed in 55% together with a minor amount of its diastereoisomer (±)-**25** that could be fully characterized by X-ray analysis (Scheme 4).



Scheme 4. Cu-catalyzed diastereoselective borylative transannular reaction on cycloundecane substrates.

Finally, to demonstrate the feasibility of developing enantioselective variants of this diastereoselective borylative transannular reaction, macrocycle **1** was subjected to standard reaction conditions using a type of Josiphos chiral ligand (Scheme 5).[18] Interestingly, in addition to the complete diastereoselectivity observed, high levels of asymmetric induction could be achieved (92% e.e. for (+)-**2**). The absolute stereostructure of the enantiomers was established by single-crystal X-ray analysis of an enantiopure sample of (+)-**17** (Scheme 5).



(+)-2, IY: [95%] 92% e.e. (16h)

(+)-4, IY: [72%] 88% e.e. (16h)

(–)-6, IY: [81%] 88% e.e. (16h)

(+)-9, IY: [89%] 74% e.e. (20h)

(–)-11, IY: [98%] >99% e.e. (24h)

(–)-15, IY: [43%] 74% e.e. (16h)

(+)-17, IY: [65%] 84% e.e. (20h)

(+)-19, IY: [74%] 88% e.e. (16h)

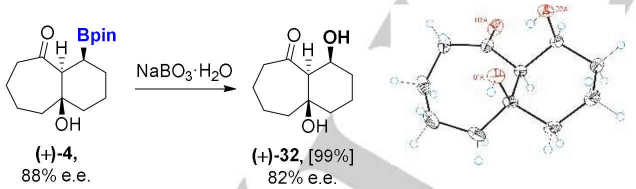
(+)-24, IY: [67%] 62% e.e. (16h)

(+)-29, IY: [44%] 64% e.e. (16h)

(+)-31, IY: [56%] 88% e.e. (16h)

Scheme 5. Cu-catalyzed enantioselective transannular conjugated borylation/aldol cyclization with decane and undecane macrocyclic substrates.

Synthetic manipulations on compound **(+)-4** as representative model of the enantioenriched polycyclic products prepared was also surveyed (Scheme 6). In particular, oxidative protocol was explored which proceeded with complete stereochemical retention from C-B to C-OH bond.



(+)-4, 88% e.e.

(+)-32, [99%] 82% e.e.

Scheme 6. Stereospecific C-B bond oxidation of **(+)-4**.

In conclusion, we have shown that copper-catalyzed conjugate borylation can be used to trigger highly diastereoselective transannular reactions that enable the construction of complex bicyclic scaffolds such as the azulene core in a simple and straightforward manner. In addition the reaction can also be carried out in a highly enantioselective fashion through the incorporation of a chiral ligand in the catalytic system. The practical synthetic utility of this transformation is noteworthy considering the possibilities for the alkyl boronate unit to undergo stereospecific transformations.

Acknowledgements

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Keywords: transannular borylation • ring closing • stereogenic alkyl boronate • copper catalysts • electrophilic intramolecular trapping

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[18] See Supporting Information for screening of chiral ligands.

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

Copper-catalyzed conjugate borylation can be used to trigger highly diastereoselective and enantioselective transannular reactions that enable the construction of complex bicyclic scaffolds.

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