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Relay Catalysis: Enantioselective Synthesis of Cyclic Benzo-Fused Homoallylic Alcohols by Chiral Brønsted Acid Catalyzed Allylboration / Ring Closing Metathesis

Santos Fustero[a,b,*], Elsa Rodríguez[a], Lidia Herrera[a], Rubén Lázaro[a], Silvia Catalán[a] and Pablo Barrio[a,*]

[a] Departamento de Química Orgánica
Universidad de Valencia
Av. Vicente Andrés Estellés s/n E-46100 Burjassot (Spain)
Phone: 96354279 Fax: 96354979 E-mail: santos.fustero@uv.es; pablo.barrio@uv.es

[b] Laboratorio de Moléculas Orgánicas
Centro de Investigación Príncipe Felipe, E-46012 Valencia (Spain)

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Abstract. Six and seven membered benzo-fused cyclic homoallylic alcohols can be readily synthesized by a Tandem Chiral Brønsted Acid Catalyzed Allyl (crotyl)boration / Ring Closing Metathesis sequence performed under orthogonal relay catalysis conditions. Excellent enantio- and diastereoselectivities are obtained in most of the cases.

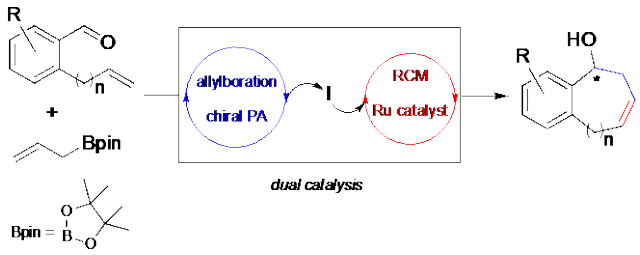
Keywords: Allylation; Asymmetric Catalysis; Fused-ring systems; Alcohols; Relay Catalysis

Tandem catalysis has attracted a great deal of interest as it provides quick access to molecular complexity usually under extremely convenient reaction conditions.[1] Among the several existing categories, relay orthogonal catalysis, which involves the consecutive action of two or more independent catalytic cycles, deserves special attention for its experimental simplicity.[2] These kinds of processes enable the combination of organocatalysis and transition-metal catalysis giving rise to products beyond the scope of each single catalytic systems.[3],[4]

Several catalyst combinations are feasible, of which chiral phosphoric acids[5],[6] have shown broad compatibility with different transition metal catalysts.[7] Specifically, tandem catalysis using chiral phosphoric acids and metathesis catalysts[8] is limited to two reports on cross-metathesis / intramolecular conjugate-addition processes,[9] being the parent ring closing metathesis unprecedented in relay catalysis, to the best of our knowledge. In most of the examples of relay catalysis using a metal complex / chiral phosphoric acid binary system, an intramolecular organocatalytic reaction takes places on the substrate generated by the organometallic catalysis.[7],[8] We have envisioned that the careful choice of transformations would permit the reverse of the order in which both catalytic cycles take place and enable an organocatalytic transformation to proceed in the presence of the metathesis catalyst. The organocatalytic transformation required must leave a pendant olefin in the intermediate for the subsequent RCM step that would take place on the α,ω-diene intermediate released by the first transformation. Asymmetric allylation[10] plays a pivotal role in organic synthesis and fulfils the cited pre-requisites. Moreover, it has never been coupled in a relay process, as far as we know. Among the existing methods for the asymmetric allylation of carbonyl compounds, asymmetric allylboration[11] has deserved special attention as an invaluable tool for the synthesis of homoallylic alcohols, versatile building blocks for the synthesis of pharmaceutical and natural products.[11a] Recently, enantioselective catalytic allylborations have emerged.[12] The chiral phosphoric acid-catalyzed allylboration of aldehydes reported by Antilla appears as an appropriate alternative for this purpose.[13a]

Considering this background, we designed the following tandem transformation for the asymmetric construction of cyclic homoallylic alcohols (Scheme 1). A suitably substituted aldehyde with a remote olefin would react with the pinacol ester of allylboronic acid in the presence of a chiral phosphoric acid and a Ru-based olefin metathesis catalyst. The chiral homoallylic alcohol obtained after the first catalytic cycle would undergo RCM affording cyclic benzo-fused homoallylic alcohols. Noteworthy, the asymmetric synthesis of 1,2-dihydronaphtalen-1-ol derivatives which are present in numerous pharmacologically relevant compounds such as the anti-tumoral podophilatoxine, [14] is rather underdeveloped being the reported examples limited

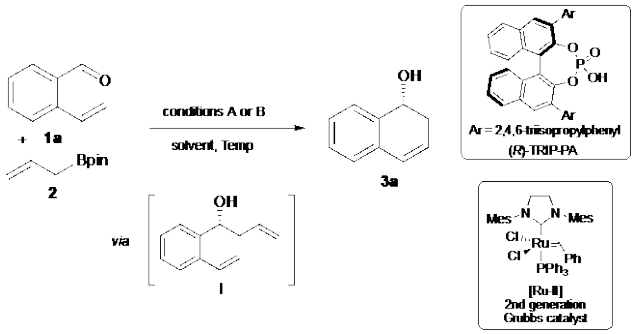
to enzymatic / microbial processes[15] and desymmetrization reactions which extremely narrow the substrate scope.[16]



Scheme 1. Tandem asymmetric allylboration / RCM.

Before essaying the relay catalysis conditions, the sequential one-pot protocol was tested on *o*-vinylbenzaldehyde **1a** as a model substrate (Table 1, entry 1). Thus, under the reported optimized conditions [(*R*)-TRIP-PA 5 mol%, toluene, -30 ºC],[13a] formation of the desired homoallylic alcohol ***I*** is observed by TLC analysis.[17] Then, Grubbs second generation catalyst (5 mol%) is added to the reaction mixture at room temperature affording 1,2-dihydronaphtalen-1-ol **3a** in good yield and excellent enantioselectivity (Table 1, entry 1). In view of this promising result, the relay catalysis conditions were essayed. Hence, treatment of a mixture of substrate **1a** and allylboronic acid pinacol ester **2** with (*R*)-TRIP-PA (5 mol%) and second generation Grubbs catalyst (5 mol%) in toluene at -30 ºC gives rise to ***I***, which spontaneously undergoes RCM upon removing the cooling bath, thus achieving **3a** in good yield and excellent enantioselectivity (Table 1, entry 2).[18] Comparable results were obtained when DCM was used as reaction solvent (Table 1, entry 3). Lowering the temperature to -78 ºC did not result in any noticeable improvement (Table 1, entry 4). Therefore toluene at -30 ºC was chosen for optimum reaction conditions. Finally, the reaction was also tested with 1 mol% of the chiral Brønsted acid [(*R*)-TRIP-PA], resulting in a remarkable drop in enantioselectivity (Table 1, entry 5).

Table 1. Optimization of the Reaction Conditions

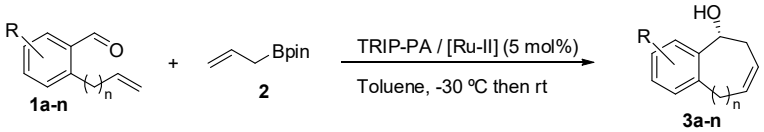


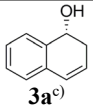
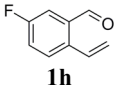
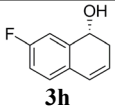
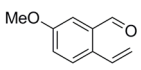
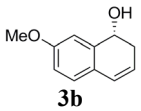
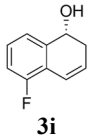
Entry	Conditions	Solvent	T (ºC)	**3a** (%)[a]	ee (%)[b]
1	A	Toluene	-30 then rt	78	98
2	B	Toluene	-30 then rt	82	>99
3	B	DCM	-30 then rt	77	98
4	B	Toluene	-78 then rt	85	98
5	B[c]	Toluene	-30 then rt	80	75

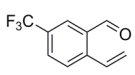
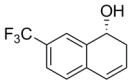
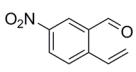
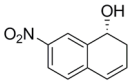
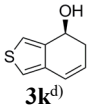
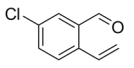
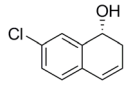
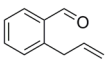
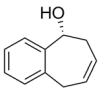
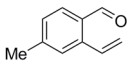
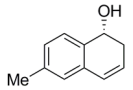
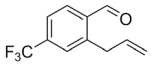
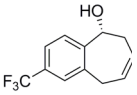
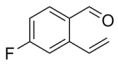
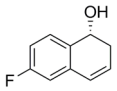
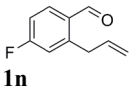
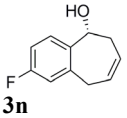
[a] Isolated yields after flash chromatography [b] Determined by HPLC [c] Reaction performed with 1 mol % of (*R*)-TRIP-PA. Conditions **A**: 1) (*R*)-TRIP-PA (5 mol%) 2) [Ru-II] (5 mol%). Conditions **B**: (*R*)-TRIP-PA / [Ru-II] (5 mol%).

Once optimized conditions had been established, the scope and limitations of the new strategy were studied (Table 2).

Table 2. Scope and limitations.



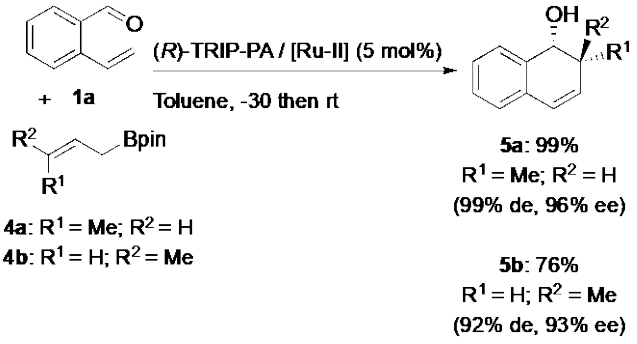
Entry	Substrate	Product	Yield (%)[a]	ee (%)[b]	Entry	Substrate	Product	Yield (%)[a]	ee (%)[b]
1	 **1a**	 **3a**[c]	82	99	8	 **1h**	 **3h**	85	99
2	 **1b**	 **3b**	74	98	9	 **1i**	 **3i**	99	92

3	 **1c**	 **3c**	88	99	10	 **1j**	 **3j**	65	40
4	 **1d**	 **3d**	80	99	11	 **1k**	 **3k**[d]	70	93
5	 **1e**	 **3e**	95	98	12	 **1l**	 **3l**	80	82
6	 **1f**	 **3f**	95	99	13	 **1m**	 **3m**	88	76
7	 **1g**	 **3g**	54	96	14	 **1n**	 **3n**	78	77

[a] Isolated yields after flash chromatography [b] Determined by HPLC [c] Absolute configuration was determined to be *R* by comparison with the reported optical rotation value (see ref. 25a). [d] Heteroaromatic aldehydes have been reported to give the opposite configuration in (*R*)-TRIP-PA catalyzed allylboration reactions (see ref. 13a); furthermore, the optical rotation for this product displays opposite sign (see SI).

Substrates bearing electron-donating (Table 2, entries 2 and 6), electron-withdrawing (Table 2, entries 3-4) or halogen substituents (Table 2, entries 5, 7-9) at the 3, 4 or 5 positions readily undergo the tandem allylboration / RCM process giving rise to the 1,2-dihydro-1-naphtol derivatives **3a-i** in good yields and excellent enantioselectivities. On the other hand, substitution at the 6 position results in a substantial drop in enantioselectivity (Table 2, entry 10).[19] It is worth noting that substitution can be introduced in any position of the aromatic ring, as exemplified by the fluorine substituent (Table 2, entries 7-10). Being the 6-fluor the only derivative for which a drop in enantioselectivity is observed steric factors may be invoked to explain this observation.[20] Remarkably, heteroarene derivatives can also participate in this tandem transformation (Table 2, entry11). In order to extend the synthetic applicability of our methodology, we then studied the synthesis of homologated 7-membered benzo-fused homoallylic alcohols using the tandem allylboration / RCM process. Thus, when substrates **1l-n** were subjected to optimized conditions homologated products **3l-n** were obtained in good yields and moderate enantioselectivities (Table 2, entries 12-14).[19] Once again, electron-withdrawing (Table 2, entry 13) and halogen (Table 2, entry 14) substituens at the 4 position of the aromatic ring are suitable for the transformation. Steric hindrance seems to be the most plausible explanation for the observed drop in enantioselectivity. The introduction of a benzylic methylene renders not only longer size but also increased flexibility to the chain in the ortho position to the reactive site (enantioselectivity is fixed during the allylboration step). This bulkier substituent may distort the highly ordered chair-like transition state proposed for this transformation.[13a],[21]

As a further extension of this work, the corresponding crotylboration / RCM was tested by using both commercially available *cis*- and *trans*-crotylboronic acid pinacol esters **4a,b**, respectively (Scheme 2).



Scheme 2. Tandem asymmetric crotylboration / RCM.

Ortho-vinylbenzaldehyde **1a** readily undergoes asymmetric crotylation under the usual conditions followed by RCM to afford dihydronaphtol derivatives bearing two consecutive stereocenters.[22] Substrate 1a reacts with *cis*-crotylboronic acid pinacol ester **4a** affording the corresponding *trans* 5a in excellent yield and enantioselectivity as a single diastereoisomer.[23] On the other hand, reaction with the *trans*-crotylboronic acid derivative **4b** results in good but somewhat lower chemical yield, enantioselectivity and diastereomeric ratio for the corresponding *cis* product **5b**.[24] Interestingly, although the crotylboration step proceeds similarly in both cases, intermediates ***IIa*** and ***IIb*** (Figure 1) display different cyclization rates. Thus, while ***IIa*** evolves to the final product in 4 hours, after the same

reaction time ***IIb*** remains mostly unreactive and an extra 5 mol% second generation Grubbs catalyst is required to promote completion of the reaction. This difference in reactivity can be explained by the conformational restrictions induced by the extra methyl group (Figure 1).[25] For *syn* intermediate ***IIa***, the preferred conformation should be ***B*** in which the two reaction centers are placed gauche to each other; while conformation ***A'***, placing the reactive ends *anti*-periplanar to each other, is expected for *anti* intermediate ***IIb*** (Figure 1).

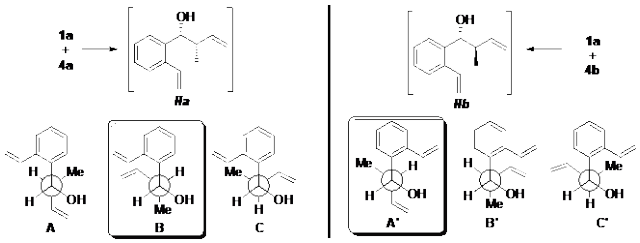


Figure 1. Preferred conformations for intermediates ***IIa*** and ***IIb***.

In conclusion, a temperature triggered tandem Brønsted acid catalyzed allyl(crotyl)boration / RCM sequence has been developed. The new methodology shows broad scope and allows for the synthesis of both six and seven-membered benzo and heteroarene-fused cyclic homoallylic alcohols, some of them otherwise inaccessible with the existing methodologies, in good to excellent enantioselectivities, in most of the cases. To the best of our knowledge this report represents the first example of a tandem asymmetric allylation / RCM process. Moreover, neither an allylboration nor a RCM process has ever been reported in a relay catalysis process before. In addition, the methodology can be extended to the analogous crotylation variant. Noteworthy, compound **3a** is a key intermediate in Lautens' synthesis of the important antidepressant sertraline.[16] Further studies aimed at the expansion of the scope of this transformation are currently underway in our laboratories.

Experimental Section

General procedure for the tandem allylboration / RCM: to a solution of vinyl- or allylbenzaldehyde **1 a-n** in toluene (0.1M) (*R*)-TRIP-PA (5 mol%) and Grubbs 2nd generation catalyst (5 mol%) were added. The reaction mixture was then cooled to -30ºC followed by the addition of the allylboronic acid pinacol ester **2** (1.2 equiv). After the allylboration step was completed (1h aprox.), the reaction mixture was allowed to reach room temperature. When the intermediate was consumed (3h aprox, TLC), solvents were removed under reduced pressure to give crude product **3**, which was purified by flash chromatography. The enantiomeric excess of the product was determined by HPLC: Chiralcel OD-H (25 cm x 0.46 cm column), hexane:isopropanol 98:2 as eluent and flow = 1 ml/min unless otherwise indicated.

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