DOI: 10.1002/adsc.201201095

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] Rubén Lázaro,[a] Lidia Herrera,[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
Fax: (+34)-96-354-979; phone: (+34)-96-354-279; e-mail: santos.fustero@uv.es or pablo.barrio@uv.es
[b] Laboratorio de Moléculas Orgánicas, Centro de Investigación Príncipe Felipe, E-46012 Valencia, Spain

Received: December 14, 2012; Revised: February 20, 2013; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201201095.

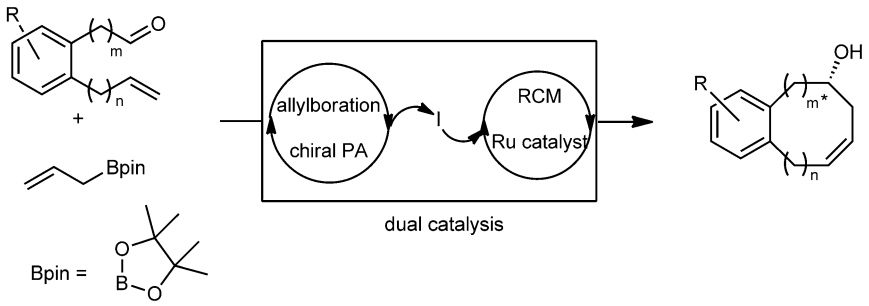
Abstract: Six- and seven-membered benzo-fused cyclic homoallylic alcohols can be readily synthesized by a tandem chiral Brønsted acid-catalyzed allyl (crotyl)boration/ring closing metathesis sequence performed under orthogonal relay catalysis conditions. Excellent enantio- and diastereoselectivities are obtained in most of the cases. In addition, the parent crotylboration/RCM process is also described. The required substrates, *ortho*-vinylbenzaldehydes, are readily available in one step from commercially available starting materials. Both catalysts and reactants are also available from commercial suppliers. The reaction shows broad functional group compatibility and is also suitable for heteroaromatic substrates. Substitution at any position of the aromatic ring is tolerated; however, substitution at position 6 results in a substantial drop in enantioselectivity.

Keywords: alcohols; allylation; asymmetric catalysis; fused-ring systems; relay catalysis

Tandem catalysis has attracted a great deal of interest as it provides a 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] and a single report on a RCM/isomerization/Pictet–Spengler cascade.[10] 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 us to reverse 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[11] plays a pivotal role in organic synthesis and fullfils the cited prerequisites. 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[12] has attracted special attention as an invaluable tool for the synthesis of homoallylic alcohols, versatile building blocks for the synthesis of pharmaceuticals and natural products.[12a] Recently, enantioselective catalytic allylborations have emerged.[13] The chiral phosphoric acid-catalyzed allylboration of aldehydes reported by Antilla appears as an appropriate alternative for this purpose.[14]

Considering this background, we designed the following tandem transformation for the asymmetric construction of cyclic homoallylic alcohols

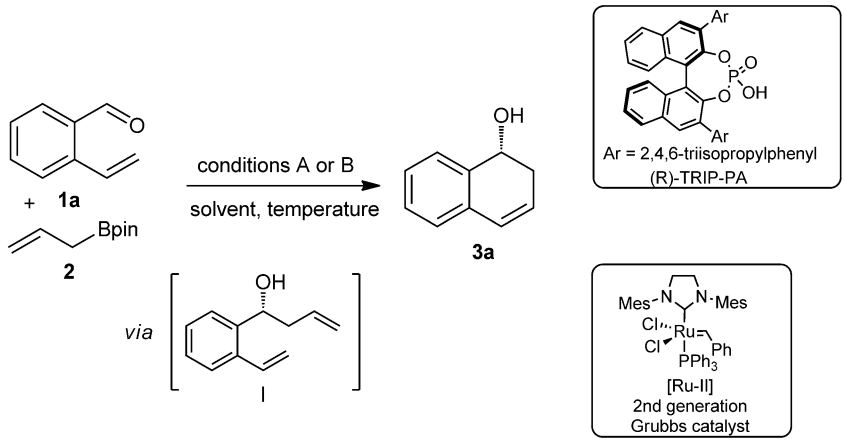


Scheme 1. Tandem asymmetric allylboration/RCM.

(Scheme 1). A suitably substituted aldehyde with a remote olefin would react with the pinacol ester of the allylboronic acid in the presence of a chiral phosphoric acid and an 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-dihydronaphthalen-1-ol derivatives which are present in numerous pharmacologically relevant compounds such as the anti-tumoral podophilatoxine,[15] is rather underdeveloped, the reported examples being limited to enzymatic/microbial processes[16] and desymmetrization reactions which extremely narrow the substrate scope.[17]

Before essaying the relay catalysis conditions, the sequential one-pot protocol was tested on *ortho*-vinylbenzaldehyde **1a** as a model substrate (Table 1, entry 1). Thus, under the reported optimized conditions [(*R*)-TRIP-PA 5 mol%, toluene, −30 °C],[14] formation of the desired homoallylic alcohol ***I*** is observed by TLC analysis.[18] Then, Grubbs second generation catalyst (5 mol%) is added to the reaction mixture at room temperature affording 1,2-dihydronaphthalen-1-ol **3a** in good yield and excellent enantioselectivity (Table 1, entry 1). In view of this promising result, the relay catalysis conditions were assayed. 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 °C gives rise to ***I***, which spontaneously undergoes RCM upon removing the cooling bath, thus achieving **3a** in good yield and ex-

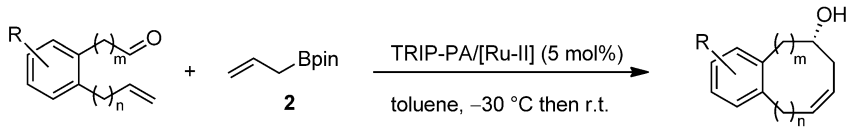
Table 1. Optimization of the reaction conditions.



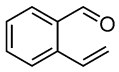
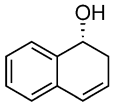
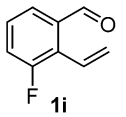
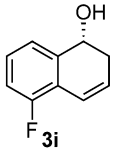
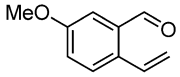
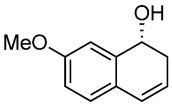
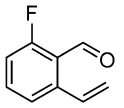
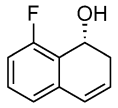
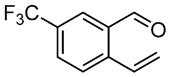
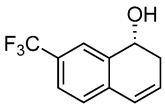
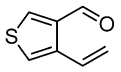
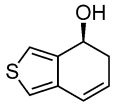
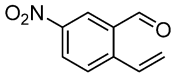
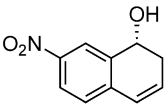
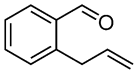
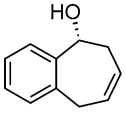
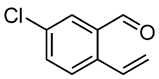
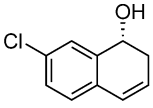
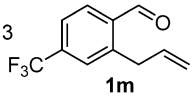
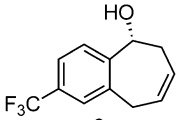
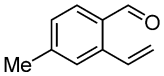
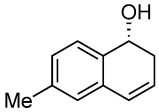
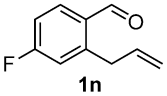
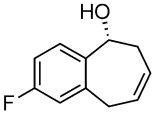
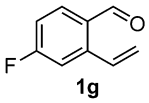
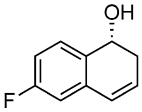
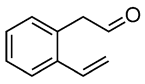
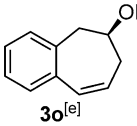
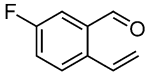
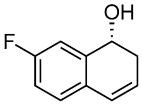
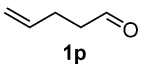
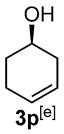
Entry	Conditions	Solvent	Temperature [°C]	**3a** Yield [%][a]	*ee* [%][b]
1	A	toluene	−30 then r.t.	78	98
2	B	toluene	−30 then r.t.	82	>99
3	B	DCM	−30 then r.t.	77	98
4	B	toluene	−78 then r.t.	85	98
5	B[c]	toluene	−30 then r.t.	80	75

[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%), 1 h 2) [Ru-II] (5 mol%) 3 h. *Conditions B:* (*R*)-TRIP-PA/[Ru-II] (5 mol%), 4–5 h (total time for the two steps).

Table 2. Scope and limitations.



1a–n 3a–n

Entry	Substrate	Product	Time [h][a]	Yield [%][b]	*ee* [%][c]	Entry	Substrate	Product	Time [h][a]	Yield [%][b]	*ee* [%][c]
1	 **1a**	 **3a**[d]	4	82	99	9	 **1i**	 **3i**	5	99	92
2	 **1b**	 **3b**	3	74	98	10	 **1j**	 **3j**	3.5	65	40
3	 **1c**	 **3c**	4	88	99	11	 **1k**	 **3k**[e]	4.5	70	93
4	 **1d**	 **3d**	5	80	99	12	 **1l**	 **3l**	2.5	80	82
5	 **1e**	 **3e**	4.5	91	98	13	 **1m**	 **3m**	3	88	76
6	 **1f**	 **3f**	3.5	95	99	14	 **1n**	 **3n**	4	78	77
7	 **1g**	 **3g**	5.5	54	96	15	 **1o**	 **3o**[e]	5	63	67
8	 **1h**	 **3h**	3.5	85	99	16	 **1p**	 **3p**[e]	5.5	55	84[f]

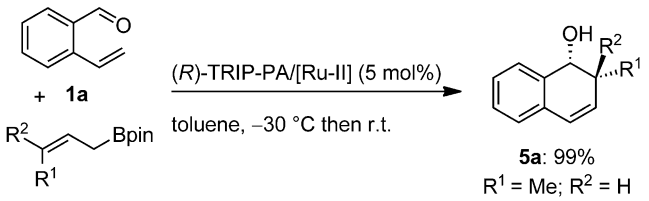
[a] Total time for the two steps (for details, see Experimental Section).
[b] Isolated yields after flash chromatography.
[c] Determined by HPLC.
[d] Absolute configuration was determined to be *R* by comparison with the reported optical rotation value (see ref.[17a]).
[e] Absolute configuration determined by analysis of the ^{1}H NMR spectra of the corresponding Mosher's esters. Heteroaromatic and some aliphatic aldehydes have been reported to give the opposite configuration in (*R*)-TRIP-PA catalyzed allylboration reactions (see ref.[14]).
[f] Determined by integration of the CF_3 signals of the diastereoisomeric Mosher's esters in their ^{19}F NMR spectra.

cellent enantioselectivity (Table 1, entry 2).[19] Comparable results were obtained when DCM was used as reaction solvent (Table 1, entry 3). Lowering the temperature to −78 °C did not result in any noticeable improvement (Table 1, entry 4). Therefore toluene at −30 °C was chosen for the 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).

Once the optimized conditions (conditions B, toluene, −30 °C, then room temperature) had been established, the scope and limitations of the new strategy were studied (Table 2).

Substrates bearing electron-donating (Table 2, entries 2 and 6), electron-withdrawing (Table 2, entries 3 and 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-naphthol 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).[20] 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). The 6-fluoro derivative is the only one for which a drop in enantioselectivity is observed and steric factors may be invoked to explain this observation.[21] Remarkably, heteroarene derivatives can also participate in this tandem transformation (Table 2, entry 11). 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).[20] Once again, electron-withdrawing (Table 2, entry 13) and halogen (Table 2, entry 14) substituents 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.[14,22] Finally, aliphatic aldehydes were also found to participate in the process, albeit in moderate yields and enantioselectivities (Table 2, entries 15 and 16). It is noteworthy that a linear aldehyde (4-pentenal **1p**) was used giving rise to a non-benzo-fused product.

As a further extension of this work, the corresponding crotylboration/RCM was tested by using both



4a: R^1 = Me; R^2 = H
4b: R^1 = H; R^2 = Me

5a: 99%
R^1 = Me; R^2 = H
(99% *de*, 96% *ee*)

5b: 76%
R^1 = H; R^2 = Me
(92% *de*, 93% *ee*)

Scheme 2. Tandem asymmetric crotylboration/RCM.

commercially available *cis*- and *trans*-crotylboronic acid pinacol esters **4a** and **4b**, respectively (Scheme 2).

ortho-Vinylbenzaldehyde **1a** readily undergoes asymmetric crotylation under the usual conditions followed by RCM to afford dihydronaphthol derivatives bearing two consecutive stereocenters.[23] Substrate **1a** reacts with *cis*-crotylboronic acid pinacol ester **4a** affording the corresponding *trans*-**5a** in excellent yield and enantioselectivity as a single diastereoisomer.[24] 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**.[25] 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 h, 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).[26] 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).

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 which are 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, no allylboration 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 Laut-

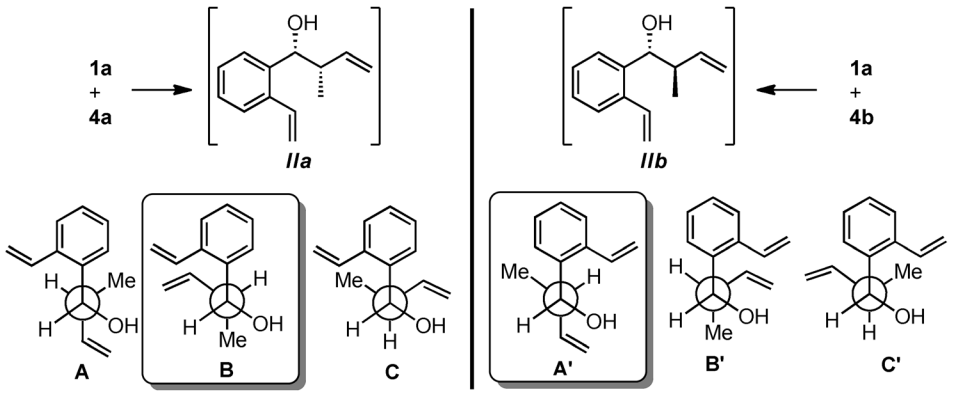


Figure 1. Preferred conformations for intermediates ***IIa*** and ***IIb***.

ens' synthesis of the important antidepressant sertraline.[17] Further studies aimed at the expansion of the scope of this transformation, with special attention to linear substrates, are currently underway in our laboratories.

Experimental Section

General Procedure for the Tandem Allylboration/RCM

T a solution of aldehyde **1a–p** in toluene (0.1 M) (*R*)-TRIPA (5 mol%) and Grubbs 2nd generation catalyst (5 mol%) were added. The reaction mixture was then cooled to −30 °C followed by the addition of the allylboronic acid pinacol ester **2** (1.2 equiv.). After the allylboration step was completed (1 h approx.), the reaction mixture was allowed to reach room temperature. When the intermediate was consumed (3 h approx., TLC), solvents were removed under reduced pressure to give crude product **3**, which was purified by flash chromatography using mixtures of hexanes and ethyl acetate as eluent (for details, see the Supporting Information). The enantiomeric excess of the product was determined by HPLC: Chiralcel OD-H (25 cm × 0.46 cm column), hexane:2-propanol 98:2 as eluent and flow = 1 mL min^{-1}, unless otherwise indicated.

Acknowledgements

We would like to thank the Spanish Ministerio de Ciencia e Innovación (CTQ2010-19774) and Generalitat Valenciana (PROMETEO/2010/061) for its financial support. P. B. and S. C. express their thanks for Juan de la Cierva contracts, E. R. thanks the Universidad de Valencia and R.L. the Spanish government for predoctoral fellowships.

References

[1] For some selected reviews on tandem catalysis, see: a) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 4; *Angew. Chem. Int. Ed.* **2012**, *51* 314; b) A. De Meijere, P. von Zezschwitz, S. Bräse, *Acc. Chem. Res.* **2005**, *38*, 413; c) A. Ajamian, J. L. Gleason, *Angew. Chem.* **2004**, *116*, 3842; *Angew. Chem. Int. Ed.* **2004**, *43*, 3754.

[2] For excellent reviews on the classification of tandem catalysis, see: a) N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* **2012**, *10*, 211; b) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001.

[3] For seminal contributions, see: a) B. J. Jellerichs, J.-R. Kong, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 7758; b) G. Chen, Y. Deng, L. Gong, A. Mi, X. Cui, Y. Jiang, M. C. K. Choi, A. S. C. Chan, *Tetrahedron: Asymmetry* **2001**, *12*, 1567; c) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *Org. Lett.* **2001**, *3*, 3329.

[4] For reviews on transition metal complex/organocatalyst combined systems, see: a) Z. Han, C. Wang, L. Gong, in: *Science of Synthesis: Asymmetric Organocatalysis*, (Ed. K. Maruoka), Georg Thieme Verlag, Stuttgart, **2012**, Vol. 2, p 697; b) C. C. Loh, D. Enders, *Chem. Eur. J.* **2012**, *18*, 10212; c) A. S. K. Hashmi, C. Hubbert, *Angew. Chem.* **2010**, *122*, 1026; *Angew. Chem. Int. Ed.* **2010**, *49*, 1010; d) P. De Armas, D. Tejedor, F. García-Tellado, *Angew. Chem.* **2010**, *122*, 1029; *Angew. Chem. Int. Ed.* **2010**, *49*, 1013; e) C. Zhong, X. Shi, *Eur. J. Org. Chem.* **2010**, 2999; f) J. Zhou, *Chem. Asian J.* **2010**, *5*, 422; g) M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350; h) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745; i) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222.

[5] For seminal contributions on chiral phosphoric acid catalysis, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356.

[6] For reviews on chiral phosphoric acid catalysis, see: a) M. Terada, *Curr. Org. Chem.* **2011**, *15*, 2227; b) M. Terada, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101; c) M. Terada, *Synthesis* **2010**, 1929; d) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262; e) M. Terada, *Chem. Commun.* **2008**,

4097; f) G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31; g) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; h) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5173; i) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; j) S. J. Connon, *Angew. Chem.* **2006**, *118*, 4013; *Angew. Chem. Int. Ed.* **2006**, *45*, 3909.

[7] For selected examples of relay catalysis using chiral phosphoric acid/transition metal binary systems, see: a) Z.-Y. Han, D.-F. Chen, Y.-Y. Wang, R. Guo, P.-S. Wang, C. Wang, L.-Z. Gong, *J. Am. Chem. Soc.* **2012**, *134*, 6532; b) M. Terada, Y. Toda, *Angew. Chem.* **2012**, *124*, 2135; *Angew. Chem. Int. Ed.* **2012**, *51*, 2093; c) C. A. Holloway, M. E. Muratore, R. I. Storer, D. J. Dixon, *Org. Lett.* **2010**, *12*, 4720; d) C. Wang, Z.-Y. Han, H.-W. Luo, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 2266; e) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796; f) Z.-Y. Han, H. Xiao, X.-H. Chen, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 9182; g) K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2008**, *130*, 14452.

[8] For reviews on olefin metathesis, see: a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; b) R. H. Grubbs, in: *Handbook of Metathesis*, Wiley-VCH, Weinheim, **2003**; c) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; d) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012.

[9] For a cross-metathesis/intramolecular aza-Michael process, see: a) Q. Cai, C. Zheng, S.-L. You, *Angew. Chem.* **2010**, *122*, 8848; *Angew. Chem. Int. Ed.* **2010**, *49*, 8666. For a cross-metathesis/intramolecular Friedel–Crafts alkylation sequence, see: b) Q. Cai, Z. A. Zhao, S.-L. You, *Angew. Chem.* **2009**, *121*, 7564; *Angew. Chem. Int. Ed.* **2009**, *48*, 7428. For analogous Ru-catalyzed tandem processes, see: c) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zhu, W.-J. Xiao, *Angew. Chem.* **2008**, *120*, 2523; *Angew. Chem. Int. Ed.* **2008**, *47*, 2489; d) S. Fustero, D. Jiménez, M. Sánchez-Roselló, C. del Pozo, *J. Am. Chem. Soc.* **2007**, *129*, 6700.

[10] Q. Cai, X.-W. Liang, S.-G. Wang, J.-W. Zhang, X. Zhang, S.-L. You, *Org. Lett.* **2012**, *14*, 5022.

[11] For a recent review on asymmetric allylation reactions, see: M. Yus, J. C. González-Gomez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774.

[12] a) E. M. Carreira, L. Kvaerno, in: *Classics in Strereoselective Synthesis* Wiley-VCH, Weinheim, **2009**, Chapter 5, p 164; b) H. Lachance, D. G. Hall, *Org. React.* **2008**, 73, 1; c) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763; d) S. E. Denmark, N. G. Almstead, in: *Modern Carbonyl Chemistry*, (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, p 299; e) S. R. Chemler, W. R. Roush, in: *Modern Carbonyl Chemistry*, (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, Chapter 10, p 403; f) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207; g) W. R. Roush, in: *Comprehensive Organic Synthesis*, Vol. 2, (Ed.: B. M. Trost), Pergamon Press, Oxford, **1991**, p 1.

[13] a) K. Furuta, M. Mouri, H. Yamamoto, *Synlett* **1991**, 561; b) A. L. Costa, M. G. Piazza, E. Tagliavini, C. Trombini, A. Umani-Ronchi, *J. Am. Chem. Soc.* **1993**, *115*, 7001; c) G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467; d) S. E. Denmark, J. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 9488; e) J. W. J. Kennedy, D. G. Hall, *J. Am. Chem. Soc.* **2002**, *124*, 11586; f) V. Rauniyar, D. G. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 4518; g) S. H. Yu, M. J. Ferguson, R. McDonald, D. G. Hall, *J. Am. Chem. Soc.* **2005**, *127*, 12808; h) V. Rauniyar, D. G. Hall, *Angew. Chem.* **2006**, *118*, 2486; *Angew. Chem. Int. Ed.* **2006**, *45*, 2426; i) V. Rauniyar, H. Zhai, D. G. Hall, *J. Am. Chem. Soc.* **2008**, *130*, 8481; j) I. S. Kim, M. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14891; k) T. Ishiyama, T.-A. Ahiko, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 12414; l) R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8910; m) S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2006**, *128*, 12660; n) D. S. Barnett, P. N. Moquist, S. E. Schaus, *Angew. Chem.* **2009**, *121*, 8835; *Angew. Chem. Int. Ed.* **2009**, *48*, 8679.

[14] P. Jain, J. C. Antilla, *J. Am. Chem. Soc.* **2010**, *132*, 11884.

[15] C. Zhao, A. Nagatsu, K. Hatano, S. Keiichiro, S. Kato, Y. Ogihara, *Chem. Pharm. Bull.* **2003**, *51*, 255.

[16] a) D. R. Boyd, R. Austin, S. McMordie, N. D. Sharma, H. Dalton, P. Williams, R. Jenkins, *J. Chem. Soc. Chem. Commun.* **1989**, 339; b) R. Agarwal, D. R. Boyd, R. Austin, S. McMordie, G. A. O'Kane, P. Porter, N. D. Sharma, H. Dalton, D. J. Gray, *J. Chem. Soc. Chem. Commun.* **1990**, 1711; c) D. R. Boyd, N. D. Sharma, N. A. Kerley, R. Austin, S. McMordie, G. N. Sheldrake, P. Williams, H. Dalton, *J. Chem. Soc. Perkin Trans. 1* **1996**, 67.

[17] a) M. Lautens, T. Rovis, *J. Org. Chem.* **1997**, *62*, 5246; b) M. Lautens, T. Rovis, *Tetrahedron* **1999**, *55*, 8967.

[18] Intermediate ***I*** could be isolated in 80% yield and >99% *ee*; treatment with catalyst [Ru-II] afforded **3a** in 75% yield and >99% *ee*. This result bears witness to the benefits of the relay catalysis in terms of overall yield.

[19] In order to confirm that the present transformation is a tandem process, the reaction was carried out at room temperature affording **3a** in 68% yield and 92% *ee*.

[20] For these substrates an alternative screening of chiral BINOL phosphoric acids was performed, see the Supporting Information.

[21] In Antilla's report, ref.[14], no example of 2,6-disubstituted benzaldehyde is described.

[22] Very recently, a thorough mechanistic study on this transformation has been carried out: M. N. Grayson, Silvina C. Pellegrinet, J. M. Goodman, *J. Am. Chem. Soc.* **2012**, *134*, 2716.

[23] The relative and absolute configuration of the newly created stereocenters in **5a** and **5b** were unambiguously determined by comparison with the reported spectroscopic and physical data. See refs.[24b,25a]

[24] For alternative enantioselective synthesis of **5a** by nucleophilic addition of either dimethylzinc or trimethylaluminium to oxabenzonorbonadiene, see: a) R. Millet, T. Bernardez, L. Palais, A. Alexakis, *Tetrahedron Lett.* **2009**, *50*, 3474; b) F. Bertozzi, M. Pineschi, F. Macchia, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2002**, *4*, 2703.

[25] For an alternative enantioselective synthesis of **5b** by palladium-catalyzed nucleophilic addition of organome-

tallic reagents to oxabenzonorbonadiene, see: a) S. Cabrera, R. Gómez Arrayás, I. Alonso, J. C. Carretero, *J. Am. Chem. Soc.* **2005**, *127*, 17938; b) T. Imamoto, K. Sugita, K. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11934; c) S. Cabrera, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem.* **2004**, *116*, 4034; *Angew. Chem. Int. Ed.* **2004**, *43*, 3944; d) M. Lautens, S. Hiebert, *J. Am. Chem. Soc.* **2004**, *126*, 1437; e) M. Lautens, J.-L. Renaud, S. Hiebert, *J. Am. Chem. Soc.* **2000**, *122*, 1804; f) M. Lautens, S. Hiebert, J. L. Renaud, *Org. Lett.* **2000**, *2*, 1971.

[26] For examples of conformationally boosted ring closing metathesis, see: a) M. T. Crimmins, A. L. Choy, *J. Am. Chem. Soc.* **1999**, *121*, 5653; b) M. T. Crimmins, K. A Emmitte, *Org. Lett.* **1999**, *1*, 2029; c) S. D. Edwards, T. Lewis, R. J. K. Taylor, *Tetrahedron Lett.* **1999**, *40*, 4267.

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

Adv. Synth. Catal. **2013**, *355*, 1 – 8

Santos Fustero,* Elsa Rodríguez, Rubén Lázaro, Lidia Herrera, Silvia Catalán, Pablo Barrio*