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Heteroatom-tethered ω -alkenylallylboronates: stereoselective synthesis of heterocyclic derived alcohols.

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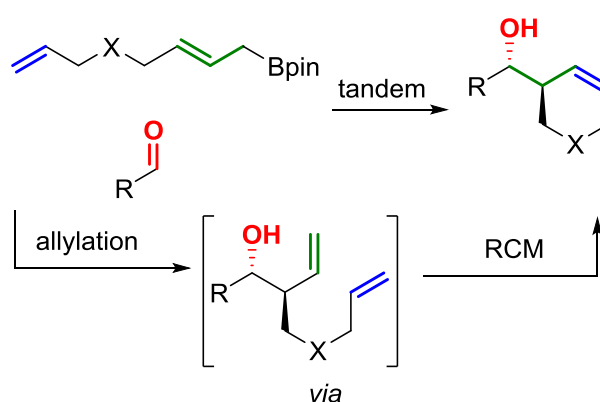
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Dedicate to Professor Fülöp, in memoriam



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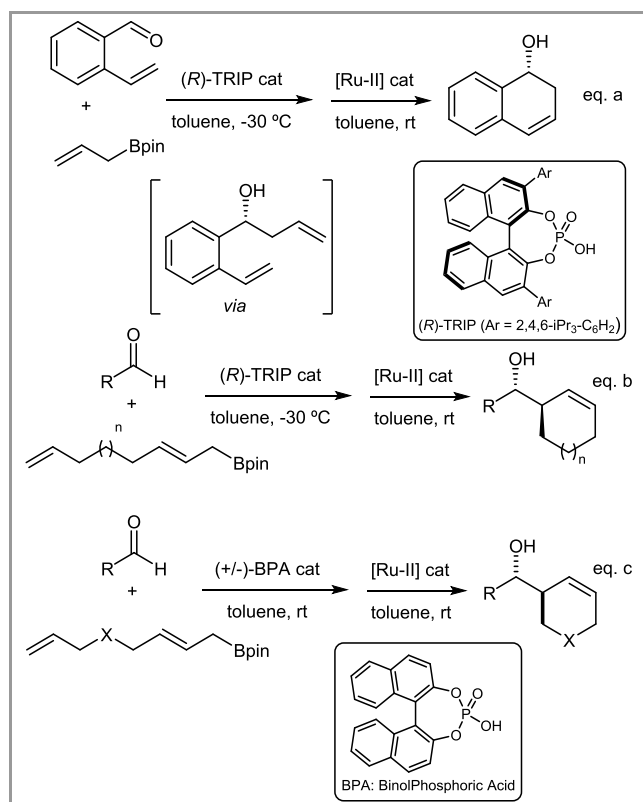
Abstract the synthesis of ω -alkenylallylboronates using a heteroaromatic tether to join both functional groups is described for the first time. Then, these unprecedented compounds are used in a tandem Brønsted-acid catalyzed allylboration / ring-closing metathesis (RCM) tandem reaction affording heterocyclic derived alcohols as single diastereoisomers. The low enantioselectivity observed in the asymmetric version using a chiral phosphoric acid catalyst was studied theoretically.

Key words allylboration, ring-closing metathesis, tandem catalysis, heterocycles, alcohols, stereoselective synthesis

The paramount importance of the allylboration reaction in organic synthesis is out of question.² In addition to the simple addition of an allyl substituent, the addition of allylboronates bearing substitution at the γ -position offers the benefit of proceeding stereospecifically, owing to a well-established six-membered chair-like transition state.³ On the other hand, olefin metathesis represents one of the most powerful C—C bond forming reactions.⁴ Among the several olefin metathesis categories, ring-closing metathesis (RCM) has found the most wide application in organic synthesis.⁵ Carbo- and, perhaps more importantly, heterocycles of several ring sizes have been constructed using this tool and it has been the key step in the synthesis of numerous natural products and pharmaceuticals.⁶ Despite the enormous synthetic importance of both reactions, it was not until 2013 that our group reported for the first time the combination of both in a tandem transformation under relay catalysis conditions (Scheme 1, equation a).⁷ In this first report, a double bond was introduced in a strategic position of the aldehyde in order to participate in the RCM step upon asymmetric allylboration. More recently, in our continuous efforts to expand the usefulness of the chiral Brønsted-catalyzed allylboration reaction,⁸ developed by Antilla,⁹ we have designed the synthesis of ω -alkenylallylboronic esters and applied them to

the tandem asymmetric allylboration/RCM tandem reaction (Scheme 1, equation b).¹⁰

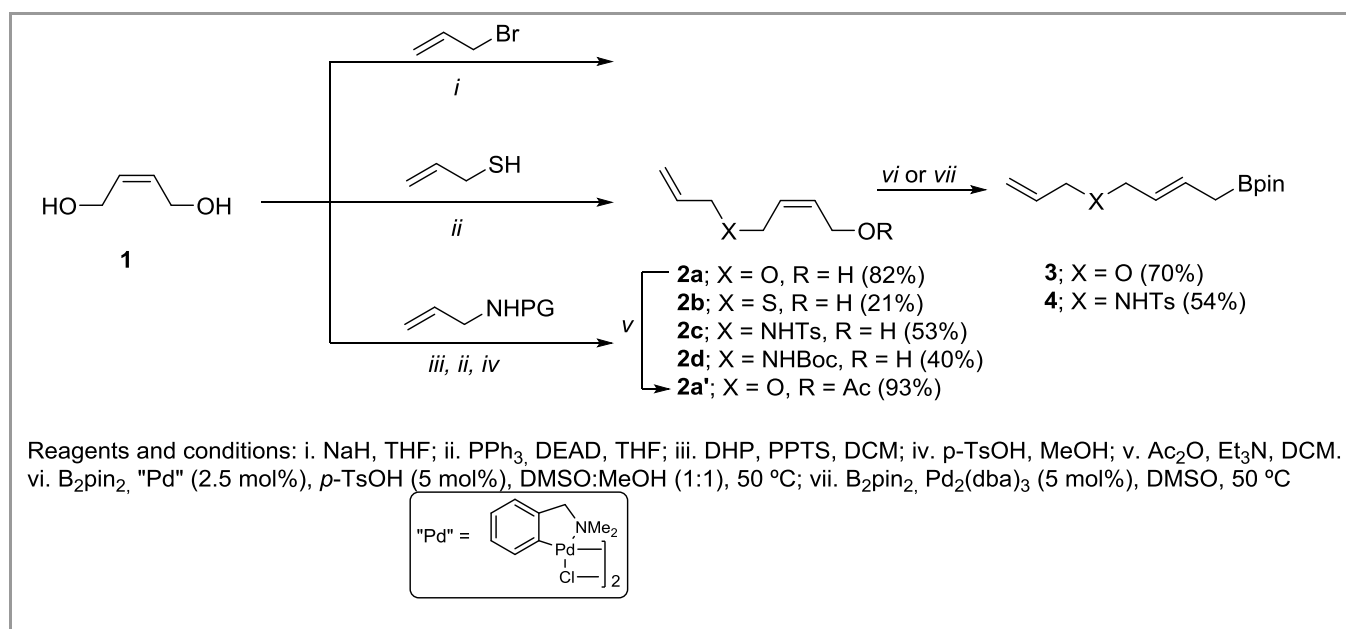
In a further stage of development, we have designed heteroatom-tethered derivatives, which by means of an analogous allylboration / RCM sequence would give rise to heterocycles (Scheme 1, equation c).



Scheme 1 Chiral phosphoric acid-catalyzed allylboration / RCM tandem reaction.

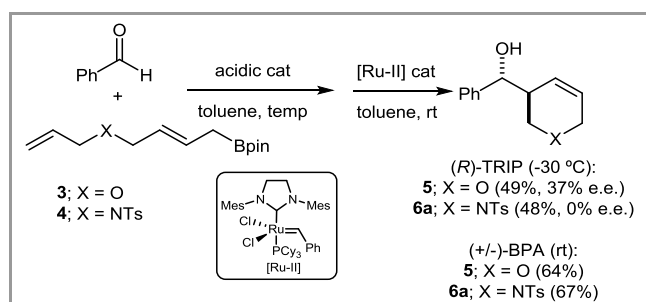
First, we faced the challenging synthesis of the previously unknown heteroatom-tethered ω -alkenylallylboronates **3,4** (Scheme 2). Based on our experience, we decided to use the allylic borylation of allylic alcohols developed by Aggarwal and Szabó for the introduction of the boronic ester.¹¹ In turn, for the synthesis of the corresponding alcohols a unified strategy was envisioned, starting for a common precursor. For that aim, (*Z*)-but-2-en-1,4-diol **1** was selected as the starting material of choice. This decision was made on the basis of its significant lower price as compared to the *E* isomer (500g-49.60€ vs 500mg-127.00€)¹² and the *Z/E* isomeration upon allylic borylation observed in our previous work that allowed to foresee exclusive formation of the *E*-isomer of the final allylboronate. Careful control over the stoichiometry allowed obtaining mainly monofunctionalized products. *O*- and *S*-tethered ω -alkenylallyl alcohols **2a,b** were obtained in one-step each, namely *O*-

allylation and Mitsunobu reaction (Scheme 2). Finally, *N*-tethered derivatives **2c,d** required extra protection / deprotection steps, since the direct Mitsunobu reaction did not afford the desired product. Regarding the final borylation step, for the *O*-tethered derivative **1d** its conversion in the corresponding acetate **2a'** was required since the direct borylation of the free alcohol was unsuccessful.¹³ Unfortunately, the palladium catalyzed allylic borylation did not work for the *S*-tethered derivative neither as the free alcohol nor as other derivatives such as the acetate or the tosylate.¹⁴ Finally, the borylation step worked uneventfully for both *N*-derivatives **2c,d**. However, while *N*-tosyl derivative **2c** was obtained in pure form, *N*-Boc analog **2d** could not be satisfactory separated from the excess B_2pin_2 , precluding its subsequent participation in the allylation/RCM tandem sequence. As expected, both allylboronates **3** and **4** were obtained as single *E*-isomers.



Scheme 2 Synthesis of the heteroatom-tethered ω -alkenylallylboronates **3**.

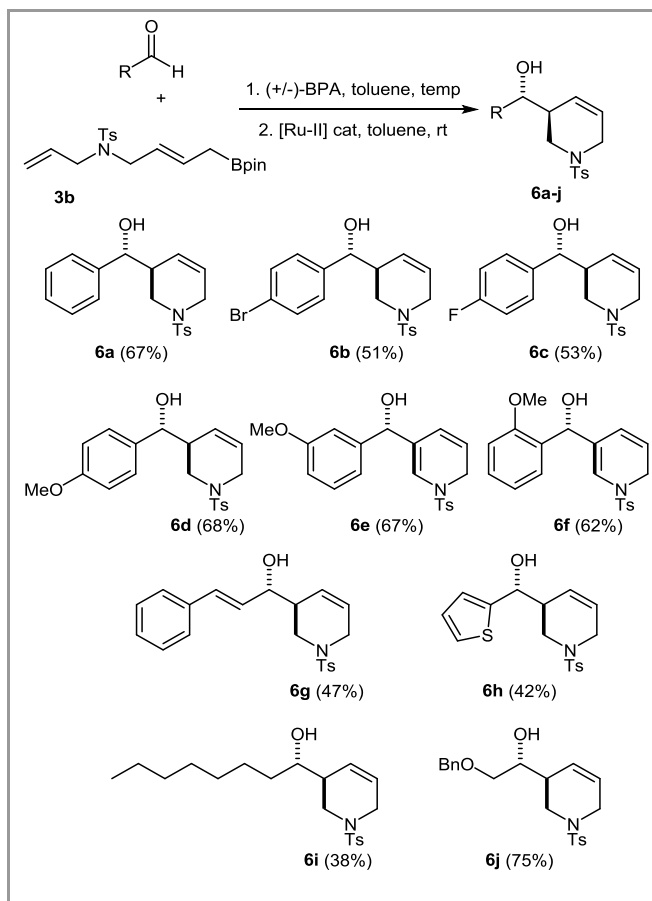
With target allylboronates **3,4** in our hands, the viability of our tandem allylboration / RCM reaction was evaluated using benzaldehyde as model substrate (Scheme 3). First, the enantioselective version was essayed with both derivatives, unfortunately without success. Hence, while the *O*-derivative afforded product **5** in a modest 37% ee, the *NTs*-derivative gave rise to **6a** in the racemic form. In view of this disappointing result, the reaction was carried out using the parent racemic binolphosphoric acid as the catalyst for the allylboration step. Under this conditions both reactions worked successfully affording the tandem products **5,6a** in good overall yields and as single *anti* diastereoisomers (Scheme 3).



Scheme 3 Initial study on the viability of the tandem allylboration / RCM sequence using **3,4**.

The complete diastereoselectivity observed along with the widespread presence of *N*-heterocycles both in natural products and pharmaceuticals prompted as to study the scope of this transformation using *N*-tosyl derivative **4** (Scheme 4). The reaction showed wide applicability with regard to aromatic aldehydes. Hence, benzaldehydes bearing both electron donating and electron withdrawing groups afforded the tandem products

in similar yields (Scheme 4, **6a-f**). Similarly, the substitution pattern did not seem to have a profound effect on the reactivity (Scheme 4, **6d-f**). Moreover, alkenyl and heteroaryl aldehydes also participated in the reaction affording interesting allylic and bisheteroaromatic derivatives (Scheme 4, **6g-h**). Finally, aliphatic aldehydes afforded the corresponding products in variable yield (Scheme 4, **6i,j**).



Scheme 4 Scope and limitations of the Brønsted acid-catalysed allylboration / RCM tandem reaction using allylboronate **4**

The lack of enantioselectivity observed for heteroatom tethered derivatives **3,4** was initially rationalized by assuming some sort of hydrogen bond-type stabilizing interaction between the heteroatomic functionality and the formyl hydrogen atom (Figure 1).¹⁵ Indeed, this interaction was observed in the uncatalyzed TS (Figure 1, left) by DFT calculations (the OMe derivative was used for simplicity, see SI for full computational details). Under catalytic conditions, the major TS involves protonation of the pseudoaxial oxygen of the boronate by the P-OH and a formyl H bond between aldehyde and P=O; in the minor TS, protonation of the pseudoequatorial oxygen is seen instead with no formyl H bond.¹⁶ Since the extra stabilization between the heteroatom tether and formyl H is only possible in the TS leading to the minor isomer (Figure 1, right), it would result in a diminished energy difference between the major and minor TSs and, hence, in the observed low enantioselectivity. This effect is expected to be more pronounced for the corresponding *N*-tosyl derivatives explaining the complete lack of stereocontrol in this case. An in-depth mechanistic study is currently underway and will be reported in due course.

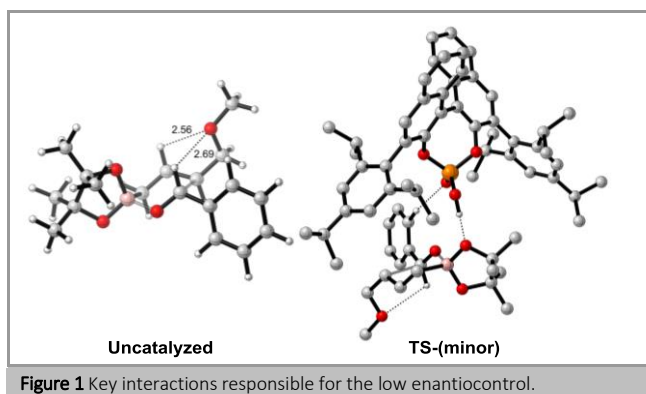


Figure 1 Key interactions responsible for the low enantiocontrol.

In summary, heteroatom-tethered ω -alkenylallylboronates have been synthesised for the first time. Furthermore, they have been used in the Brønsted acid-catalysed allylboration /RCM tandem reaction affording tetrahydropyridine derived alcohols in good yields and with complete diastereoselectivity. The possibility of affording the corresponding dihydro-2h-pyrans has also been preliminary showcased. Further studies aimed to widening the scope of this transformation, especially with respect to dihydro-2h-pyrans, and implementing its enantioselective variant are currently ongoing and will be reported in due course.

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Unless otherwise indicated, all reactions were carried out under an atmosphere of nitrogen or argon.

¹H and ¹³C NMR spectra were recorded in either an AV300 MHz or a dpx 300 MHz spectrophotometers using deuterated chloroform (CDCl₃) as solvent. The chemical shift values of the different nuclei are expressed as δ (ppm), taking as reference the residual peak of chloroform (7.26 ppm) and the intermediate signal of the triplet corresponding to deuterated chloroform (77.2) for the ¹H and ¹³C NMR spectra, respectively. Coupling constants are given in Hertz (Hz).

Mass spectra have been recorded in a TripleTOF™ 5600 LC/MS/MS System spectrometer, (AB SCIEX), at 400°C and at 5500V ions spray voltage. The listed values for each compound are express as *m/z* units.

Flash column chromatography purifications were carried out using Merck 60 mesh silica gel (particle size 40-63 μ m) and mixtures of *n*-hexane and ethyl acetate as eluent. Thin layer chromatography (TLC) analysis was carried out using Merk aluminum plates and were visualized using 254 nm UV light and/or developed using KMnO₄ or Ce(SO₄)₂ stains.

Solvents used in the reactions were dried and distilled under inert atmosphere before their use. 28 Dichloromethane was dried over CaH₂ kept under nitrogen. Anhydrous THF and toluene were dried over sodium and distilled under nitrogen. All the other solvents were purchased in anhydrous quality from commercial sources and used without further purification.

All reagents were purchased at the highest available grade from commercial sources and used without any previous purification. Reagents sensible to oxygen or moisture were handled with the aid of syringes, under a positive pressure of inert gas.

Procedures

(*E*)-2-(4-(Allyloxy)but-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3**):** in a Schlenk flash under Ar, Pd(dba)₂ (17 mg, 0.03 mmol) y B₂Pin₂ (165 mg, 0.65 mmol) were placed. Then, dry DMSO (3.6 mL) and (*Z*)-but-2-en-1-yl-4-(allyloxy) acetate **2a'** (63 mg, 0.49 mmol) and the resulting solution was stirred overnight at 50 °C. The reaction mixture was quenched with water, extracted with AcOEt (3x5ml), the aqueous layer washed with brine and dried over Na₂SO₄ filtered and concentrated in vacuum. The crude residue was purified by means of flash column chromatography (silica gel, hexane / ethyl acetate 20:1), affording **3a** (83 mg, 70%) as a pale yellow oil.

¹H NMR (300 MHz): δ = 5.91 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H), 5.81 – 5.66 (m, 1H), 5.63 – 5.46 (m, 1H), 5.26 (ddt, J = 17.2, 1.6 Hz, 1H), 5.16 (ddt, J = 10.4, 1.9, 1.2 Hz, 1H), 3.99 – 3.87 (m, 4H), 1.72 (d, J = 7.3 Hz, 2H), 1.24 (s, 12H).

¹³C NMR (75 MHz): δ = 135.2 (CH), 130.5 (CH), 126.8 (CH), 17.0 (CH₂), 83.4 (C), 71.2 (CH₂), 70.7 (CH₂), 24.9 (CH₃).

HRMS (ESI): m/z [M+NH₄]⁺ calcd for C₁₃H₂₃BO₃: 256.2084; found: 256.2081.

(E)-N-Allyl-4-metil-N-(4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-yl)but-2-en-1-yl) benzenesulfonamide (4): in a Schlenck flask under Ar, **2b** (1g, 3,6 mmol) was dissolved in a DMSO:MeOH 1:1 mixture (0,25M). Then, *p*-TsOH (0,05 equiv.), di- μ -chlorobis[2-[[dimethylamino)methyl]-phenyl-C,N]dipaladium (II) (0,025 eq) and B₂pin₂ (2equiv.) were added. The resulting solution was stirred overnight at 50 °C. The reaction mixture was quenched with water, extracted with Et₂O (3x5ml), the aqueous layer washed with brine and dried over Na₂SO₄ filtered and concentrated in vacuum. The crude residue was purified by means of flash column chromatography (silica gel, hexane / ethyl acetate 10:1), affording **3b** (763 mg, 54%) as a pale colourless oil.

¹H NMR (300 MHz): δ = 7.69 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 5.70 – 5.50 (m, 1H), 5.25 – 5.02 (m, 2H), 3.79 (d, J = 6.4 Hz, 1H), 3.74 (d, J = 7.3 Hz, 1H), 2.42 (s, 2H), 1.62 (d, J = 7.4 Hz, 2H), 1.22 (s, 7H).

¹³C NMR (75 MHz): δ = 143.1 (C), 137.8 (C), 133.1 (CH), 131.8 (CH), 129.7 (CH), 127.3 (CH), 124.2 (CH), 118.9 (CH₂), 83.5 (C), 49.0 (CH₂), 48.8 (CH₂), 24.9 (CH₃), 21.7 (CH₃).

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₀H₃₀BNO₄S: 392.2061; found: 392.2068.

General procedure for the allylboration / RCM tandem sequence:

(+/-)-BPA (3.5 mg, 10 mol%) was weighed in a schlenck flask. The schlenck was then evacuated and back filled with N₂. Dry toluene (1ml), the corresponding aldehyde (0.1mmol) and the appropriate allylboration (0.12mmol, 1.2 equiv) were successively added. The reaction mixture was stirred at room temperature overnight. Then, second generation Grubbs catalyst (4 mg, 5 mol %) was added and the resulting solution was stirred for further 4 hours at room temperature. Solvent was removed under vacuum and the residue purified by means of flash column chromatography in silica gel, using mixtures of hexane and ethyl acetate as eluent.

(R*)-((S*)-3,6-Dihydro-2H-piran-3-yl)(phenyl)methanol (5): was obtained following the general procedure affording a colourless oil (12mg, 64%).

¹H NMR (300 MHz): δ = 7.32 – 7.17 (m, 5H), 5.85 (dtd, J = 10.4, 2.5, 1.6 Hz, 1H), 5.78 – 5.65 (m, 1H), 4.77 (d, J = 5.6 Hz, 1H), 4.27 – 3.94 (m, 2H), 3.87 – 3.46 (m, 2H), 2.81 (s, 1H), 2.48 – 2.15 (m, 1H).

¹³C NMR (75 MHz): δ = 142.7, 128.8 (C), 128.4 (CH), 127.7 (CH), 126.2 (CH), 124.2 (CH), 76.9 (CH), 68.3 (CH₂), 66.1 (CH₂), 41.61 (CH).

HRMS (ESI): m/z [M+H]⁺ calcd for C₁₂H₁₄O: 189.0910; found: 189.0903.

(R*)-Phenyl((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (6a): was obtained following the general procedure affording a colourless oil (23mg, 67%).

¹H NMR (300 MHz): δ = 7.60–7.49 (m, 2H), 7.37–7.19 (m, 7H), 5.95–5.47 (m, 2H), 4.67 (d, J = 6.9 Hz, 1H), 3.60 (dq, J = 16.4, 2.6 Hz, 1H), 3.40 (dq, J = 16.4, 2.7 Hz, 1H), 3.07–2.78 (m, 2H), 2.60–2.46 (m, 1H), 2.36 (s, 3H), 2.09 (s, 1H).

¹³C NMR (75 MHz): δ = 143.7 (C), 142.3 (C), 132.7 (C), 129.7 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 126.4 (CH), 125.8 (CH), 124.4 (CH), 76.1 (CH), 45.4 (CH₂), 45.2 (CH₂), 42.6 (CH), 21.5 (CH₃).

HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₂₁NO₃S: 344.1315; found: 344.1316.

(R*)-(4-Bromophenyl)((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (6b): was obtained following the general procedure affording a colourless oil (22mg, 51%).

¹H NMR (300 MHz): δ = 7.66–7.55 (m, 2H), 7.56–7.44 (m, 2H), 7.35–7.25 (m, 4H), 5.85–5.72 (m, 2H), 4.74 (d, J = 7.3 Hz, 1H), 3.80–3.62 (m, 1H), 3.38 (dq, J = 16.2, 2.4 Hz, 1H), 3.15 (dd, J = 11.8, 4.6 Hz, 1H), 2.83 (dd, J = 11.8, 4.6 Hz, 1H), 2.59–2.47 (m, 1H), 2.42 (s, 3H), 2.26 (d, J = 3.1 Hz, 1H).

¹³C NMR (75 MHz): δ = 143.9 (C), 141.4 (C), 132.5 (C), 131.6 (CH), 129.7 (CH), 128.2 (CH), 127.8 (CH), 125.4 (CH), 124.7 (CH), 121.8 (C), 75.7 (CH), 45.3 (CH₂), 45.3 (CH₂), 42.5 (CH), 21.6 (CH₃).

HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₂₀BrNO₃S: 422.0420; found: 422.0422.

(R*)-(4-Fluorophenyl)((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (6c): was obtained following the general procedure affording a colourless oil (19mg, 53%).

¹H NMR (300 MHz): δ = 7.63 (d, J = 8.1 Hz, 2H), 7.41 (dd, J = 8.4, 5.5 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 8.7 Hz, 2H), 5.99–.89 (m, 1H), 5.85–5.78 (m, 1H), 4.78 (d, J = 7.2 Hz, 1H), 3.83–3.65 (m, 1H), 3.41 (dd, J = 16.4, 2.7 Hz, 1H), 3.14 (dd, J = 11.8, 4.7 Hz, 1H), 2.84 (dd, J = 11.8, 4.6 Hz, 0H), 2.56 (s, 1H), 2.44 (s, 3H), 1.89 (s, 1H).

¹³C NMR (75 MHz): δ = 162.4 (C, d, J = 246.0 Hz), 143.8 (C), 138.1 (C, d, J = 3.1 Hz), 132.6 (C), 129.7 (CH), 128.2 (CH, d, J = 8.0 Hz), 127.8 (CH), 125.6 (CH), 124.6 (CH), 115.4 (CH, d, J = 21.3 Hz), 75.7 (CH), 45.31 (CH₂), 45.3 (CH₂), 42.7 (CH), 21.5 (CH₃).

¹⁹F NMR (282 MHz, CDCl₃) δ = -114.31.

HRMS (ESI): m/z [M+H]⁺ calcd for C₁₉H₂₀FNO₃S: 362.1221; found: 362.1225.

(R*)-(4-Methoxyphenyl)((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (6d): was obtained following the general procedure affording a colourless oil (25mg, 68%).

¹H NMR (300 MHz): δ = 7.62 (d, J = 8.2 Hz, 2H), 7.47–7.22 (m, 4H), 6.94 (d, J = 8.7 Hz, 2H), 5.98 (dd, J = 10.3, 3.5 Hz, 1H), 5.79 (d, J = 9.4 Hz, 1H), 4.68 (d, J = 7.6 Hz, 1H), 3.85 (s, 3H), 3.69 (dd, J = 16.3, 2.9 Hz, 1H), 3.56–3.36 (m, 1H), 3.04 (dd, J = 11.8, 5.3 Hz, 1H), 2.89 (dd, J = 11.8, 4.7 Hz, 1H), 2.58 (s, 1H), 2.44 (s, 3H), 1.87 (s, 1H)..

¹³C NMR (75 MHz): δ = 143.7 (C), 142.3 (C), 132.7 (C), 129.7 (CH), 128.6 (CH), 128.0 (CH), 127.8 (CH), 126.4 (CH), 125.8 (CH), 124.4 (CH), 76.1 (CH), 45.4 (CH₂), 45.2 (CH₂), 42.6 (CH), 21.5 (CH₃).

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₀H₂₃NO₄S: 374.1421; found: 374.1414.

(R*)-(3-Methoxyphenyl)((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (6e): was obtained following the general procedure affording a colourless oil (24mg, 67%).

¹H NMR (300 MHz): δ = 7.63 (d, J = 8.1 Hz, 2H), 7.40–7.21 (m, 3H), 7.08–6.98 (m, 2H), 6.88 (dd, J = 8.0, 2.5 Hz, 1H), 6.04–5.89 (m, 1H), 5.87–5.70 (m, 1H), 4.74 (d, J = 7.1 Hz, 1H), 3.87 (s, 3H), 3.70 (dd, J = 16.5, 2.8 Hz, 1H), 3.46 (dd, J = 16.4, 2.8 Hz, 1H), 3.13 (dd, J = 11.7, 5.2 Hz, 1H), 2.92 (dd, J = 11.7, 4.7 Hz, 1H), 2.61 (s, 1H), 2.44 (s, 3H), 2.18 (s, 1H).

¹³C NMR (75 MHz): δ = 159.8 (C), 144.1 (C), 143.7 (C), 132.7 (C), 129.7 (CH), 129.6 (CH), 127.8 (CH), 125.9 (CH), 124.4 (CH), 118.5 (CH), 113.9 (CH), 111.7 (CH), 76.1 (CH), 55.3 (CH₃), 45.4 (CH₂), 45.2 (CH₂), 42.6 (CH), 21.5 (CH₃).

HRMS (ESI): m/z [M+H]⁺ calcd for C₂₀H₂₃NO₄S: 374.1421; found: 374.1436.

(R*)-(2-Methoxyphenyl)((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (6f): was obtained following the general procedure affording a colourless oil (17mg, 47%).

¹H NMR (300 MHz): δ = 7.91–7.65 (m, 2H), 7.55–7.12 (m, 4H), 6.68 (d, J = 16.0 Hz, 1H), 6.27 (dd, J = 15.9, 6.8 Hz, 1H), 6.05–5.89 (m, 1H), 5.81 (dt, J = 8.7, 3.0 Hz, 1H), 4.38 (t, J = 6.5 Hz, 1H), 3.79–3.61 (m, 1H), 3.59–3.45 (m, 1H), 3.33–3.05 (m, 2H), 2.56 (s, 1H), 2.45 (d, J = 2.4 Hz, 3H).

¹³C NMR (75 MHz): δ = 143.7 (C), 136.4 (C), 132.9 (C), 132.2 (CH), 129.7 (CH), 129.5 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 126.7 (CH), 125.6 (CH), 124.7 (CH), 74.7 (CH), 45.1 (CH₂), 44.9 (CH₂), 41.2 (CH), 21.5 (CH₃).

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{23}NO_3S$: 370.1477; found: 370.1466.

(S*,E)-3-phenyl-1-((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)prop-2-en-1-ol (6g): was obtained following the general procedure affording a colourless oil (22mg, 63%).

1H NMR (300 MHz): δ = 7.63 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 7.8 Hz, 4H), 7.00 (t, J = 7.5 Hz, 2H), 6.92 (d, J = 8.1 Hz, 1H), 5.96–5.86 (m, 1H), 5.82–5.69 (m, 1H), 4.90–4.74 (m, 1H), 3.87 (s, 3H), 3.74–3.59 (m, 1H), 3.51 (dq, J = 16.2, 2.6 Hz, 1H), 3.18 (dd, J = 11.0, 4.4 Hz, 1H), 3.00–2.74 (m, 3H), 2.44 (s, 3H).

^{13}C NMR (75 MHz): δ = 156.4 (C), 143.6 (C), 132.9 (C), 129.6 (CH), 128.8 (CH), 128.0 (CH), 127.8 (CH), 126.2 (CH), 123.9 (CH), 120.8 (CH), 73.0 (CH), 55.3 (CH₃), 45.9 (CH₂), 45.1 (CH₂), 40.6 (CH), 21.5 (CH₃).

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{23}NO_4S$: 374.1421; found: 374.1428.

(R*)-thiophen-2-yl((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (6h): was obtained following the general procedure affording a colourless oil (15mg, 42%).

1H NMR (300 MHz): δ = 7.64 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.2 Hz, 3H), 7.12 (d, J = 3.5 Hz, 1H), 7.08–7.02 (m, 1H), 6.12–5.96 (m, 1H), 5.91–5.76 (m, 1H), 5.03 (d, J = 7.3 Hz, 1H), 3.83–3.65 (m, 1H), 3.47 (dd, J = 16.4, 2.8 Hz, 1H), 3.16 (dd, J = 11.9, 5.1 Hz, 1H), 2.97 (dd, J = 11.8, 4.6 Hz, 1H), 2.67 (s, 1H), 2.45 (s, 3H), 1.64 (s, 1H).

^{13}C NMR (75 MHz): δ = 146.2 (C), 143.7 (C), 132.9 (C), 129.7 (CH), 127.8 (CH), 126.9 (CH), 125.7 (CH), 125.2 (CH), 125.1 (CH), 124.8 (CH), 72.5 (CH), 45.2 (CH₂), 45.1 (CH₂), 43.1 (CH), 21.5 (CH₃).

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{23}NO_4S$: 374.1421; found: 374.1428.

(S*)-1-((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)octan-1-ol (6i): was obtained following the general procedure affording a colourless oil (14mg, 38%).

1H NMR (300 MHz): δ = 7.69 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 5.82 (t, J = 3.0 Hz, 2H), 3.74 – 3.63 (m, 1H), 3.58 (d, J = 9.8 Hz, 2H), 3.27 (dd, J = 11.6, 5.0 Hz, 1H), 2.45 (s, 4H), 2.37 (t, J = 7.5 Hz, 1H), 1.51 (d, J = 5.1 Hz, 3H), 1.31 (s, 15H), 0.97 – 0.76 (m, 6H).

^{13}C NMR (75 MHz): δ = 143.7(C), 132.9 (C), 129.7 (CH), 127.8 (CH), 125.4 (CH), 124.8 (CH), 73.5 (CH), 45.7 (CH₂), 45.1 (CH₂), 40.8 (CH), 34.6 (CH₂), 31.8 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 25.9 (CH₂), 22.7 (CH₂), 21.5 (CH₃), 14.1 (CH₃).

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{14}O$: 374.1421; found: 374.1414.

(R*)-2-(benzyloxy)-1-((S*)-1-tosyl-1,2,3,6-tetrahydropyridin-3-yl)ethan-1-ol (6j): was obtained following the general procedure affording a colourless oil (29mg, 75%).

1H NMR (300 MHz): δ = 7.66 (d, J = 8.1 Hz, 2H), 7.45–7.23 (m, 7H), 5.85 (dd, J = 10.3, 3.0 Hz, 1H), 5.79–5.69 (m, 1H), 4.58 (s, 2H), 3.93–3.79 (m, 1H), 3.75–3.44 (m, 4H), 3.18 (dd, J = 11.8, 5.8 Hz, 1H), 3.09 (dd, J = 11.7, 4.9 Hz, 1H), 2.65–2.52 (m, 1H), 2.44 (s, 3H).

^{13}C NMR (75 MHz): δ = 143.7 (C), 137.8 (C), 132.8 (C), 129.7 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 125.9 (CH), 124.3 (CH), 73.5 (CH₂), 71.8 (CH₂), 71.8 (CH), 44.9 (CH₂), 44.4 (C.H₂), 38.3 (CH), 21.5 (CH₃).

HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{25}NO_4S$: 388.1583; found: 388.1570.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References

- (1) New address: F. Garnes-Portolés, Instituto de Tecnología Química (UPV-CSIC), Universitat Politècnica de València-Consejo Superior de Investigaciones Científicas, Valencia, Spain.
- (2) For reviews on the allylboration reaction, see: (a) C. Diner, K. J. Szabo, *J. Am. Chem. Soc.* **2017**, *139*, 2. (b) H.-X. Huo, J. R. Duvall, M.-Y. Huang, R. Hong, *Org. Chem. Front.* **2014**, *1*, 303. (c) E. M. Carreira, L. Kvaerno, in: *Classics in Stereoselective Synthesis* Wiley-VCH, Weinheim, **2009**, Chapter 5, p 164. (d) H. Lachance, D. G. Hall *Org. React.* **2008**, *73*, 1. (e) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763. (f) S. E. Denmark, N. G. Almstead, in: *Modern Carbonyl Chemistry*; (Ed: J. Otera), Wiley-VCH, Weinheim, **2000**, 299. (g) S. R. Chemler, W. R. Roush in: *Modern Carbonyl Chemistry* (Ed: J. Otera), Wiley-VCH, Weinheim, **2000**, Chapter 10, 403. (h) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207. (i) W. R. Roush, W. R. in: *Comprehensive Organic Synthesis, Vol. 2B*. (Ed: M. Trost), Pergamon Press, Oxford, **1991**, p 1.
- (3) For an excellent account on chair-like six-membered transition states, see: T. Mejuch, N. Gilboa, E. Gayon, H. Wang, K. N. Houk, I. Marek *Acc. Chem. Res.* **2013**, *46*, 1659.
- (4) The Nobel Prize in chemistry 2005 was awarded to R. H. Grubbs, R. Schrock and Y. Chauvin for the development of this reaction: (a) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760. (b) Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748. (c) Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3740.
- (5) For selected reviews on ring-closing metathesis, see: (a) Groso, E. J.; Schindler, C. S. *Synthesis* **2019**, *51*, 1100-1114. (b) Klare, H. F. T.; Oestreich, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2085. (c) Kurteva, V. B.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 6809. (d) Monfette, S.; Fogg, D. E. *Chem. Rev.* **2009**, *109*, 3783.
- (6) For selected reviews, see: (a) Glas, A.; Grossmann, T. N. *Synlett* **2015**, *26*, 1. (b) Cusak, A. *Chem. Eur. J.* **2012**, *18*, 5800. (c) Wakchaure, S.; Einsiedel, J.; Waibel, R.; Gmeiner, P. *Synthesis* **2012**, *44*, 2682.
- (7) Fustero, S.; Rodríguez, E.; Lázaro, R.; Herrera, L.; Catalán, S.; Barrio, P. *Adv. Synth. Catal.* **2013**, *355*, 1058.
- (8) (a) Rodríguez, E.; Grayson, M. N.; Asensio, A.; Barrio, P.; Houk, K. N.; Fustero, S. *ACS Catal.* **2016**, *6*, 2506. (b) Barrio, P.; Rodríguez, E.; Saito, K.; Fustero, S.; Akiyama, T. *Chem. Comm.* **2015**, *51*, 5246. For a review on our contribution on the field, see: (c) Barrio, P.; Rodríguez, E.; Fustero, S. *Chem. Rec.* **2016**, *16*, 2046.
- (9) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884.
- (10) Garnes-Portolés, F.; Miguélez, R.; Grayson, M. N.; Barrio, P. *Eur. J. Org. Chem.* **2021**, 3492.
- (11) Dutheil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. *Synthesis*, **2008**, 2293.
- (12) Prices from SigmaAldrich, October 2021.
- (13) The new reaction conditions for the acetate derivative were taken from: Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889.
- (14) For examples of palladium catalyst poisoning by sulfur species, see: (a) Choudhary, V. R.; Sane, M. G. *J. Chem. Technol. Biotechnol.* **1998**, *73*, 336. (b) Zwicky, J. J.; Gut, G. *Chem. Eng. Science* **1978**, *33*, 1363. (c) Fuji, Y.; Bailar, J. C. *J. Catal.* **1978**, *52*, 342. (d) Williams, F. L.; Baron, K. *J. Catal.* **1975**, *40*, 108.
- (15) (a) Grayson, M. N.; Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 2716. (b) Grayson, M. N.; Yang, Z.; Houk, K. N. *J. Am. Chem. Soc.* **2017**, *139*, 7717. (c) Grayson, M. N.; Goodman, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 6142. (d) Grayson, M. N.; Krische, M. J.;

Goodman, J. M. *J. Am. Chem. Soc.* **2015**, *137*, 8838. (e) Farrar, E. H. E.; Grayson, M. N. *J. Org. Chem.* **2020**, *85*, 15449.

(16) (a) Sedgwick, D. M.; Grayson, M. N.; Fustero, S.; Barrio, P. *Synthesis* **2018**, *50*, 1935.

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