

Homoallylic *o*-halobenzylamines: asymmetric diversity-oriented synthesis of benzo-fused cyclic amines

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Abstract The presence of a halogen atom in the proximity of a homoallylic amine, obtained by asymmetric addition of allylzinc bromide to the corresponding *tert*-butyl sulfinimine, makes them versatile building blocks suitable to participate in several palladium-catalyzed processes, such as the intramolecular Heck reaction or the Sonogashira cross-coupling. The thus obtained *ortho*-alkynyl derivatives display two unsaturated functional groups which may be further modified by means of the intramolecular Pauson–Khand reaction or the ring-closing enyne metathesis. In this way, a variety of benzo-fused amines can be obtained in 2–3 steps from readily available starting materials.

Keywords Homoallylic amine · Pauson–Khand reaction · Sonogashira cross-coupling · Intramolecular Heck reaction · Diversity-oriented synthesis · Asymmetric synthesis

Introduction

Diversity-oriented synthesis (DOS) aims to provide maximum coverage of the chemical space, from a common precursor, by using the minimum number of steps (usually 4–5) [1–6]. Usually, the key for the success of such a strategy is the identification of a suitable substrate carrying specific functional groups at appropriate positions. In this way, the product of a given transformation becomes the substrate of the subsequent. These functional groups must be able to participate in as many different reactions as possible, thus increasing the achievable molecular complexity. In this context, during the last few years, our group has studied the use of 2-halobenzaldehyde derivatives as common building blocks for the asymmetric synthesis of benzo-fused carbo—[7–11] and heterocycles [12–15] (Scheme 1) [16].

The use of this strategy has allowed us to synthesize interesting building blocks such as fluorinated [13, 14] and non-fluorinated isoindolines [14], indanones [11] and, more recently, fluorinated isoindolinones [12] and amino steroid derivatives [8]. In the course of the latter study, we found that significant amounts of an undesired intramolecular Heck reaction by-product **4a** was obtained upon Sonogashira cross-coupling of homoallylic *o*-bromobenzylsulfonamide **3a** (Scheme 2). The formation of **4a** was unambiguously determined by the presence of two characteristic methylene protons at 5.1 and 5.5 ppm in the ¹H-NMR spectrum, as well as the corresponding signal at 104.4 ppm at the ¹³C-NMR spectrum.

In our previous communication [7], the formation of this undesired by-product could be suppressed by increasing the amount of alkyne (from 3 to 5 equivalents) and the reaction concentration (from 0.1 to 0.5 M), thus favoring the intermolecular Sonogashira cross-coupling over the

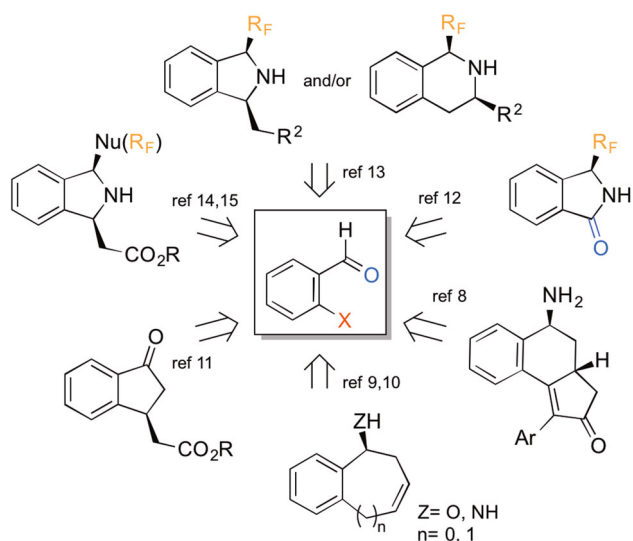
Dedicated to Professor George A. Olah on the occasion of his 90th birthday.

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Scheme 1 2-Halobenzaldehyde in DOS

intramolecular Heck reaction. In this report, we describe the optimization of the intramolecular Heck reaction along with the implementation of a one-pot condensation/asymmetric allylation/intramolecular PKR protocol for the synthesis of tricyclic amines. In addition, the RCEYM reaction of intermediates **3** will also be discussed.

Results and discussion

Intramolecular Heck reaction

Obtaining the undesired intramolecular Heck reaction product as a by-product of the Sonogashira reaction of substrate **1a** was the starting point for trying to optimize this process, as mentioned in the introduction (Scheme 2). Of course, we started by removing the no-longer necessary alkyne and the CuI from the reaction medium (Table 1, Entry 1). By doing so, we obtained an overall moderate yield; however, a significant amount of it in the form of the isomerized product **6**. Replacing Et₃N with an inorganic base (Ag₂CO₃) suppressed the formation of the undesired isomerized product, giving exclusively the desired product in moderate yield (Table 1, Entry 2). The use of microwave irradiation both in toluene and THF did not bring any beneficial effect, nor did the addition of external ligands (Table 1, Entries 3–6). Finally, the use of an equimolar ratio of Et₃N and Ag₂CO₃ as base gave rise to an optimized 70 % yield (Table 1, Entry 7). It should be noted that recently, Yus et al. [17] have described similar reaction conditions for this transformation.

Once an optimized set of reaction conditions had been established, a small library of 3-methylene-1-aminoindane derivatives were synthesized in moderate to good yields

(Scheme 3). For substrate **1b**, the isomerized product **4b'** was obtained in 68 % yield.¹

Aiming toward a more sustainable and practical methodology, and in view of our own experience in the use of one-pot reactions in the context of DOS, we then studied the one-pot condensation/asymmetric allylation/Heck reaction sequence on 2-iodobenzaldehyde **8a** achieving the desired product in 70 % yield over the three steps and as a single diastereoisomer (Scheme 4).

In order to increase the range of molecular structures available through our methodology, two simple transformations were carried out on the exocyclic double bond of the unsubstituted substrate **4a**, namely the hydrogenation and the oxidative cleavage (Scheme 5). As expected, the Pd/C-catalyzed heterogeneous hydrogenation of the double bond proceeded with high *anti* selectivity affording the *cis* product **9** in excellent yield (Scheme 5). On the other hand, the oxidative cleavage of the *exo*-methylene afforded the 3-aminoindanone derivative **10** in good yield (Scheme 5). Note that the –SO_tBu group was concomitantly oxidized to the –SO₂tBu group under the reaction conditions. Compound **10** was further transformed into *cis* 1,3-aminoalcohol **11** by BH₃·THF-mediated diastereoselective reduction of the ketone (Scheme 5).

The relative configuration of the chiral centers in products **9** and **11** was determined by means of 2D-NMR NOESY experiments, which showed cross peaks between the NH and the CH₃ protons, and also between the two benzylic methyne protons H_a and H_b (Fig. 1). In both cases, these observations are in agreement with a *cis* arrangement. For compound **9**, this result could be foreseen since catalytic heterogeneous hydrogenations usually proceed on the less hindered face of the olefin, in this case *anti* to the bulky NHSOtBu group, resulting in the observed *cis* product.

Ring-closing enyne metathesis (RCEYM)

Taking advantage of the densely functionalized intermediates **3** synthesized in our recent report [8], we envisioned to expand their reactivity to other well-established transformations of enynes. Among these, RCEYM has become a powerful tool for the creation of carbo- and heterocycles of several ring sizes with the added value of presenting an exocyclic conjugated vinyl moiety amenable for subsequent transformations [18].

Using **3a** as a model substrate, an optimization of the reaction conditions was carried out using our recently reported parent transformation on the corresponding

¹ Under the reaction conditions described by Yus the isomerized product is also obtained, see Sirvent et al. [17].

Scheme 2 Preliminary results

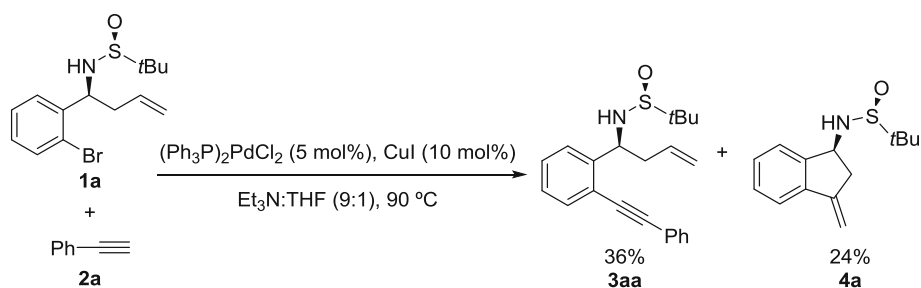
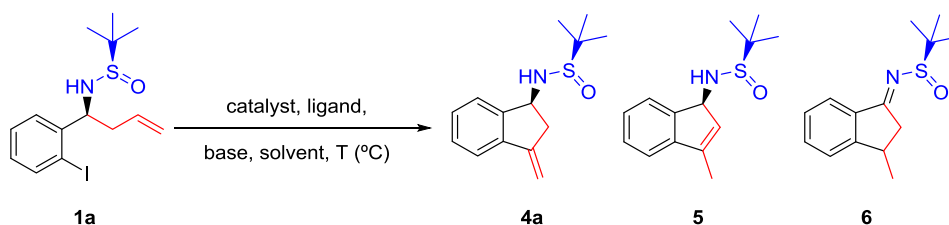
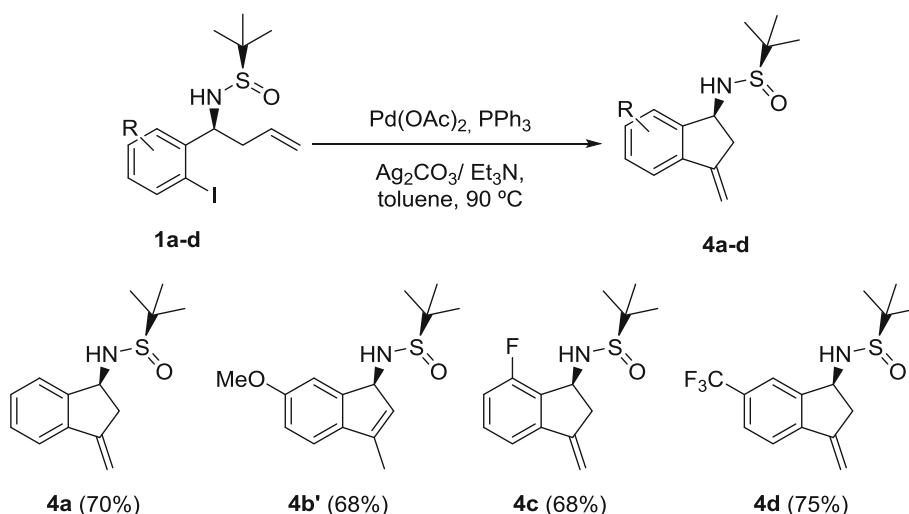


Table 1 Optimization of the intramolecular Heck reaction conditions



Entry	Catalyst	Ligand	Base	Solvent	<i>T</i> (°C)	1 (%)	4 (%)	5 (%)	6 (%)
1	Pd(OAc) ₂	PPh ₃	Et ₃ N	Tol.	120	–	25	–	31
2	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	Tol.	120	–	66	–	–
3	Pd(dba) ₂	PPh ₃	Ag ₂ CO ₃	Tol.	120 MW	–	50	–	–
4	Pd(dba) ₂	PPh ₃	Ag ₂ CO ₃	THF	100 MW	–	25	25	–
5	Pd(dba) ₂	XANP	Ag ₂ CO ₃	THF	100 MW	–	37.5	12.5	–
6	Pd(dba) ₂	JOHNP	Ag ₂ CO ₃	THF	100 MW	80	–	–	–
7	Pd(OAc) ₂	PPh ₃	Et ₃ N/Ag ₂ CO ₃	Tol.	90	–	70	–	–

Scheme 3 Scope and limitations



alcohols as starting point (second generation Grubbs' catalyst [Ru-II], DCM, 45 °C, 1,7-octadiene) (Table 2) [19, 20].

Under the original reaction conditions, a moderate 55 % yield was obtained (Table 2, entry 1). We envisioned that this modest result might be the result of an inefficient in situ ethylene formation along with some catalyst

deactivation. In an attempt to tackle these issues, we carried out the reaction in a sealed tube and added two portions of both the catalyst and 1,7-octadiene, obtaining an excellent yield (Table 2, entry 2). The reaction time could be shortened by rising the temperature, however, at expense of chemical yield (Table 2, entry 3). Finally, while the addition of a Lewis acid improved the catalytic activity

(Table 2, entry 4), the results were not as satisfactory as the ones obtained in entry 2. Hence, the reaction conditions shown in entry 2 were used for the study of the reaction scope.

With a small library of enynes **12** from our previous study in hand [8], the scope of this transformation was studied using the optimized conditions shown in Table 2, entry 2 (Scheme 6).

Substitution at both aromatic rings is well tolerated without significantly modifying the high chemical yield (Scheme 6, **12a–e**). On the other hand, replacing the aryl substituent at the triple bond by an alkyl one results in a significant drop, although still obtaining a synthetically useful 50 % yield (Scheme 6, **12f**). The better performance of aryl- over alkyl-substituted triple bonds might be rationalized by the higher stabilization of the resulting diene by conjugation with the aromatic ring, since RCEYM is an enthalpy driven transformation.

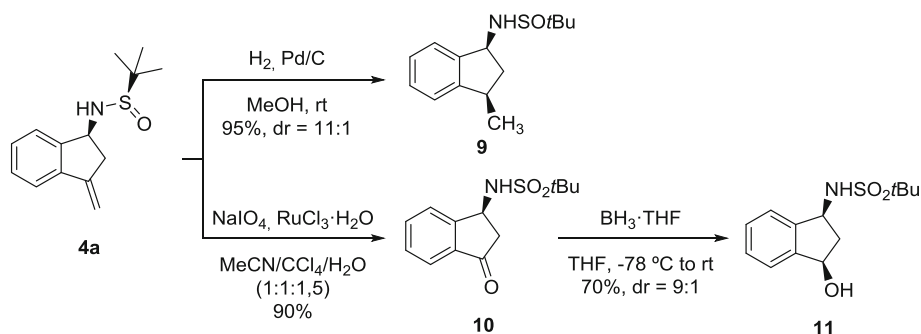
With the aim of further increasing the structural complexity and diversity affordable with our strategy, a Diels–Alder reaction of diene **12a** with dimethyl acetylene dicarboxylate (DMAD) was envisioned. However, no reaction was observed even after prolonged heating in DCE (Scheme 7).

We believe the reason behind this unexpectedly low reactivity of diene **12a** in Diels–Alder reactions could be its preference for the *s-trans* over the required *s-cis* conformation, due to the steric hinderance between the *ortho* protons at the aromatic substituents of the dienic moiety, which would clash by adopting such conformation (Fig. 2).



Scheme 4 One-pot condensation/asymmetric allylation/Heck reaction sequence

Scheme 5 Transformations on the 1-amino-3-methyleneindane skeleton



Study of the one-pot condensation/asymmetric allylation/intramolecular Pauson–Khand reaction (PKR) sequence

Finally, building on our own experience in the area of one-pot transformations with Ellman's sulfinimides [9], we envisioned setting up a one-pot protocol for our recently reported asymmetric synthesis of tricyclic enones by means of intramolecular PKR [8]. We started our study using the simplest starting material and tackling the most ambitious four-step one-pot transformation (condensation/allylation/

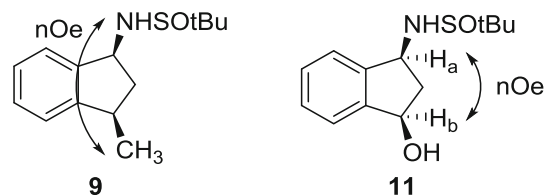
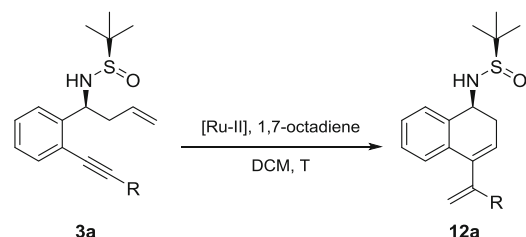


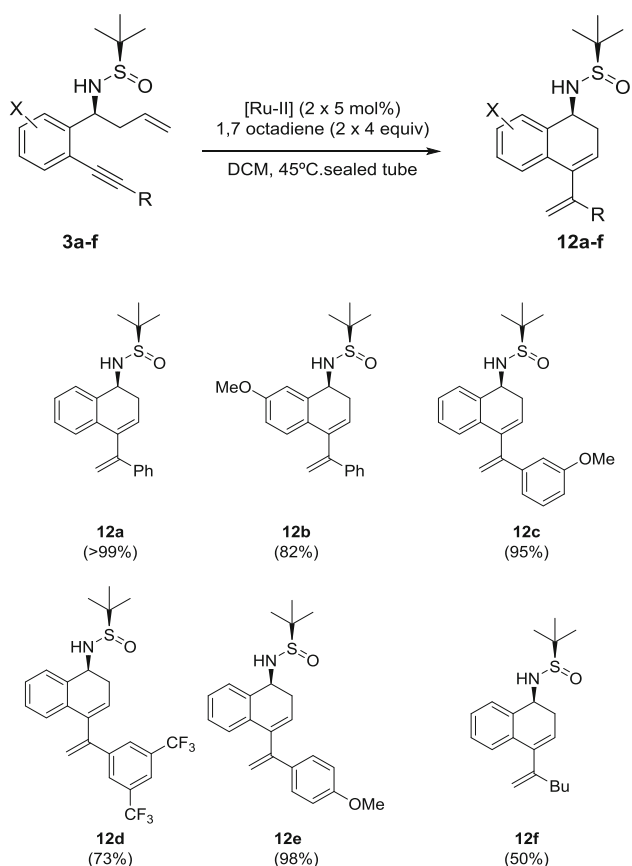
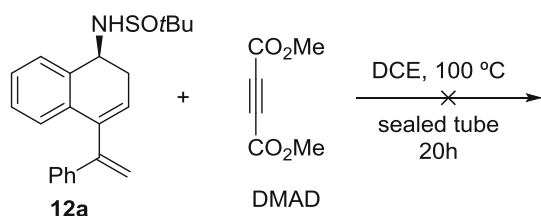
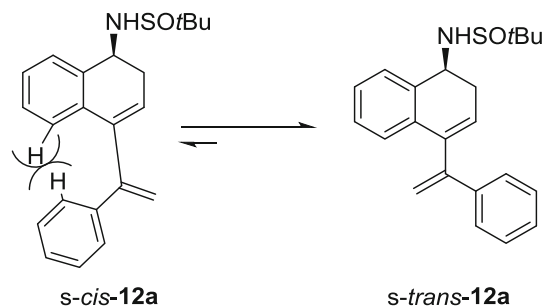
Fig. 1 Assignment of the relative stereochemistry of products **9** and **11**

Table 2 Optimization of the RCEYM reaction conditions



Entry	<i>T</i> (°C)	12a (%)
1	45	55
2 ^{a,b,c}	45	>99
3 ^{a,b,c}	90	73
4 ^{a,d}	45	84

^a Sealed tube, ^b 2 × 5 mol % catalyst loading, ^c 2 × 4 equiv 1,7-octadiene, ^d 1 equiv Ti(OEt)₄

**Scheme 6** Scope and limitations**Scheme 7** Failed Diels–Alder reaction between **12a** and **DMAD****Fig. 2** *S-cis/S-trans* conformational equilibrium of **12a**

Sonogashira/PKR). However, although the desired product **13a** was detected in the crude reaction mixture, most of the recovered material was identified as **1a**, suggesting that the

Sonogashira reaction was not fully compatible with the reaction medium from the previous condensation/allylation steps (Scheme 8).

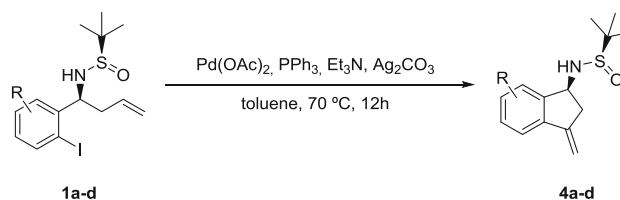
Since the Sonogashira coupling seemed to be the bottleneck for this one-pot procedure, we decided to carry out this step independently and then run the one-pot procedure on the corresponding *o*-alkynylbenzaldehyde derivatives **14a, b** (Scheme 9). In both examples, the chemical yield of the one-pot procedure is significantly lower than the corresponding stepwise protocol (Scheme 9). The one-pot methodology, though, benefits from operational simplicity. Regarding the diastereoselectivity, for **14a**, a diminished *dr* was obtained, as expected (Scheme 9). This is due to the dependence of the diastereoselectivity with the substitution at the triple bond that we described in our previous report [8]. The isolation of a single diastereoisomer for **14b** might be due to the loss of small quantities of minor diastereoisomers during purification, which would also account for the low chemical yield (Scheme 9).

Conclusions

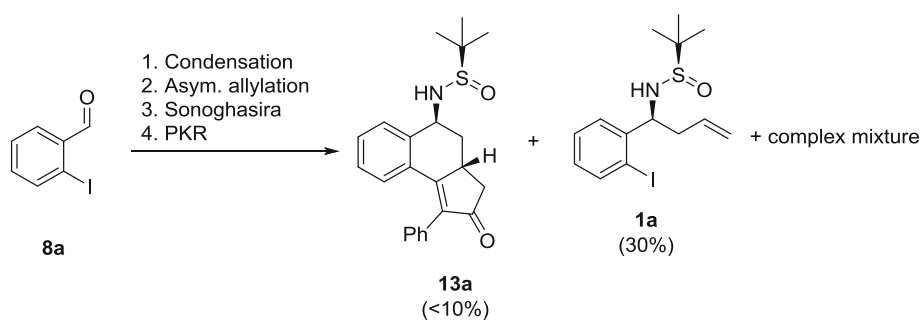
In recent years, 2-iodobenzaldehyde has shown its superior performance as a substrate for diversity-oriented synthesis. In this report, we have further increased the molecular variability accessible from this readily available starting material. More specifically, the asymmetric allylation of the corresponding Ellman's imines followed by intramolecular Heck reaction affords 3-methylene-1-aminoindane derivatives. On the other hand, the introduction of an alkynyl group at the *ortho*-position affords substrates suitable for a RCEYM reaction achieving conjugated dienes. One-pot procedures have been developed for both the asymmetric allylation/intramolecular Heck reaction and the condensation/asymmetric allylation/Pauson–Kahnd reaction sequence.

Experimental section

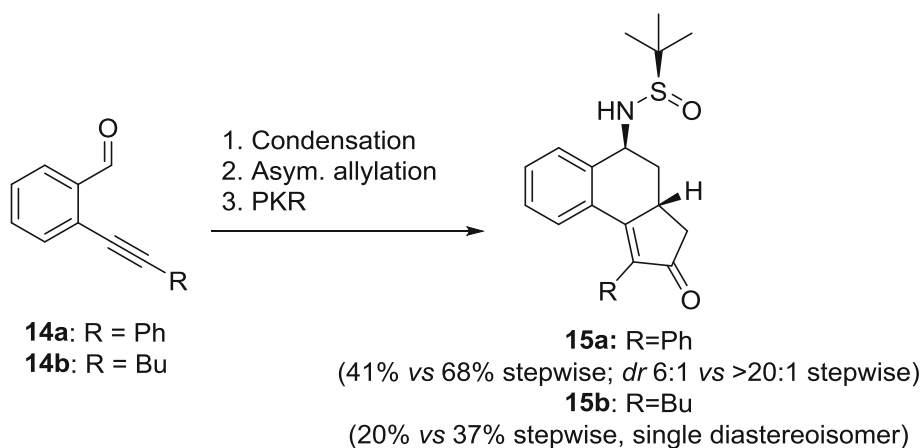
General procedure for the intramolecular Heck reaction



Scheme 8 One-pot condensation/asymmetric allylation/Sonogashira coupling//PKR



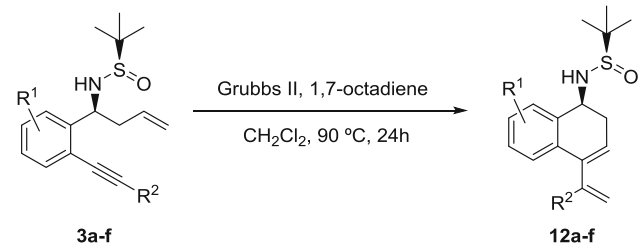
Scheme 9 One-pot condensation/asymmetric allylation/PKR sequence



A solution of the corresponding substituted 2-iodobenzyl sulfinyl amide **1** (1.0 equiv), Pd(OAc)₂ (0.1 equiv), PPh₃ (0.2 equiv), Et₃N (2.0 equiv) and Ag₂CO₃ (2.0 equiv) in toluene (0.1 M) was heated to 70 °C for 12 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography to give compounds **4**.

Compounds **4a–d** have previously been described, and their spectroscopic data are in fully agreement with the literature [17].

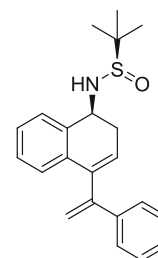
General procedure for the ring-closing enyne metathesis



A solution of **3** (1.0 equiv), 1,7-octadiene (8.0 equiv) and Grubbs II catalyst (0.05 equiv) in CH₂Cl₂ (0.1 M) was

heated to 90 °C for 24 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography to give compounds **12**.

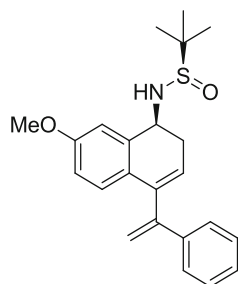
(*R*_S)-2-Methyl-*N*-[(*S*)-4-(1-phenylvinyl)-1,2-dihydronaphthalen-1-yl]propane-2-sulfinamide (**12a**)



The title compound was obtained following the general procedure described above. Flash chromatography [*n*-hexane/EtOAc (1:1)] afforded compound **12a** as a brown solid (>99 %). [α]_D²⁵ = +24.3 (c 1.0; CHCl₃). ¹H RMN (300 MHz, CDCl₃) δ 1.23 (s, 9H), 2.68 (ddd, *J* = 17.2, 7.1, 4.9 Hz, 1H), 2.89 (ddd, *J* = 17.2, 5.7, 4.3 Hz, 1H), 3.51 (d, *J* = 8.1 Hz, 1H), 4.59 (dd, *J* = 13.7, 7.2 Hz, 1H), 5.35 (d, *J* = 1.6 Hz, 1H), 5.67 (d, *J* = 1.6 Hz, 1H), 6.10 (t, *J* = 4.5 Hz, 1H), 7.00 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.10 (td, *J* = 7.5, 1.5 Hz, 1H), 7.17 (td, *J* = 7.4, 1.5 Hz, 1H), 7.23 (d, *J* = 1.9 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.26 (s, 1H), 7.36–7.43 (m, 3H). ¹³C RMN (75 MHz, CDCl₃)

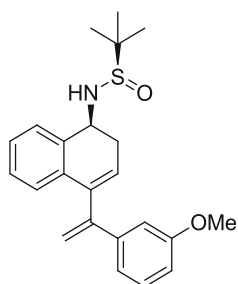
δ 22.7 (3xCH₃), 32.6 (CH₂), 54.3 (CH), 56.1 (C), 115.4 (CH₂), 125.1 (CH), 126.3 (CH), 126.6 (2xCH), 126.8 (CH), 127.3 (CH), 127.7 (CH), 128.0 (CH), 128.3 (2xCH), 133.5 (C), 135.6 (C), 139.6 (C), 139.7 (C), 147.9 (C). HRMS (EI) calcd for C₂₂H₂₅NOS [M + H]⁺: 352.1730, found: 352.1737.

(*R*_S)-*N*-[(*S*)-7-Methoxy-4-(1-phenylvinyl)-1,2-dihydronaphthalen-1-yl]-2-methylpropane-2-sulfinamide (12b)



The title compound was obtained following the general procedure described above. Flash chromatography [*n*-hexane/EtOAc (1:1)] afforded compound **12b** as a brown solid (82 %). [α]_D²⁵ = + 21.0 (c 1.0; CHCl₃). ¹H RMN (300 MHz, CDCl₃) δ 1.25 (s, 9H), 2.62 (ddd, *J* = 16.9, 8.0, 4.6 Hz, 1H), 2.87 (ddd, *J* = 16.9, 5.7, 4.5 Hz, 1H), 3.49 (d, *J* = 7.5 Hz, 1H), 3.76 (s, 3H), 4.49–4.60 (m, 1H), 5.34 (d, *J* = 1.7 Hz, 1H), 5.64 (d, *J* = 1.7 Hz, 1H), 5.97 (t, *J* = 4.5 Hz, 1H), 6.61 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 2.7 Hz, 1H), 7.21–7.26 (m, 3H), 7.37–7.42 (m, 2H). ¹³C RMN (75 MHz, CDCl₃) δ 22.7, 32.7, 54.9, 55.2, 56.2, 112.3, 112.8, 115.2, 122.7, 126.6, 127.7, 128.3, 137.7, 139.3, 139.8, 148.1, 158.8. HRMS (EI) calcd for C₂₃H₂₇NO₂S [M + H]⁺: 382.1762, found: 382.1760.

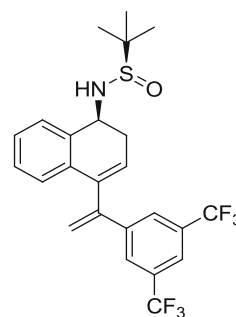
(*R*_S)-*N*-[(*S*)-4-(1-(3-Methoxyphenyl)vinyl)-1,2-dihydronaphthalen-1-yl]-2-methylpropane-2-sulfinamide (12c)



The title compound was obtained following the general procedure described above. Flash chromatography [*n*-hexane/EtOAc (1:1)] afforded compound **12c** as a brown solid (95 %). [α]_D²⁵ = + 5.0 (c 1.0; CHCl₃). ¹H RMN

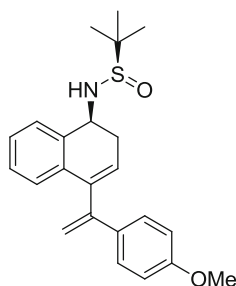
(300 MHz, CDCl₃) δ 1.23 (s, 9H), 2.67 (ddd, *J* = 17.2, 7.3, 4.8 Hz, 1H), 2.88 (ddd, *J* = 17.2, 5.8, 4.3 Hz, 1H), 3.51 (d, *J* = 8.5 Hz, 1H), 3.76 (s, 3H), 4.57 (dd, *J* = 13.9, 7.6 Hz, 1H), 5.34 (d, *J* = 1.6 Hz, 1H), 5.66 (d, *J* = 1.6 Hz, 1H), 6.08 (t, *J* = 4.5 Hz, 1H), 6.78 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 6.95–6.99 (m, 2H), 7.01 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.08–7.20 (m, 3H), 7.35–7.41 (m, 1H). ¹³C RMN (75 MHz, CDCl₃) δ 22.7 (3xCH₃), 32.7 (CH₂), 54.5 (CH), 55.2 (CH₃), 56.1 (C), 112.7 (CH), 112.7 (CH), 115.7 (CH₂), 119.3 (CH), 125.2 (CH), 126.3 (CH), 126.6 (2xCH), 127.4 (CH), 127.9 (2xCH), 129.3 (CH), 133.5 (C), 135.7 (C), 139.6 (C), 141.3 (C), 147.8 (C), 159.6 (C). HRMS (EI) calcd for C₂₃H₂₇NO₂S [M + H]⁺: 382.1835, found: 382.1819.

(*R*_S)-*N*-[(*S*)-4-(1-(3,5-Bis(trifluoromethyl)phenyl)vinyl)-1,2-dihydronaphthalen-1-yl]-2-methylpropane-2-sulfinamide (12d)



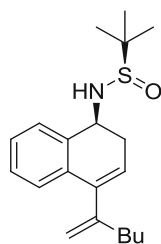
The title compound was obtained following the general procedure described above. Flash chromatography [*n*-hexane/EtOAc (1:1)] afforded compound **12d** as a brown solid (73 %). [α]_D²⁵ = + 15.0 (c 1.0; CHCl₃). ¹H RMN (300 MHz, CDCl₃) δ 1.22 (s, 9H), 2.74 (ddd, *J* = 17.4, 7.1, 4.8 Hz, 1H), 2.92 (ddd, *J* = 17.3, 6.0, 4.3 Hz, 1H), 3.48 (d, *J* = 8.8 Hz, 1H), 4.58 (dd, *J* = 15.2, 6.7 Hz, 1H), 5.56 (d, *J* = 0.7 Hz, 1H), 5.78 (d, *J* = 0.9 Hz, 1H), 6.15 (t, *J* = 4.5 Hz, 1H), 6.90 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.13 (td, *J* = 7.5, 1.4 Hz, 1H), 7.22 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.75 (s, 1H), 7.80 (s, 2H). ¹⁹F RMN (282 MHz, CDCl₃) δ -62.84 (2xCF₃). ¹³C RMN (75 MHz, CDCl₃) δ 22.6 (3xCH₃), 32.7 (CH₂), 54.4 (CH), 56.2 (C), 119.1 (CH₂), 121.5 (d, ³*J*_{CF} = 5.5 Hz, 2xCH), 125.9 (CH), 126.6 (CH), 126.8 (q, ¹*J*_{CF} = 272.9 Hz, 2xCF₃), 126.9 (CH), 127.1 (CH), 127.9 (CH), 128.1 (CH), 131.8 (d, ²*J*_{CF} = 33.2 Hz, 2xC), 132.4 (C), 135.9 (C), 138.2 (C), 142.2 (C), 145.7 (C). HRMS (EI) calcd for C₂₄H₂₃NOF₆S [M + H]⁺: 488.1477, found: 488.1464.

(*R*_S)-*N*-[(*S*)-4-(1-(4-Methoxyphenyl)vinyl)-1,2-dihydronaphthalen-1-yl]-2-methylpropane-2-sulfinamide (12e)



The title compound was obtained following the general procedure described above. Flash chromatography [*n*-hexane/EtOAc (1:1)] afforded compound **12e** as a brown solid (98 %). $[\alpha]_{\text{D}}^{25} = +6.0$ (c 1.0; CHCl₃). ¹H RMN (300 MHz, CDCl₃) δ 1.23 (s, 9H), 2.66 (ddd, *J* = 17.2, 7.2, 4.8 Hz, 1H), 2.88 (ddd, *J* = 17.1, 5.7, 4.3 Hz, 1H), 3.52 (d, *J* = 8.1 Hz, 1H), 3.76 (s, 3H), 4.58 (dd, *J* = 13.7, 7.4 Hz, 1H), 5.24 (d, *J* = 1.6 Hz, 1H), 5.57 (d, *J* = 1.7 Hz, 1H), 6.08 (t, *J* = 4.5 Hz, 1H), 6.74–6.80 (m, 2H), 7.00 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.10 (td, *J* = 7.5, 1.5 Hz, 1H), 7.17 (td, *J* = 7.4, 1.5 Hz, 1H), 7.30–7.36 (m, 2H), 7.39 (d, *J* = 6.9 Hz, 1H). ¹³C RMN (75 MHz, CDCl₃) δ 22.7 (3xCH₃), 32.6 (CH₂), 54.4 (CH), 55.2 (CH₃), 56.1 (C), 113.6 (CH₂), 113.7 (CH), 124.9 (CH), 126.4 (2xCH), 126.7 (CH), 127.3 (CH), 127.8 (2xCH), 128.0 (CH), 132.3 (C), 133.6 (C), 135.6 (C), 139.8 (C), 147.3 (C), 159.3 (C). HRMS (EI) calcd for C₂₃H₂₇NO₂S [M + H]⁺: 382.1835, found: 382.1833.

(*R*_S)-*N*-[(*S*)-4-(Hex-1-en-2-yl)-1,2-dihydronaphthalen-1-yl]-2-methylpropane-2-sulfonamide (**12f**)



The title compound was obtained following the general procedure described above. Flash chromatography [*n*-hexane/EtOAc (1:1)] afforded compound **12f** as a brown solid (50 %). $[\alpha]_{\text{D}}^{25} = +7.9$ (c 1.0; CHCl₃). ¹H RMN (300 MHz, CDCl₃) δ 0.86 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 9H), 1.28–1.35 (m, 2H), 1.47 (d, *J* = 4.8 Hz, 2H), 2.24 (t, *J* = 7.0 Hz, 2H), 2.58 (ddd, *J* = 17.0, 6.9, 5.0 Hz, 1H),

2.73 (ddd, *J* = 17.0, 5.6, 4.3 Hz, 1H), 3.47 (d, *J* = 8.7 Hz, 1H), 4.45 (dd, *J* = 14.8, 6.5 Hz, 1H), 5.00 (d, *J* = 2.3 Hz, 1H), 5.08 (ddd, *J* = 2.3, 1.2 Hz, 1.2 Hz, 1H), 5.86 (t, *J* = 4.5 Hz, 1H), 7.19–7.28 (m, 3H), 7.35–7.40 (m, 1H). ¹³C RMN (75 MHz, CDCl₃) δ 13.9 (CH₃), 22.2 (CH₂), 22.6 (3xCH₃), 30.5 (CH₂), 32.4 (CH₂), 35.5 (CH₂), 54.7 (CH), 56.1 (C), 114.2 (CH₂), 122.0 (CH), 125.7 (CH), 126.7 (CH), 127.3 (CH), 127.9 (CH), 133.3 (C), 136.3 (C), 140.8 (C), 148.7 (C). HRMS (EI) calcd for C₂₀H₂₉NOS [M + H]⁺: 332.2043, found: 332.2040.

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References

- Collins S, Barlett S, Nie F, Sore HF, Spring DR (2016) *Synthesis* 48:1457
- Serba C, Winsinger N (2013) *Eur J Org Chem* 2013:4195
- MacLellan P, Nelson A (2013) *Chem Commun* 49:2383
- O'Connor CJ, Beckmann HSG, Spring DR (2012) *Chem Soc Rev* 41:4444
- For some representative early reports, see: Burke MD, Schreiber SL (2004) *Angew Chem Int Ed* 43:46
- Schreiber SL (2000) *Science* 287:1964
- Lázaro R, Román R, Sedgwick DM, Haufe G, Barrio P, Fustero S (2016) *Org Lett* 18:948
- Fustero S, Lázaro R, Aiguabella N, Riera A, Simón-Fuentes A, Barrio P (2014) *Org Lett* 16:1224
- Fustero S, Lázaro R, Herrera L, Rodríguez E, Mateu N, Barrio P (2013) *Org Lett* 15:3770
- Fustero S, Rodríguez E, Lázaro R, Herrera L, Catalán S, Barrio P (2013) *Adv Synth Catal* 355:1058
- Fustero S, Rodríguez E, Herrera L, Asensio A, Maestro MA, Barrio P (2011) *Org Lett* 13:6564
- Barrio P, Ibañez I, Herrera L, Román R, Catalán S, Fustero S (2015) *Chem Eur J* 21:11579
- Fustero S, Ibañez I, Barrio P, Maestro MA, Catalán S (2013) *Org Lett* 15:832
- Fustero S, Herrera L, Lázaro R, Rodríguez E, Maestro MA, Mateu N, Barrio P (2013) *Chem Eur J* 19:11776
- Fustero S, Moscardó J, Sánchez-Roselló M, Rodríguez E, Barrio P (2010) *Org Lett* 12:5494
- Barrio P, Rodríguez E, Fustero S (2016) *Chem Rec* 18(4):2046
- Sirvent JA, Foubelo F, Yus M (2013) *Eur J Org Chem* 2013:2461
- Villar H, Frings M, Bolm C (2007) *Chem Soc Rev* 36:55
- Rodríguez E, Grayson MN, Asensio A, Barrio P, Houk KN, Fustero S (2016) *ACS Cat* 6:2506
- Fustero S, Bello P, Miró J, Simón A, del Pozo C (2012) *Chem Eur J* 18:10991

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