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Metathesis Reactions

The Ruthenium-Catalyzed Domino Cross Enyne Metathesis/ Ring-Closing Metathesis in the Synthesis of Enantioenriched Nitrogen-Containing Heterocycles

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Abstract: The tetrahydropyridine structure is present in a wide variety of natural and synthetic compounds with interesting pharmacological properties. Therefore, the search for new chemical routes capable of yielding this valuable nitrogen-containing heterocycle is of utmost interest. Herein, we report the use of the ruthenium-catalyzed ring-closing enyne metathesis (RCEYM) and cross enyne metathesis/ring-closing metathesis (CEYM/RCM) reactions of chiral nitrogen-containing 1,7-enynes as an efficient route to synthesize a variety of enantioenriched tetrahydropyridine-based conjugated 1,3-dienes. The RCEYM presented wide functional group tolerance and took place in moderate to high yields, with no significant differences when carried out on gram scale. These 1,3-dienes were suitable for further transformations, such as the Diels–Alder reaction, effectively yielding more complex enantioenriched bicyclic structures.

Introduction

Nitrogen-containing heterocycles are important motifs present in a wide variety of natural products and biologically active molecules, i.e. pharmaceuticals and agrochemicals.[1] This is evident when looking at the alkaloid class of natural products, many of which have served as starting points in modern drug discovery processes.[2] Among this class of heterocycles, tetrahydropyridines and piperidines have emerged as promising targets with potential applications in the treatment of schizophrenic syndromes, sleep disorders and Parkinson's disease, among others (Figure 1).[3] However, the synthesis of such compounds can often be fairly laborious and require several synthetic steps to achieve the desired substitution patterns.[4] On the other hand, a key feature of many natural products and biologically active compounds is their optical purity; most exist as a single enantiomer due to their biosynthetic origins.[5] This is crucial in drug discovery, since opposing enantiomers may present very different biological activity.[6] For this reason, great efforts have been invested in the development of novel synthetic strategies for the construction of enantioenriched nitrogen-containing heterocycles throughout the past few decades.[7] However, the emergence of alternative methodologies capable of easily constructing such target molecules remains scarce in medicinal and synthetic organic chemistry.[8]

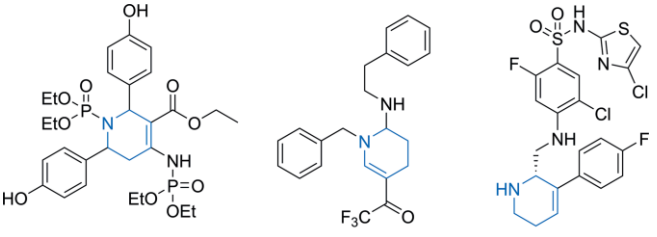

Figure 1. Interesting biological activities of tetrahydropyridine derivatives.

In view of the need for alternative and more efficient strategies for the synthesis of these valuable olefin-containing building blocks, metathesis reactions offer easy access to worthwhile alkenes with high efficiency and atom economy. Since the seminal report by Grubbs in 1992,[9] metathesis reactions have become some of the most powerful for carbon–carbon bond for-

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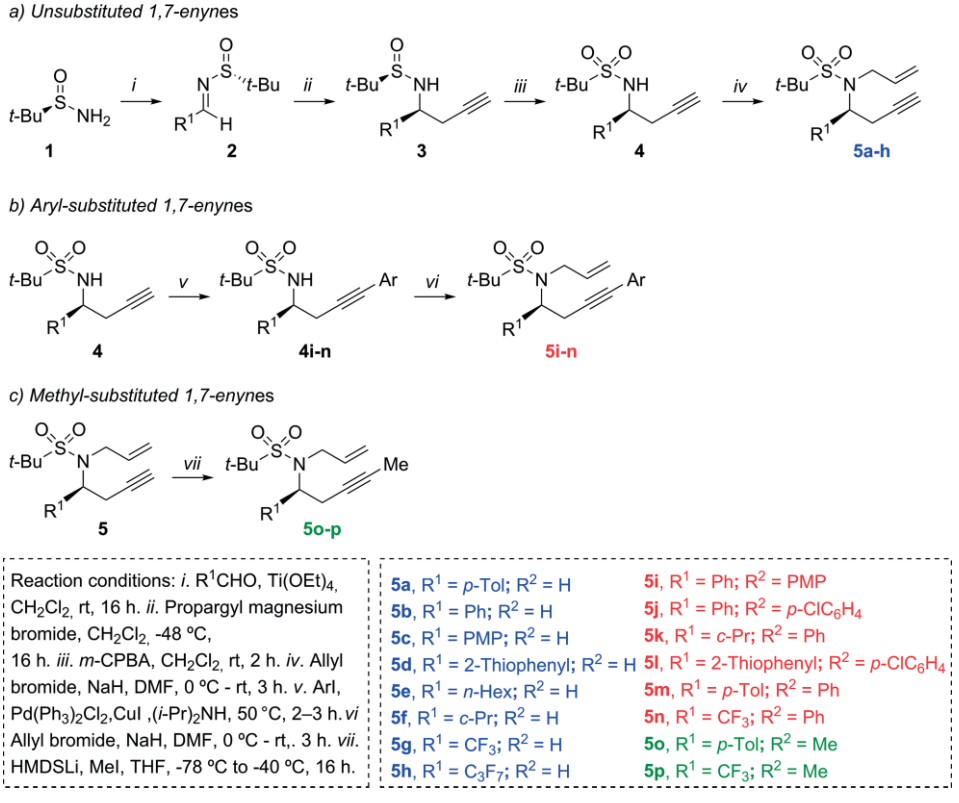
mation in recent organic chemistry, especially the ring-closing metathesis (RCM) reaction between two olefins.[10] Another interesting variant is the ring-closing enyne metathesis (RCEYM) reaction which, under mild conditions, generates conjugated cyclic 1,3-dienes with an exocyclic double bond.[11] RCEYM reactions have been widely applied to the synthesis of medium- and large-sized rings containing 1,3-dienes, which are interesting building blocks amenable to further synthetic transformations and are present in many drugs and natural products.[12] The RCEYM reaction is also compatible with nitrogen-based functional groups, and *N*-tethered enynes can also be used to afford desirable tetrahydropyridine-based 1,3-dienes.[13] Furthermore, the possibility of performing an *exo* cross enyne metathesis reaction between the triple bond of the enyne and a monoalkene would widen the structural diversity of the final products.[14] For this reason, as well as their wide functional-group tolerance, they have become a fundamental part of the modern synthetic chemist's toolkit.[15] These ruthenium-catalyzed transformations have also been applied to various cascade reaction during the past decade,[16] often leading to the introduction of high molecular complexity in a single step, for example through coupling with Diels–Alder or other cyclization reactions to form polycyclic systems,[17] as well as in the synthesis of alkaloids and other natural products.[18]

In the quest for novel chemical routes capable of generating enantioenriched tetrahydropyridine derivatives, herein we report the use of chiral *N*-tethered 1,7-enynes in the ruthenium-catalyzed RCEYM reaction to form aza-cyclic conjugated 1,3-dienes. The chiral *N*-tethered 1,7-enynes were synthesized from Ellman's *tert*-butanesulfinyl imines in good yields following a simple four-step synthetic route. The building blocks obtained through the efficient RCEYM reaction could be used in subsequent Diels–Alder reactions to access piperidine-based bicyclic scaffolds.

Discussion

The synthesis of the chiral *N*-tethered 1,7-enyne building blocks was performed in good yields following a previously reported four-step synthetic sequence (Scheme 1).[19] The initial condensation reaction of *tert*-butanesulfinamide **1** with aldehydes in CH_2Cl_2 provided Ellman's *tert*-butanesulfinyl imines **2** in high yields.[20] Over the past decade, *N*-*tert*-butanesulfinyl imines have been widely used in synthetic applications, since they provide easy access to both enantiomers from commercially available *tert*-butanesulfinamide.[21] Following this, the diastereoselective propargylation of imines **2** using propargylmagnesium bromide in CH_2Cl_2 at –48 °C afforded the chiral homopropargyl sulfinamides **3**,[22] which were oxidized to the corresponding sulfonamides **4** using *m*-CPBA in CH_2Cl_2 at 0 °C in high yields. Finally, allylation with allyl bromide in the presence of NaH in DMF yielded the chiral *N*-tethered 1,7-enyne derivatives **5a–f** in good to high global yields (Scheme 1a). Additionally, enantioenriched *N*-tethered fluorinated enynes (R = CF_3 or C_3F_7) were also synthesized in good to high yields (**5g** and **5h**). Substitution at the triple bond with aryl groups via Sonogashira reaction with homopropargylic sulfonamides **4**, and subsequent all-



Scheme 1. Synthesis of chiral *N*-tethered 1,7-enynes.

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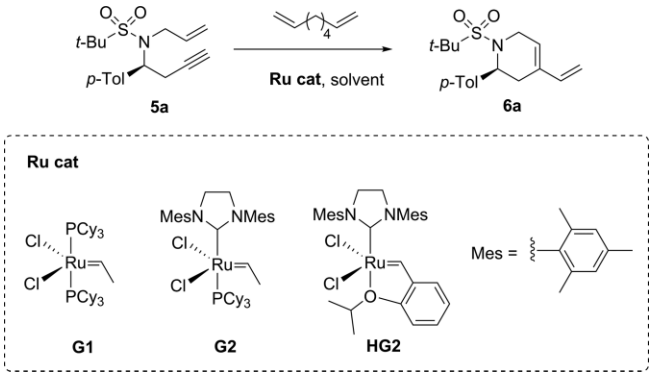
ylation as previously mentioned, allowed the preparation of aryl-substituted 1,7-enynes (**5i–n**) (Scheme 1b). On the other hand, methyl-substituted enynes (**5o** and **5p**) were synthesized via direct methylation of the triple bond using HMDSLi and methyl iodide (Scheme 1c). With these versatile substrates in hand, we began to explore the ring closing enyne metathesis reaction, using 1,7-octadiene as an in situ source of ethylene.[23] Under metathesis conditions, 1,7-octadiene undergoes a highly favorable ring-closing metathesis reaction without interfering with the substrate.

This process releases cyclohexene and ethylene into the reaction mixture, generating the reactive ruthenium carbene catalyst in the process, ready to enter the catalytic cycle that leads to the formation of the desired conjugated 1,3-diene. To our delight, enyne **5a** successfully took part in a ruthenium-catalyzed intramolecular RCEYM reaction yielding the corresponding enantioenriched tetrahydropyridine-based 1,3-diene **6a** (Table 1).

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	[Ru cat]	cat loading [%]	Yield [%][b]
1	Toluene	**G1**	10	52
2	Toluene	**G2**	10	56
3	Toluene	**HG2**	10	83
4	MeCN	**HG2**	10	81
5	CH_2Cl_2	**HG2**	10	89
6	THF	**HG2**	10	65
7	CH_2Cl_2	**HG2**	5	87
8	CH_2Cl_2	**HG2**	3	85
9	CH_2Cl_2	**HG2**	1	57
10[c]	CH_2Cl_2	**HG2**	3	0

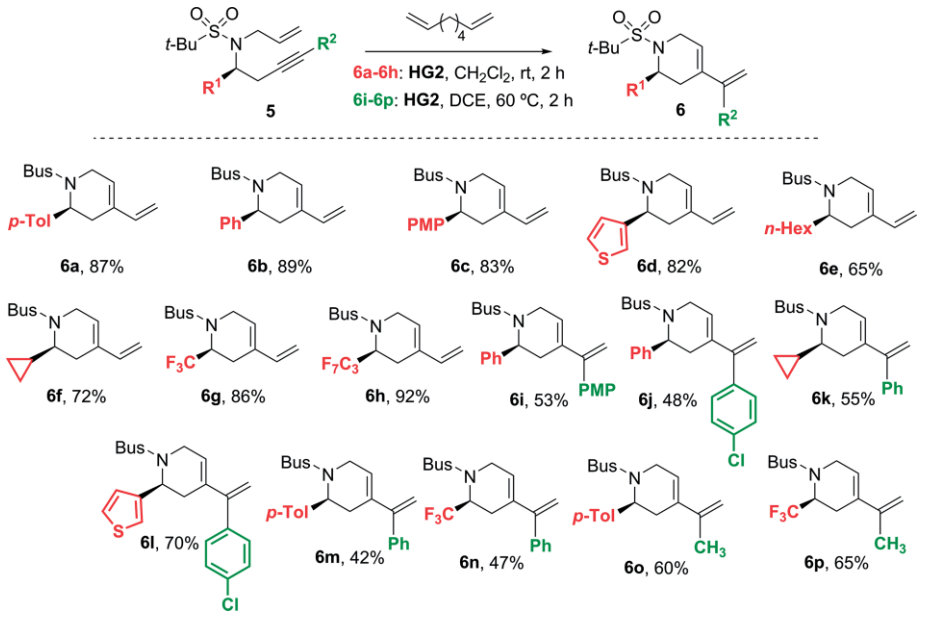
[a] Reaction conditions: **5a** (0.1 mmol), 1,7-octadiene (0.4 mmol), r.t., 2 h. [b] Yields of the isolated product **6a**. [c] In the absence of 1,7-octadiene.

An initial screening of the reaction conditions was carried out using enyne **5a** (R^1 = *p*Tol) as the model substrate for the ruthenium-catalyzed RCEYM (Table 1). First, a screening of the different Grubbs catalysts (10 mol-%) was performed using toluene as solvent. Our model substrate was efficiently cyclized to give the cyclic 1,3-diene in all cases (entries 1–3, Table 1), but second-generation Hoveyda–Grubbs catalyst (**HG2**) proved the most efficient in terms of yield of **6a** (entry 3, Table 1). We then explored the use of different solvents using the **HG2** catalyst (10 mol-%). Similar yields were observed when using other non-coordinating solvents such as acetonitrile or CH_2Cl_2 (entries 4 and 5, Table 1), although the yield was slightly higher in CH_2Cl_2. On the contrary, the use of THF, a coordinating solvent, remarkably decreased the formation of the cyclic 1,3-diene (entry 6, Table 1). The catalyst loading could be lowered to 3 mol-% without a significant decrease in the reaction yield (entries 7 and 8, Table 1); however, the yield decreased under same reaction conditions (2 h) beyond this value (entry 9, Table 1). When the reaction was assayed in the absence of 1,7-octadiene (entry 10, Table 1), the formation of **6a** was not observed, but a triene resulting from a homo cross metathesis was formed in 48 % yield. The formation of this from a cross metathesis of **6a** has also been recently reported by Foubelo and co-workers under high dilution conditions.[12a]

With the optimal reaction conditions in hand (CH_2Cl_2, **HG2** catalyst 3 mol-%; (entry 8 Table 1), the formation of the corresponding tetrahydropyridine-based 1,3-dienes through our ring-closing enyne metathesis (RCEYM) procedure was then evaluated (Scheme 2). For this purpose, a set of chiral 1,7-enynes with different substituents at the stereogenic carbon was submitted to our optimized RCEYM reaction conditions, usually resulting in complete conversion of the chiral 1,7-enyne after 2 h (determined by TLC analysis). The resulting 1,3-dienes could be isolated through simple flash column chromatography. As a general trend, substrates with aromatic substituents (R^1 = Ph, *p*Tol, PMP) at the stereogenic center gave higher yields than those bearing aliphatic substituents such as *n*-hexyl or cyclopropyl (**6e** and **6f**, Scheme 2). Interestingly, 1,7-enynes containing fluorinated substituents (R^1 = CF_3 or C_3F_7) afforded the corresponding 1,3-diene compounds with high yields (**6g** and **6h**, Scheme 2). Fluorinated substitutions are of great importance in modern organic and medicinal chemistry, since the unique properties of the C-F bond allow the fine-tuning of the acidity/basicity, metabolic stability and lipophilicity of biologically active compounds as desired.[24] A gram-scale synthesis of diene **6b** was also successfully performed through the ruthenium catalyzed metathesis reaction with 1,7-octadiene in good global yield (70 %, 4 steps, see Supporting Information for details).

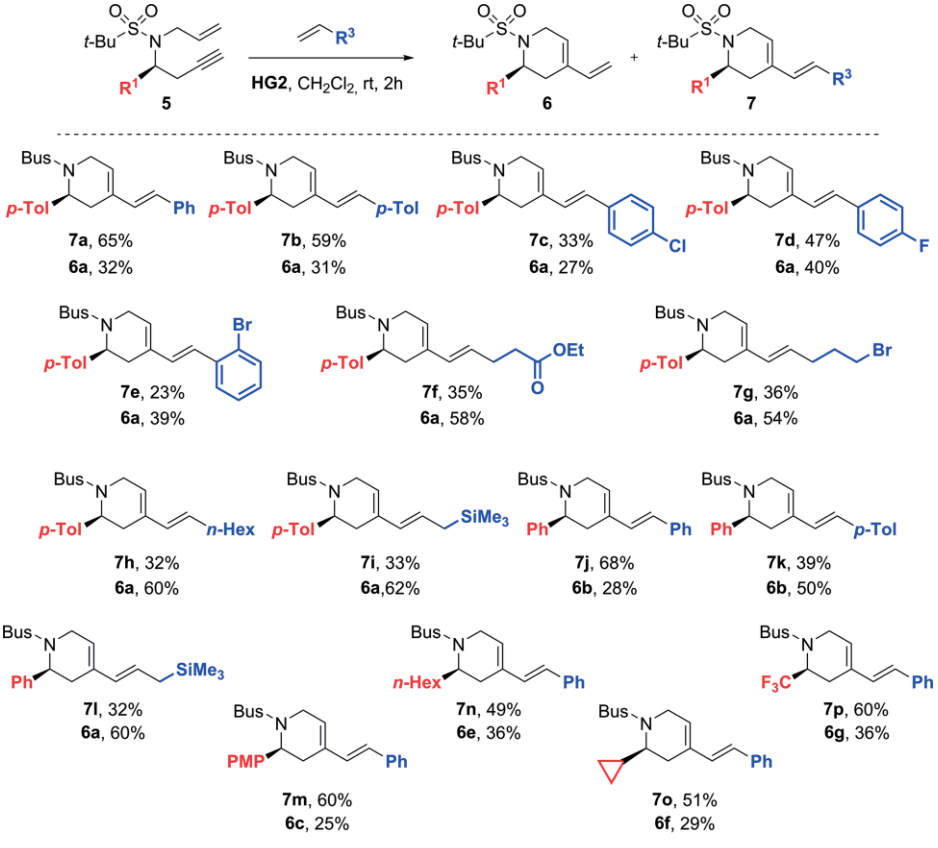
The influence of the alkyne substitution was also evaluated in the RCEYM. To this end, alkyl and aryl substituents were introduced at the corresponding chiral propargyl sulfonamides **4** following a previously escribed synthetic route by our group.[19] The ruthenium-catalyzed RCEYM in the presence of 1,7-octadiene afforded the corresponding aryl- or alkyl-substituted 1,3-dienes (**6i**–**6p**, Scheme 2) in moderate yields after 2 h in DCE at 60 °C. In general, lower yields were obtained when compared to the unsubstituted analogues (Scheme 2). Our results indicate that enyne substituents have an important effect on the reactivity of the process, as observed in similar systems.[25]

Next, a ruthenium-catalyzed domino cross enyne metathesis/ring-closing metathesis (CEYM/RCM) of enyne **5a** and styrene was assayed.[26] In this case, we observed the formation of a mixture of products easily separable by flash chromatoraphy: **7**, presumably via a cross enyne metathesis (CEYM) followed by a ring closing metathesis (RCM) reaction; and **6**, through the simple RCEYM previously discussed. When performing the reaction of enyne **5a** (R^1 = *p*Tol) with styrene in the presence of **HG2** catalyst (3 mol-%), both **6a** and **7a** were isolated with yields of



Scheme 2. Ruthenium-catalyzed RCEYM of chiral *N*-tethered 1,7-enynes.

32 and 65 %, respectively. Under the aforementioned conditions, the formation of the CEYM product, i.e. conjugated (*E*)-diene **7a**, was favored over the RCEYM product **6a**. Slow addition of the catalyst was assayed with the aim of preserving catalytic activity, but this yielded **7a** in lower yields and slightly favored the formation of RCEYM product **6a**.[27] The use of other aromatic olefins afforded the corresponding compound **7** in similar yields to that observed for styrene. However, electron-withdrawing substituents in the *ortho* or *para* position of the styrene derivative had a dramatic effect and decreased the isolated yield of the CEYM product (**7c–e**, Scheme 3). A similar negative effect was observed in compounds **7f–i** when carrying



Scheme 3. Scope of the CEYM/RCM of *N*-tethered 1,7- enynes.

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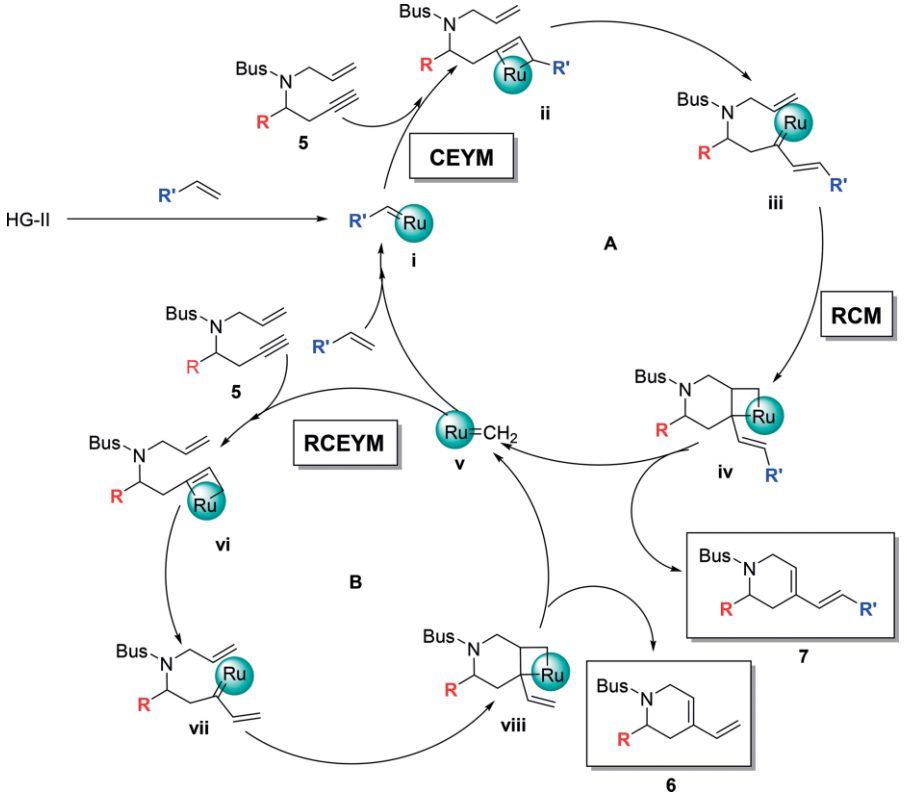
out the metathesis reaction with aliphatic olefins which, in contrast, favored the formation of the RCEYM product over that of CEYM.

Next, we evaluated the effect of the substituent on the stereogenic center of 1,7-enyne. The presence of aromatic substituents (R^1 = Ph, *p*Tol, PMP) on the stereogenic center resulted in higher yields of the corresponding CEYM/RCM product **7** with slight variations depending on the aromatic substituents (**7a**, **7j** and **7m**, Scheme 3). On the contrary, the aliphatic substituents (R^1 = *n*-Hex, *c*Pr) on the chiral center lowered the formation of the CEYM/RCM product (**7n** and **7o**, Scheme 3), similar to the previously observed results with 1,7-octadiene. Finally, fluorine-containing 1,7-enyne (R^1 = CF_3) afforded the corresponding 1,3-diene derived from the CEYM/RCM with a 60 % yield (**7p**).

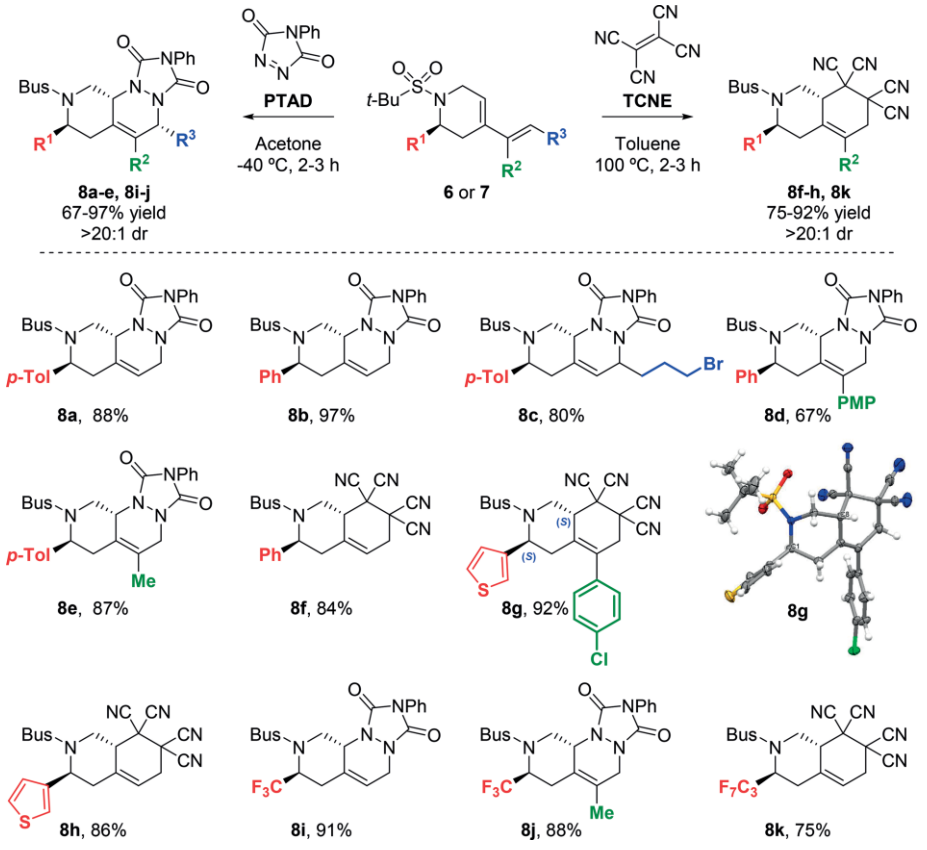
To account for the formation of 1,3-dienes **6** and **7** from the corresponding chiral *N*-tethered 1,7-enynes, a possible catalytic cycle is depicted in Scheme 4. Accordingly, diene **7** should be the result of a domino cross enyne metathesis/ring-closing metathesis (CEYM/RCM) process. The initial formation of the intermediate ruthenium complex **i** would come from the reaction of second-generation Hoveyda–Grubbs catalyst (**HG2**) with the monoalkene. Next, a [2+2] cycloaddition with 1,7-enyne **5** would take place to form ruthenacyclobutene **ii**. This intermediate would be then converted into the vinylcarbene complex **iii** via ring-opening, and followed by RCM with the alkene group of the 1,7-enyne yielding cyclic compound ruthenacyclobutane **iv**. Subsequent ring-opening of **iv** should give the cyclized 1,3-diene **7**, and a methylidene ruthenium complex **v**, which could then react with the monoalkene and restart the catalytic cycle.

On the other hand, should intermediate **v** react with enyne **5**, a second cycle could be formed leading to the formation of diene **6**. For this to take place, methylidene ruthenium complex **v** should undergo a [2+2] cycloaddition with the 1,7-enyne **5**, giving ruthenacyclobutene **vi**, which is then converted into vinylcarbene complex **vii** via ring-opening. Subsequent reaction with the alkene group of the 1,7-enyne gives ruthenacyclobutane **viii**. Finally, ring opening of ruthenacyclobutane **viii** gives cyclized diene **6**, and the methylidene ruthenium complex **v** is regenerated. The whole process could also start with a RCEYM followed by a CM, especially if the RCEYM goes by the ene-first mechanism (not shown in Scheme 4), which would directly lead to the carbene needed for the subsequent cross-metathesis reaction. The one-pot reaction of **5a** with 1,7-octadiene in the presence of **HG2** catalyst (3 mol-%), followed by the addition of styrene after complete conversion to **6a**, failed to give **7a**. However, the cross-metathesis reaction from isolated **6a** with styrene was partly successful in forming **7a**, although the reaction was much more sluggish and resulted in a low yield (45 %). The hypothesized pathway was in agreement with the results reported by Park et al. in the tandem CM/RCM reaction of alkynyl silyloxy-tethered enynes.[28]

In order to achieve more complex chemical structures and form polycyclic heterocycles, the reactivity of several chiral 1,3-dienes was evaluated through Diels–Alder reaction with readily available carbo- and heterodienophiles, such as tetracyanoeth-



Scheme 4. Tentative catalytic cycle for the domino CEYM/RCM and RCEYM of chiral 1,7-*N*-tethered enynes.

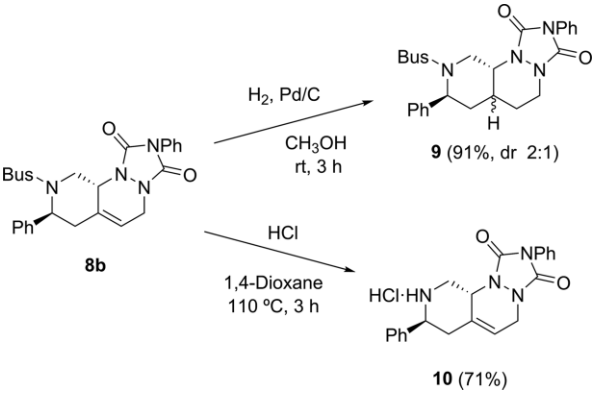


Scheme 5. Scope of the Diels–Alder reaction of 1,3-dienes derived from RCEYM of chiral *N*-tethered 1,7-enynes and ORTEP representation of compound **8g**.

ylene (TCNE) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD). Notably, all reactions took place efficiently to give cycloadducts **8** in high diastereoselectivity (dr > 20:1) (Scheme 5).

Cycloaddition of **6a** and **6b**, both bearing an aromatic substituent on the stereogenic center, with PTAD yielded Diels–Alder adducts **8a** and **8b** in high yields of 88 % and 97 % respectively. The Diels–Alder reaction affording **8b** was also carried out at gram scale with no loss of yield. However, a decrease in yield was observed when performing the reaction with **6i** and **7g**, affording the corresponding cycloadducts **8c** and **8d**, respectively, in lower yields (80 and 67 %). Similar yields were obtained when performing the reaction with TCNE for example, **6b** afforded cycloadduct **8f** in 84 % yield. The absolute stereochemistry of product **8g** was determined to be (*S*,*S*) according to X-ray crystallography analysis,[29] and was confirmed by a NOESY experiment using compound **8c**. This absolute stereochemistry was extrapolated to the rest of the Diels–Alder cycloadducts displayed in Scheme 5. Following our ongoing interest in the development of new fluorinated building blocks, we extended the scope of the Diels–Alder reaction to fluorinated derivatives. In this regard, these chiral fluorinated compounds were subjected to the cycloaddition conditions with PTAD and TCNE, again yielding the corresponding cycloadducts in high yields and diastereoselectivities (**8i**–**8k**, Scheme 5).

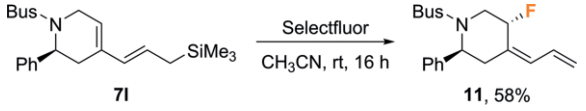
Further modifications to the final Diels–Alder adducts were also assayed. In this regard, the double bond in the resulting cycloadduct **8b** could be efficiently hydrogenated using palladium over activated charcoal under an atmosphere of hydrogen with high yield (91 %) but low diastereoselectively (dr 2:1) (Scheme 6). The removal of the *tert*-butanesulfonyl group was also assayed. An initial attempt to remove it was performed in hydrochloric acid in methanol at room temperature, but no reaction took place. However, through treatment of **8b** with HCl in 1,4-dioxane at 110 °C the *tert*-butylsulfonyl group could be cleanly removed and hydrochloride salt **10** was successfully isolated in a 71 % yield, with no loss in optical purity (Scheme 6). The protecting group could also be removed with $AlCl_3$ in anisole, albeit in a lower yield (50 %).



Scheme 6. Examples of further modifications to the final Diels–Alder adducts.

Considering the rapidly growing number of marketed fluorine-containing drugs, it is of utmost interest to access these

drugs through short and easy synthetic routes. In this regard, our metathesis products could be efficiently used in the preparation of more complex heterocyclic systems containing fluorine atoms. In our case, the incorporation of a fluorine atom into the piperidine ring was possible through the electrophilic fluorodesilylation of the allylsilane-bearing metathesis product **7l**, as described by Thibaudeau and Gouverneur.[30] The aforementioned transformation was carried out in acetonitrile at room temperature in the presence of Selectfluor, yielding fluorinated compound **11** in 58 % yield with high diastereoselectively (dr >20:1) (Scheme 7).



7l **11**, 58%

Scheme 7. Fluorodesilylation of metathesis product **7l**.

The stereochemistry of **11** was tentatively assigned by a series of 2D NMR experiments (see Supporting Information). It should be emphasized that the aforementioned method can be successfully applied to the preparation of derivatives featuring α-fluoroalkyl-amino moieties as a part of structurally complex heterocyclic systems.[31]

Conclusion

In conclusion, the effective use of RCEYM and domino CEYM/RCM reactions for the preparation of enantioenriched tetrahydropyridine-based conjugated 1,3-dienes has been demonstrated using chiral nitrogen-containing 1,7-enynes as starting materials. Noteworthy, the obtained chiral 1,3-dienes were suitable substrates for Diels–Alder reactions with tetracyanoethylene and 4-phenyl-1,2,4-triazoline-3,5-dione, yielding more complex bicyclic scaffolds in high diastereoselectivity (dr > 20:1). These structures could potentially be used in medicinal or biological studies given the prevalence of the tetrahydropyridine moiety in pharmaceutical contexts. The RCEYM and Diels–Alder reaction was also carried out at gram scale with no loss of yield. Further synthetic applications of these chiral nitrogen-containing 1,7-enynes are under investigation.

Experimental Section

General methods. Reactions were carried out under nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: tetrahydrofuran (THF) and toluene were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). The reactions were monitored by thin layer chromatography (TLC) using 0.25 mm pre-coated silica-gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate ($KMnO_4$) stain. Flash column chromatography was performed with the indicated solvents on silica gel 60 (particle size: 0.040–0.063 mm). ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a 300 MHz spectrometer (Bruker 300 MHz DPX). Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents ($CHCl_3$: δ 7.26 ppm for proton and δ 77.0 ppm for carbon). Coupling constants (*J*) are reported in Hertz (Hz). The notation s, d, dd, ddd, t, q, m, and bs in NMR signals stands for singlet, doublet, doublet of doublets, doublet of dd, triplet, quartet, multiplet and broad singlet, respectively. DEPT experiments were performed to assign CH, CH_2 and CH_3. A QTOF mass analyzer system has been used for HRMS measurements. Melting points were measured on a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured on a Jasco *P*1020 polarimeter at 25 °C.

I. General procedure for the propargylation reaction to sulfinamides 3. A 1 M solution of propargylmagnesium bromide in THF was prepared by stirring propargyl bromide (14 mmol) and activated Mg (28 mmol) in anhydrous THF (1 M, 14 mL) at 50 °C for 2 h. This freshly prepared solution was then added (1.5 equiv., 13.5 mmol) to a solution of corresponding imine (9.0 mmol) in CH_2Cl_2 (0.1 M, 90 mL) at –48 °C. After stirring during 18 h at this temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with brine (3 × 10 mL), dried with anhydrous $MgSO_4$, and the solvent evaporated. The residue was purified by flash column chromatography to yield the corresponding sulfinamide **3**. Sulfinamides **3a–h** were prepared according to previously published procedures.[19]

II. General procedure for oxidation reaction to sulfonamides. To a solution of corresponding sulfinamide **3** (12.3 mmol) in CH_2Cl_2 (120 mL) at 0 °C, *m*-CPBA (14.8 mmol) was added and the mixture was stirred at room temperature for 2 h. After this time, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine (3 × 10 mL), dried with anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography affording sulfonamides **4**. Sulfonamides **4a–h**,[19a] were prepared according to previously published procedures.[19]

III. General procedure for Sonogashira reaction. CuI (8 mmol-%) and $Pd(PPh_3)_2Cl_2$ (4 mmol-%) were added to iPr_2NH (0.06 M) and the mixture was stirred at room temperature for 10 min. The solution was then heated to 50 °C, and a solution of sulfonamide **4** (0.3 mmol) in iPr_2NH (0.06 M) was added slowly for 1 h (slow addition pump), and the resulting mixture was stirred at 50 °C for a further 2 h. The reaction was quenched with a saturated solution of aqueous NH_4Cl and extracted with EtOAc. The combined organic phases were dried with anhydrous Na_2SO_4, concentrated under reduced pressure and the crude mixture was purified by column chromatography (*n*-hexane/EtOAc). Compound **4n** was prepared according to previously published procedures.[19a]

(*S*)-*N*-(4-(4-Methoxyphenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4i). According to general procedure III, **4i** was obtained as a white solid (68 mg, 49 % yield). M.p. 102–104 °C; $[\alpha]_D^{25}$ = –39.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.18 (m, 7H), 6.75–6.70 (m, 2H), 4.80–4.68 (m, 2H), 3.71 (s, 3H), 3.00–2.77 (m, 2H), 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.5, 141.2, 133.1, 128.6, 127.8, 126.4, 115.2, 113.9, 84.2, 83.2, 60.1, 56.9, 55.3, 30.2, 24.2. HRMS (ESI): *m/z* calcd. for $C_{21}H_{29}N_2O_3S$ [M + NH_4^+]: 389.1893, found 389.1891.

(*S*)-*N*-(4-(4-Chlorophenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4j). According to general procedure III, **4j** was obtained as a white solid 68 mg, (78 % yield). M.p. 138–140 °C; $[\alpha]_D^{25}$ = –37.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.15 (m, 9H), 4.77–4.64 (m, 2H), 3.01–2.91 (m, 2H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.8, 134.1, 132.9, 128.7, 128.6, 127.9, 126.3, 121.5, 85.9, 83.2, 60.1, 56.8, 30.3, 24.2. HRMS (ESI): *m/z* calcd. for $C_{20}H_{26}ClN_2O_2S$ [M + NH_4^+]: 393.1398, found 393.1396.

(*S*)-*N*-(1-Cyclopropyl-4-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4k). According to general procedure III, **4k** was

obtained as a yellowish oil 49 mg, (62 % yield). $[\alpha]_D^{25}$ = +33.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 2H), 7.34–7.27 (m, 3H), 3.06–2.94 (m, 1H), 2.89 (dd, *J* = 16.7, 5.2 Hz, 1H), 2.77 (dd, *J* = 16.7, 4.3 Hz, 1H), 1.42 (s, 1H), 1.27–1.13 (m, 1H), 0.70–0.55 (m, 3H), 0.44–0.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 131.8, 128.4, 128.2, 123.4, 85.7, 83.7, 60.0, 57.9, 27.6, 24.4, 17.0, 4.6, 4.5. HRMS (ESI): *m/z* calcd. for $C_{20}H_{26}ClN_2O_2S$ [M + NH_4^+]: 323.1787, found 323.1789.

(*S*)-*N*-(4-(4-Chlorophenyl)-1-(thiophen-3-yl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (4l). According to general procedure III, **4l** was obtained as a white solid (61 mg, 44 % yield). M.p. 153–154 °C; $[\alpha]_D^{25}$ = –32.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.16 (m, 6H), 7.06 (dd, *J* = 5.0, 1.4 Hz, 1H), 4.84–4.77 (m, 1H), 4.59 (d, *J* = 9.6 Hz, 1H), 3.04–2.85 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.0, 134.2, 132.9, 128.6, 126.6, 126.0, 121.8, 121.5, 86.0, 83.2, 60.2, 53.1, 29.4, 24.2. HRMS (ESI): *m/z* calcd. for $C_{18}H_{24}ClN_2O_2S_2$ [M + NH_4^+]: 399.0962, found 399.0958.

(*S*)-2-Methyl-*N*-(4-phenyl-1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfonamide (4m). According to general procedure III, **4m** was obtained as a white solid (63 mg, 70 % yield). M.p. 133–135 °C; $[\alpha]_D^{25}$ = –47.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.29–7.27 (m, 5H), 7.20–7.17 (m, 2H), 4.97–4.94 (m, 1H), 4.81–4.74 (m, 1H), 3.08–2.87 (m, 2H), 2.36 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.1, 137.5, 1331.7, 129.3, 128.3, 128.1, 126.3, 123.2, 85.1, 84.1, 60.1, 56.8, 30.3, 24.2, 21.2. HRMS (ESI): *m/z* calcd. for $C_{21}H_{29}N_2O_2S$ [M + NH_4^+]: 373.1944, found 373.1951.

IV. General procedure for allylation reaction. To a suspension of NaH (60 %, 6.8 mmol) in dry DMF (40 mL), the corresponding sulfonamide (4.5 mmol) was added dropwise at 0 °C. After stirring at this temperature for 20 min, allyl bromide (9.1 mmol) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was quenched with NH_4Cl aq. and extracted with diethyl ether. The organic layer was then dried with anhydrous Na_2SO_4, concentrated under vacuum and the crude reaction mixture was then purified by flash column chromatography to yield **5**. Compounds **5g–h**[19a] and **5n**[19b] were prepared according to previously published procedures.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl) but-3-yn-1-yl) propane-2-sulfonamide (5a). According to general procedure IV, **5a** was obtained as a white solid (63 mg, 94 % yield). M.p. 93–94 °C. $[\alpha]_D^{25}$ = –28.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.92–5.73 (m, 1H), 5.15 (dd, *J* = 10.1, 5.3 Hz, 1H), 5.07 (bs, 1H), 5.03 (ddd, *J* = 7.5, 2.7, 1.3 Hz, 1H), 4.02–3.82 (m, 1H), 3.52 (dd, *J* = 16.5, 8.0 Hz, 1H), 3.16 (ddd, *J* = 16.8, 10.2, 2.6 Hz, 1H), 2.97 (ddd, *J* = 16.8, 5.3, 2.7 Hz, 1H), 2.36 (s, 3H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.1, 137.2, 134.2, 129.3, 128.9, 117.4, 81.2, 71.4, 62.2, 61.4, 49.0, 25.2, 24.3, 21.3. HRMS (ESI): *m/z* calcd. for $C_{18}H_{29}N_2O_2S$ [M + NH_4^+]: 337.1943, found 337.1944.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-phenylbut-3-yn-1-yl) propane-2-sulfonamide (5b). According to general procedure IV, **5b** was obtained as a white solid (102 g, 91 % yield). M.p. 134–136 °C. $[\alpha]_D^{25}$ = –43.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.28 (m, 5H), 5.97–5.70 (m, 1H), 5.18 (dd, *J* = 10.0, 5.4 Hz, 1H), 5.06 (bs, 1H), 5.02 (dd, *J* = 8.1, 1.4 Hz, 1H), 3.95 (ddd, *J* = 16.5, 3.1, 1.9 Hz, 1H), 3.54 (dd, *J* = 16.5, 7.9 Hz, 1H), 3.18 (ddd, *J* = 16.8, 10.0, 2.6 Hz, 1H), 2.99 (ddd, *J* = 16.8, 5.4, 2.7 Hz, 1H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.3, 137.0, 128.9, 128.6, 128.3, 117.5, 81.0, 71.6, 62.2, 61.5, 49.1, 25.2, 24.1. HRMS (ESI): *m/z* calcd. for $C_{17}H_{27}N_2O_2S$ [M + NH_4^+]: 306.1549, found 306.1522.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl) but-3-yn-1-yl) propane-2-sulfonamide (5c). According to general procedure IV, **5c** was obtained as a colorless oil (67 mg, 35 % yield). $[\alpha]_D^{25}$ = –20.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.89–5.70 (m, 1H), 5.13 (dd, *J* = 10.2, 5.3 Hz, 1H), 5.06 (bs, 1H), 5.02 (dd, *J* = 7.0, 1.3 Hz, 1H), 4.02–3.86 (m, 1H), 3.82 (s, 3H), 3.51 (dd, *J* = 16.5, 8.0 Hz, 1H), 3.14 (ddd, *J* = 16.8, 10.3, 2.6 Hz, 1H), 2.96 (ddd, *J* = 16.8, 5.3, 2.7 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.4, 137.2, 130.2, 129.2, 117.3, 113.9, 81.1, 71.4, 62.2, 61.0, 55.4, 48.9, 25.2, 24.3. HRMS (ESI): *m/z* calcd. for $C_{18}H_{29}N_2O_3S$ [M + NH_4^+]: 353.1891, found 353.1893.

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(tiophen-2-yl)but-3-yn-1-yl)propane-2-sulfonamide (5d). According to general procedure IV, **5d** was obtained as a white solid (122 mg, 74 % yield). M.p. 118–120 °C. $[\alpha]_D^{25}$ = –22.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.31 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.16–7.14 (dt, *J* = 3.6, 0.9 Hz, 1H), 7.00–6.98 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.93–5.80 (m, 1H), 5.33–5.27 (dd, *J* = 9.3, 6.0 Hz, 1H), 5.08–5.05 (dd, *J* = 6.0, 1.5 Hz, 1H), 5.02 (s, 1H), 3.99–3.92 (dd, *J* = 16.5, 5.1 Hz, 1H), 3.63–3.55 (dd, *J* = 16.5, 7.8 Hz, 1H), 3.18–2.97 (m, 2H), 2.05–2.03 (t, *J* = 2.7 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.2, 137.0, 127.5, 126.6, 126.0, 117.4, 80.6, 71.7, 62.3, 57.9, 48.7, 26.0, 24.9. HRMS (ESI): *m/z* calcd. for $C_{15}H_{25}N_2O_2S_2$: 329.1350 [M + NH_4^+], found 329.1352.

(*R*)-*N*-Allyl-*N*-(dec-1-yn-4-yl)-2-methylpropane-2-sulfonamide (5e). According to general procedure IV, **5e** was obtained as a colorless oil (110 mg, 50 % yield). $[\alpha]_D^{25}$ = +4.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 6.09–5.87 (m, 1H), 5.18 (ddd, *J* = 17.2, 2.7, 1.4 Hz, 1H), 5.09 (ddd, *J* = 10.1, 1.2 Hz, 1H), 3.93 (t, *J* = 6.9 Hz, 2H), 3.84–3.78 (m, 1H), 2.60–2.49 (m, 2H), 2.06 (t, *J* = 2.7 Hz, 1H), 1.82–1.63 (m, 2H), 1.41 (s, 9H), 1.28 (dd, *J* = 9.7, 6.5 Hz, 8H), 0.87 (t, *J* = 5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.0, 117.1, 81. 8, 71.2, 62.2, 59.2, 48.6, 31.8, 29.3, 27.2, 25.0, 22.7, 14.2. HRMS (ESI): *m/z* calcd. for $C_{17}H_{36}N_2O_2S$ [M + NH_4^+]: 331.2414, found 331.2414.

(*S*)-*N*-Allyl-*N*-(1-cyclopropylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5f). According to general procedure IV, **5f** was obtained as a white solid (97 mg, 84 % yield). M.p. 62–63 °C. $[\alpha]_D^{25}$ = –2.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 6.11–5.95 (m, 1H), 5.21 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.11 (dd, *J* = 10.1, 1.4 Hz, 1H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.16 (dt, *J* = 9.5, 7.1 Hz, 1H), 2.72 (dt, *J* = 5.3, 2.3 Hz, 2H), 2.05 (t, *J* = 2.7 Hz, 1H), 1.40 (s, 9H), 1.22–1.01 (m, 1H), 0.79–0.58 (m, 2H), 0.59–0.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137. 9, 117.0, 81.7, 71.1, 63. 6, 62.2, 49.5, 25.1, 15.9, 7.2, 4.2. HRMS (ESI): *m/z* calcd. for $C_{14}H_{27}N_2O_2S$ [M + NH_4^+]: 287.1776, found 287.1788.

(*S*)-*N*-Allyl-*N*-(4-(4-methoxyphenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5i). According to general procedure IV, **5i** was obtained as a colorless oil (43 mg, 53 % yield). $[\alpha]_D^{25}$ = –36.6 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56–7.21 (m, 5H), 7.21–7.18 (m, 2H), 6.78–6.75 (m, 2H), 5.92–5.82 (m, 1H), 5.25 (dd, *J* = 9.0, 6.4 Hz, 1H), 5.10–5.07 (m, 1H), 5.04–5.03 (m, 1H), 4.03 (dd, *J* = 16.7, 5.2 Hz, 1H), 3.65 (dd, *J* = 16.5, 7.5 Hz, 1H), 3.33 (dd, *J* = 16.9, 9.1 Hz, 1H), 3.19 (dd, *J* = 16.9, 6.3 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.3, 137.9, 137.0, 132.9, 128.8, 128.4, 128.0, 117.2, 115.5, 113.8, 85.1, 83.4, 62.1, 61.6, 55.3, 49.1, 25.1, 25.0. HRMS (ESI): *m/z* calcd. for $C_{24}H_{33}N_2O_3S$ [M + H^+]: 412.1941, found 412.1931.

(*S*)-*N*-Allyl-*N*-(4-(4-chlorophenyl)-1-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5j). According to general procedure IV, **5j** was obtained as a colorless oil (44 mg, 48 % yield). $[\alpha]_D^{25}$ = –38.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.30 (m, 5H), 7.22–7.14 (m, 4H), 5.95–5.81 (m, 1H), 5.26–5.10 (m, 1H), 5.18 (dd, *J* = 9.3, 6.2 Hz, 1H), 5.10–5.04 (m, 2H), 4.05–3.98 (m, 1H), 3.62 (dd, *J* = 16.5, 7.8 Hz, 1H), 3.35 (dd, *J* = 16.9, 9.4 Hz, 1H), 3.21 (dd, *J* = 16.9, 6.1 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.6, 137.0, 133.8,

132.7, 128.8, 128.5, 128.1, 121.9, 117.3, 87.8, 82.5, 62.1, 61.6, 49.1, 25.1, 25.0. HRMS (ESI): *m/z* calcd. for $C_{23}H_{30}ClN_2O_2S$ [M + NH_4^+]: 433.1711, found 433.1706.

(*S*)-*N*-Allyl-*N*-(1-cyclopropyl-4-phenylbut-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5k). According to general procedure IV, **5i** was obtained as a colourless oil (68 mg, 93 % yield). $[\alpha]_D^{25}$ = –9.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2H), 7.33–7.27 (m, 3H), 6.16–6.01 (m, 1H), 5.23 (dq, *J* = 17.3, 1.4 Hz, 1H), 5.12 (dq, *J* = 10.1, 1.3 Hz, 1H), 4.12 (t, *J* = 6.5 Hz, 2H), 3.25 (dt, *J* = 9.4, 7.2 Hz, 1H), 2.94 (dd, *J* = 7.2, 1.9 Hz, 2H), 1.41 (s, 9H), 1.24–1.10 (m, 1H), 0.81–0.66 (m, 2H), 0.59–0.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.0, 131.5, 128.4, 128.0, 123.64 116.9, 87.4, 83.0, 63.8, 62.1, 49.5, 25.0, 16.2, 7.1, 4.4. HRMS (ESI): *m/z* calcd. for $C_{24}H_{33}N_2O_3S$ [M + H^+]: 363.2110, found 363.2101.

(*S*)-*N*-Allyl-*N*-(4-(4-chlorophenyl)-1-(thiophen-3-yl)but-3-yn-1-yl)-2-methylpropane-2-sulfonamide (5l). According to general procedure IV, **5l** was obtained as a colorless oil (61 mg, 70 % yield). $[\alpha]_D^{25}$ = –30.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.20–7.16 (m, 5H), 5.83–5.72 (m, 1H), 5.18 (dd, *J* = 8.4, 6.8 Hz, 1H), 5.01–4.98 (m, 1H), 4.95 (s, 1H), 3.94 (dd, *J* = 16.4, 5.5 Hz, 1H), 3.56 (dd, *J* = 16.4, 7.4 Hz, 1H), 3.32 (dd, *J* = 16.9, 8.7 Hz, 1H), 3.2 (dd, *J* = 16.9, 6.5 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.5, 136.9, 134.0, 132.8, 128.6, 128.1, 125.8, 124.2, 121.8, 117.2, 87.7, 82.5, 62.1, 57.8, 49.0, 25.9, 25.0. HRMS (ESI): *m/z* calcd. for $C_{21}H_{28}ClN_2O_2S_2$ [M + NH_4^+]: 439.1275, found 439.1273.

(*S*)-*N*-Allyl-2-methyl-*N*-(4-phenyl-1-(*p*-tolyl)but-3-yn-1-yl)propane-2-sulfonamide (5m). According to general procedure IV, **5m** was obtained as a colorless oil (147 mg, 99 % yield). $[\alpha]_D^{25}$ = –21.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.30–7.19 (m, 7H), 5.98–5.84 (m, 1H), 5.25 (dd, *J* = 9.4, 6.4 Hz, 1H), 5.11 (dd, *J* = 6.4, 1.2 Hz, 1H), 5.06 (s, 1H), 4.03 (dd, *J* = 16.5, 5.1 Hz, 1H), 3.64 (dd, *J* = 16.5, 7.7 Hz, 1H), 3.35 (dd, *J* = 16.9, 9.2 Hz, 1H), 3.22 (dd, *J* = 16.9, 6.2 Hz, 1H), 2.37 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.8, 137.2, 131.5, 129.1, 128.7, 128.2, 127.8, 123.5, 117.2, 86.9, 83.4, 62.1, 61.4, 48.9, 25.1, 22.7, 21.1. HRMS (ESI): *m/z* calcd. for $C_{21}H_{28}ClN_2O_2S_2$ [M + NH_4^+]: 413.2259, found 413.2257.

V. General procedure for the methylation reaction. The corresponding enyne (0.17 mmol) was dissolved in THF (0.4 mL) at –78 °C under an argon atmosphere. HMDSLi (1 M in toluene, 0.34 mmol) was then added dropwise to the reaction mixture. After 1 h, MeI (0.84 mmol) was added to the reaction mixture and the temperature was increased to –40 °C. After 12 h the solvent was then removed and the reaction mixture was purified by flash column chromatography in *n*-hexane/EtOAc (10:1).

(*S*)-*N*-Allyl-2-methyl-*N*-(1-(*p*-tolyl)pent-3-yn-1-yl)propane-2-sulfonamide (5o). According to general procedure V, **5o** was obtained as a colorless oil (194 mg, 93 % yield). $[\alpha]_D^{25}$ = –24.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 5.87–5.73 (m, 1H), 5.09 (dd, *J* = 9.3, 6.2 Hz, 1H), 5.02 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.98 (s, 1H), 3.93 (dd, *J* = 16.5, 5.3 Hz, 1H), 3.55 (dd, *J* = 16.5, 7.5 Hz, 1H), 3.09–2.84 (m, 2H), 2.34 (s, 3H), 1.67 (t, *J* = 2.5 Hz, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.5, 137.2, 134.9, 129.0, 128.6, 116.9, 78.7, 76.0, 62.0, 61.4, 48.7, 25.0, 24.3, 21.1, 3.6. HRMS (ESI): *m/z* calcd. for $C_{19}H_{31}N_2O_2S$ [M + NH_4^+]: 351.2101, found 351.2101.

((*S*)-*N*-Allyl-2-methyl-*N*-(1,1,1-trifluorohex-4-yn-2-yl)propane-2-sulfonamide (5p). According to general procedure V, **5p** was obtained as a white solid (87 mg, 83 % yield). M.p. 42–44 °C; $[\alpha]_D^{25}$ = –26.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.05–5.91 (m, 1H), 5.22–5.10 (m, 2H), 4.52–4.40 (m, 1H), 3.99 (qd, *J* = 16.7, 6.5 Hz, 1H), 2.78–2.66 (m, 2H), 1.77 (t, *J* = 2.6 Hz, 3H), 1.44 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = –68.64 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.7, 124.7 (q, $^1J_{CF}$ = 285.8 Hz, C), 117.8, 80.1, 73.0, 63.0, 59.6 (q, $^2J_{CF}$ = 29.7 Hz, CH), 49.4, 24.7, 19.0, 3.5. HRMS (ESI): *m/z* calcd. for $C_{13}H_{24}F_3N_2O_2S$ [M + NH_4^+]: 329.1505, found 329.1504.

VI. General procedure for the RCEYM reaction to 6. The corresponding enyne (0.2 mmol) and 1,7-octadiene (0.8 mmol) were dissolved in CH_2Cl_2 (5 mL) at room temperature under argon atmosphere. Hoveyda Grubbs II generation catalyst (3 mol-%, 0.003 mmol) was dissolved in CH_2Cl_2 and slowly added to the reaction mixture. Finally, after removal of the solvent, the reaction mixture was purified by flash column chromatography in *n*-hexane/Et_2O (5:1).

(*S*)-1-(*tert*-Butylsulfonyl)-4-vinyl-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6a). According to general procedure VI, **6a** was obtained as a white solid (96 mg, 87 % yield). M.p. 72–73 °C; $[\alpha]_D^{25}$ = +67.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.44 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.69 (s, 1H), 5.32–5.20 (m, 2H), 5.11 (d, *J* = 10.7 Hz, 1H), 4.03 (dd, *J* = 19.3, 4.3 Hz, 1H), 3.50 (d, *J* = 19.2 Hz, 1H), 2.84 (bs, 2H), 2.31 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.3, 137.4, 136.1, 133.9, 129.3, 127.6, 125.2, 112.3, 61.8, 54.1, 43.0, 27.2, 24.8, 21.1. HRMS (ESI): *m/z* calcd. for $C_{18}H_{29}N_2O_2S$ [M + NH_4^+]: 337.1937, found 337.1944.

(*S*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-vinyl-1,2,3,6-tetrahydropyridine (6b). According to general procedure VI, **6b** was obtained as a colorless oil (89 mg, 89 % yield). $[\alpha]_D^{25}$ = +36.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.24 (m, 5H), 6.45 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.69 (bs, 1H), 5.36–5.22 (m, 2H), 5.12 (d, *J* = 10.7 Hz, 1H), 4.04 (dd, *J* = 19.5, 4.2 Hz, 1H), 3.50 (d, *J* = 19.3 Hz, 1H), 2.86 (bs, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.1, 138.2, 133.8, 128.6, 127.7, 127.6, 125.2, 112.4, 61.8, 54.3, 43.0, 27.2, 24.8. HRMS (ESI): *m/z* calcd. for $C_{17}H_{27}N_2O_2S$ [M + NH_4^+]: 323.1785, found 323.1788.

(*S*)-1-(*tert*-Butylsulfonyl)-2-(4-methoxyphenyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6c). According to general procedure VI, **6c** as obtained as a colorless oil (79 mg, 83 % yield). $[\alpha]_D^{25}$ = +55.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.45 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.70 (bs, 1H), 5.37–5.18 (m, 2H), 5.12 (d, *J* = 10.8 Hz, 1H), 4.01 (dd, *J* = 19.1, 4.5 Hz, 1H), 3.78 (s, 3H), 3.48 (dd, *J* = 19.2, 1.3 Hz, 1H), 2.82 (bs, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.0, 138.2, 133.9, 131.2, 129.0, 125.2, 113.8, 112.4, 61.8, 55.4, 53.8, 42.9, 27.4, 24.8. HRMS (ESI): *m/z* calcd. for $C_{18}H_{29}N_2O_3S$ [M + NH_4^+]: 353.1880, found 353.1893.

(*S*)-1-(*tert*-Butylsulfonyl)-2-(thiophen-3-yl)-4-vinyl-1,2,3,6-tetrahydropyridine (6d). According to general procedure VI, **6d** was obtained as a colorless oil (75 mg, 82 % yield). $[\alpha]_D^{25}$ = +84.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.13 (m, 3H), 6.44 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.69 (s, 1H), 5.29–5.23 (m, 2H), 5.11 (d, *J* = 10.8 Hz, 1H), 3.99 (d, *J* = 19.1 Hz, 1H), 3.53 (d, *J* = 19.1 Hz, 1H), 2.81 (s, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.4, 138.1, 133.4, 127.9, 125.6, 124.9, 122.8, 112.2, 61.6, 51.1, 43.1, 28.3, 24.5. HRMS (ESI): *m/z* calcd. for $C_{15}H_{22}NO_2S_2$ [M + H^+]: 312.1086, found 312.1083.

(*R*)-1-(*tert*-Butylsulfonyl)-2-hexyl-4-vinyl-1,2,3,6-tetrahydropyridine (6e). According to general procedure VI, **6e** was obtained as a colorless oil (66 mg, 65 % yield). $[\alpha]_D^{25}$ = –17.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.35 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.65 (bs, 1H), 5.11 (d, *J* = 17.5 Hz, 1H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.08–3.87 (m, 2H), 3.73 (d, *J* = 19.0 Hz, 1H), 2.49 (dd, *J* = 16.9, 2.9 Hz, 1H), 2.18 (d, *J* = 16.9 Hz, 1H), 1.60–1.40 (m, 3H), 1.31 (s, 9H), 1.25–1.23 (m, 7H), 0.83 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.6, 132.9, 123.9, 111.7, 61.2, 52.3, 42.4, 31.9, 31.7, 29.2, 27.7, 26.7, 24.4, 22.6,

14.1. HRMS (ESI): *m/z* calcd. for $C_{17}H_{35}N_2O_2S$ [M + NH_4^+]: 331.2419, found 331.2412.

(*S*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-vinyl-1,2,3,6-tetrahydropyridine (6f). According to general procedure VI, **6f** was obtained as a colorless oil (72 mg, 72 % yield). $[\alpha]_D^{25}$ = –13.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.42 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.75 (bs, *J* = 2.4 Hz, 1H), 5.17 (d, *J* = 17.5 Hz, 1H), 5.05 (d, *J* = 10.7 Hz, 1H), 4.06 (bs, 2H), 3.28 (dd, *J* = 9.0, 6.2 Hz, 1H), 2.58 (ddd, *J* = 16.8, 6.1, 3.0 Hz, 1H), 2.37 (d, *J* = 16.8 Hz, 1H), 1.33 (s, 9H), 1.16–1.01 (m, 1H), 0.77–0.63 (m, 1H), 0.58–0.49 (m, 2H), 0.33–0.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.7, 133.6, 124.2, 112.1, 61.4, 57.4, 43.4, 29.2, 24.6, 13.7, 5.0, 4.1. HRMS (ESI): *m/z* calcd. for $C_{14}H_{27}N_2O_2S$ [M + NH_4^+]: 287.1795, found 287.1788.

***(S)*-1-(*tert*-Butylsulfonyl)-2-(trifluoromethyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6g).** According to general procedure VI, **6g** was obtained as a colorless oil (61 mg, 86 % yield). $[\alpha]_D^{25}$ = –1.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.38 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.75 (s, 1H), 5.13 (dd, *J* = 23.4, 14.2 Hz, 2H), 4.67–4.57 (m, 1H), 4.27–4.21 (m, 1H), 3.91–3.84 (m, 1H), 2.71–2.50 (m, 2H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = –72.08 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.5, 131.3, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 123.5, 112.5, 62.4, 52.7 (q, *J* = 31.1 Hz, CH), 43.7, 24.4, 22.6. HRMS (ESI): *m/z* calcd. for $C_{12}H_{22}F_3N_2O_2S$ [M + NH_4^+]: 315.1349, found 315.1343.

(*S*)-1-(*tert*-Butylsulfonyl)-2-(perfluoropropyl)-4-vinyl-1,2,3,6-tetrahydropyridine (6h). According to general procedure VI, **6h** was obtained as a colorless oil (79 mg, 92 % yield). $[\alpha]_D^{25}$ = +14.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.36 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.74 (s, 1H), 5.10 (dd, *J* = 22.0, 14.2 Hz, 2H), 4.80 (d, *J* = 22.8 Hz, 1H), 4.20 (d, *J* = 18.5 Hz, 1H), 3.88 (d, *J* = 18.5 Hz, 1H), 2.75–2.51 (m, 2H), 1.36 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = –80.56 (t, *J* = 10.7 Hz, 3F), –114.37 to –115.52 (m, 1F), –119.15 to –120.15 (m, 1F), –124.81 to –127.66 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.3, 131.7, 123.3, 120.1–104.9 (C_3F_7), 112.4, 62.4, 51.1 (dd, $^2J_{CF}$ = 23.2, 18.7 Hz, CH), 44.1, 24.3, 23.6. HRMS (ESI): *m/z* calcd. for $C_{14}H_{22}F_7N_2O_2S$ [M + NH_4^+]: 415.1285, found 415.1291.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-methoxyphenyl)vinyl)-2-phenyl-1,2,3,6-tetrahydropyridine (6i). According to general procedure VI, **6i** was obtained as a colorless oil (41 mg, 53 % yield). $[\alpha]_D^{25}$ = +22.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.39 (m, 2H), 7.30–7.19 (m, 3H), 7.10–7.07 (m, 2H), 6.80–6.77 (m, 2H), 5.52–5.50 (m, 1H), 5.23–5.21 (m, 2H), 5.07 (s, 1H), 3.97 (d, *J* = 18.5 Hz, 1H), 3.74 (s, 3H), 3.46 (d, *J* = 18.5 Hz, 1H), 3.01–2.80 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 149.4, 139.2, 135.1, 133.2, 129.8, 128.5, 127.5, 124.5, 113.5, 112.3, 61.7, 55.3, 54.6, 43.2, 29.8, 24.7. HRMS (ESI): *m/z* calcd. for $C_{24}H_{33}N_2O_3S$ [M + NH_4^+]: 429.2206, found 429.2208.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-chlorophenyl)vinyl)-2-phenyl-1,2,3,6-tetrahydropyridine (6j). According to general procedure VI, **6j** was obtained as a colorless oil (79 mg, 48 % yield). $[\alpha]_D^{25}$ = +33.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.06 (m, 9H), 5.46–5.54 (m, 1H), 5.30–5.09 (m, 3H), 3.97 (d, *J* = 18.7 Hz, 1H), 3.45 (d, *J* = 18.7 Hz, 1H), 3.00–2.80 (m, 2H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.7, 139.2, 139.1, 134.6, 133.5, 130.1, 128.6, 128.3, 127.6, 127.4, 125.0, 113.5, 61.8, 54.6, 43.2, 29.6, 24.7. HRMS (ESI): *m/z* calcd. for $C_{23}H_{30}ClN_2O_2S$ [M + NH_4^+]: 433.1711, found 433.1708.

(*S*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-(1-phenylvinyl)-1,2,3,6-tetrahydropyridine (6k). According to general procedure VI, **6k** was obtained as a colorless oil (38 mg, 55 % yield). $[\alpha]_D^{25}$ = +2.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.20 (m, 5H), 5.64 (dd, *J* = 5.7, 3.1 Hz, 1H), 5.28 (s, 1H), 5.13 (s, 1H), 4.04 (s, 2H), 3.30 (dd, *J* = 8.7, 6.2 Hz, 1H), 2.83–2.66 (m, 1H), 2.44 (d, *J* = 16.9 Hz, 1H), 1.35 (s, 9H), 1.24–1.12 (m, 1H), 0.77–0.65 (m, 1H), 0.63–0.53 (m, 2H), 0.37–0.26 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.2, 141.1, 134.9, 128.8, 128.2, 127.6, 123.9, 113.0, 61.4, 57.7, 43.6, 31.6, 24.7, 13.7, 5.0, 4.2. HRMS (ESI): *m/z* calcd. for $C_{20}H_{31}N_2O_2S$ [M + NH_4^+]: 363.2111, found 363.2101.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-(4-chlorophenyl)vinyl)-2-(thiophen-3-yl)-1,2,3,6-tetrahydropyridine (6l). According to general procedure VI, **6l** was obtained as a colorless oil (70 mg, 70 % yield). $[\alpha]_D^{25}$ = +31.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.27 (m, 3H), 7.20–7.14 (m, 4H), 5.54–5.51 (m, 1H), 5.35 (s, 1H), 5.29 (d, *J* = 6.0 Hz, 1H), 5.16 (s, 1H), 4.00 (d, *J* = 18.6 Hz, 1H), 3.55 (d, *J* = 18.6 Hz, 1H), 3.06–2.80 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.7, 140.6, 139.2, 134.3, 130.1, 128.4, 127.7, 125.8, 124.9, 122.7, 113.5, 61.6, 51.6, 43.3, 30.7, 24.5. HRMS (ESI): *m/z* calcd. for $C_{21}H_{28}ClN_2O_2S_2$ [M + NH_4^+]: 439.1275, found 439.1278.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-phenylvinyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6m). According to general procedure VI, **6m** were obtained as a colorless oil (37 mg, 42 % yield). $[\alpha]_D^{25}$ = +25.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 7.24–7.15 (m, 4H), 5.56–5.55 (m, 1H), 5.37 (s, 1H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.19 (s, 1H), 4.03 (d, *J* = 19.0 Hz, 1H), 3.53 (d, *J* = 19.0 Hz, 1H), 3.08–2.88 (m, 2H), 2.35 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.9, 140.9, 137.2, 136.1, 134.9, 129.2, 128.8, 128.1, 127.5, 127.4, 124.8, 113.0, 61.7, 54.4, 43.1, 29.6, 24.7, 21.1. HRMS (ESI): *m/z* calcd. for $C_{24}H_{33}N_2O_2S$ [M + NH_4^+]: 391.1650, found 391.1644.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(1-phenylvinyl)-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (6n). According to general procedure VI, **6n** was obtained as a colorless oil (44 mg, 47 % yield). $[\alpha]_D^{25}$ = +33.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 5.58 (s, 1H), 5.14 (d, *J* = 29.0 Hz, 2H), 4.60–4.54 (m, 1H), 4.17–4.11 (m, 1H), 3.82–3.76 (m, 1H), 2.79–2.49 (m, 2H), 1.34 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.77 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.3, 140.4, 132.8, 128.6, 128.2, 127.7, 125.4 (q, $^1J_{CF}$ = 285.2 Hz, C), 123.4, 113.3, 62.4, 52.9 (q, $^2J_{CF}$ = 31.1 Hz, CH), 43.9, 25.0, 24.5. HRMS (ESI): *m/z* calcd. for $C_{18}H_{26}F_3N_2O_2S$ [M + NH_4^+]: 391.1650, found 391.1644.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(prop-1-en-2-yl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (6o). According to general procedure VI, **6o** was obtained as a colorless oil (150 mg, 60 % yield) $[\alpha]_D^{25}$ = +33.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 5.77 (s, 1H), 5.24–5.22 (m, 1H), 5.15 (s, 1H), 5.03 (s, 1H), 4.06 (d, *J* = 19.4 Hz, 1H), 3.54 (d, *J* = 19.4 Hz, 1H), 2.32 (s, 3H), 1.95 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.1, 137.1, 136.2, 134.5, 129.1, 127.5, 120.8, 111.6, 61.6, 54.2, 43.0, 28.5, 24.7, 21.0, 20.5. HRMS (ESI): *m/z* calcd. for $C_{19}H_{31}N_2O_2S$ [M + NH_4^+]: 351.2101, found 351.2093.

(*S*)-1-(*tert*-Butylsulfonyl)-4-(prop-1-en-2-yl)-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (6p). According to general procedure VI, **6p** was obtained as a colorless oil (73 mg, 65 % yield). $[\alpha]_D^{25}$ = +12.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (s, 1H), 5.00–4.99 (m, 2H), 4.62–4.57 (m, 1H), 4.26 (d, *J* = 18.6 Hz, 1H), 3.89 (d, *J* = 18.6 Hz, 1H), 2.80–2.56 (m, 2H), 1.91 (s, 3H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.99 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.5, 132.1, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 119.5, 111.8, 62.3 (q, $^2J_{CF}$ = 30.6 Hz, CH), 43.9, 24.4, 23.9, 20.2. HRMS (ESI): *m/z* calcd. for $C_{13}H_{24}F_3N_2O_2S$ [M + NH_4^+]: 329.1505, found 329.1511.

VII. General procedure for the CEYM/RCM reaction to 7. The enyne (0.2 mmol) and the corresponding olefin (0.8 mmol) were dissolved in CH_2Cl_2 (5 mL) at room temperature under argon atmosphere. Hoveyda Grubbs II generation catalyst (3 mol-%, 0.003 mmol) was dissolved in CH_2Cl_2 and slowly added to the reaction mixture.

Finally, after removal of the solvent, the reaction mixture was purified by flash column chromatography in hexane/ether (5:1).

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-styryl-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7a). According to general procedure VII, **7a** was obtained as a colorless oil (40 mg, 65 % yield). $[\alpha]_D^{25}$ = +116.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.14 (m, 7H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 16.2 Hz, 1H), 6.54 (d, *J* = 16.2 Hz, 1H), 5.71 (bs, 1H), 5.19 (bs, 1H), 3.99 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.47 (dd, *J* = 19.4, 1.6 Hz, 1H), 2.89 (bs, 2H), 2.22 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.8, 137.6, 136.5, 134.1, 130.7, 129.7, 129.3, 128.1 (d, *J* = 13.7 Hz), 127.5, 127.0, 126.1, 62.2, 54.6, 43.6, 28.4, 25.2, 21.6, 1.6. HRMS (ESI): *m/z* calcd. for $C_{24}H_{35}N_2O_2S$ [M + NH_4^+]: 415.2250, found 415.2257.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-methylstyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7b). According to general procedure VII, **7b** was obtained as a colorless oil (32 mg, 59 % yield). $[\alpha]_D^{25}$ = +128.9. (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.1, 1.7 Hz, 4H), 7.14 (dd, *J* = 11.1, 8.0 Hz, 4H), 6.83 (d, *J* = 16.2 Hz, 1H), 6.61 (d, *J* = 16.3 Hz, 1H), 5.78 (bs, 1H), 5.29 (bs, 1H), 4.08 (dd, *J* = 19.4, 4.4 Hz, 1H), 3.56 (dd, *J* = 19.6, 2.3 Hz, 1H), 2.98 (bs, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.7, 137.4, 136.1, 134.3, 133.8, 129.6, 129.4, 129.3, 127.6, 127.0, 126.4, 125.0, 61.8, 54.2, 43.2, 28.0, 24.8, 21.4, 21.2. HRMS (ESI): *m/z* calcd. for $C_{25}H_{37}N_2O_2S$ [M + NH_4^+]: 429.2418, found 429.2414.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-chlorostyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7c). According to general procedure VII, **7c** was obtained as a white solid (22 mg, 33 % yield). M.p. 139–140 °C; $[\alpha]_D^{25}$ = +102.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m,6), 7.12 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 16.2 Hz, 1H), 6.57 (d, *J* = 16.2 Hz, 1H), 5.82 (bs, 1H), 5.29 (bs, 1H), 4.09 (dd, *J* = 19.1, 4.4 Hz, 1H), 3.56 (d, *J* = 19.5 Hz, 1H), 2.96 (bs, 2H), 2.31 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.4, 135.9, 135.6, 133.4, 133.2, 130.8, 129.2, 128.9, 127.6, 127.4, 126.2, 125.7, 61.7, 54.0, 43.1, 27.8, 24.7, 21.0. HRMS (ESI): *m/z* calcd. for $C_{24}H_{34}ClN_2O_2S$ [M + NH_4^+]: 449.1863, found 449.1868.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-fluorostyryl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7d). According to general procedure VII, **7d** was obtained as a white solid (30 mg, 47 % yield). mp 110–111 °C; $[\alpha]_D^{25}$ = +110.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 16.2 Hz, 1H), 6.59 (d, *J* = 16.2 Hz, 1H), 5.80 (bs, 1H), 5.29 (bs, 1H), 4.09 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.56 (dd, *J* = 19.5, 2.0 Hz, 1H), 2.96 (bs, 2H), 2.32 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.4 (d, *J* = 247.3 Hz), 137.4, 136.0, 133.6, 133.4 (d, *J* = 3.4 Hz), 130.1 (d, *J* = 2.2 Hz), 129.3, 128.1 (s, *J* = 7.9 Hz), 128.0, 127.6, 125.8 (d, *J* = 11.4 Hz), 115.8 (d, *J* = 21.7 Hz), 61.8, 54.1, 43.2, 28.0, 24.8, 21.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −14.14 (t, *J* = 9.0 Hz). HRMS (ESI): *m/z* calcd. for $C_{24}H_{34}FN_2O_2S$ [M + NH_4^+]: 433.2172, found 433.2163.

(*S,E*)-4-(2-Bromostyryl)-1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7e). According to general procedure VII, **7e** was obtained as a white solid (17 mg, 23 % yield). M.p. 226–228 °C; $[\alpha]_D^{25}$ = +105.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (td, *J* = 7.9, 1.3 Hz, 2H), 7.39–7.28 (m, 3H), 7.16–7.07 (m, 3H), 7.00 (d, *J* = 16.2 Hz, 1H), 6.79 (d, *J* = 16.2 Hz, 1H), 5.87 (bs, 1H), 5.30 (bs, 1H), 4.10 (dd, *J* = 19.4, 4.3 Hz, 1H), 3.58 (dd, *J* = 19.6, 1.9 Hz, 1H), 3.03 (bs, 2H), 2.32 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.5, 136.9, 136.0, 133.9, 133.3, 132.9, 129.4, 129.0, 127.7, 127.6, 126.8, 126.6, 125.8, 124.3, 61.9, 54.2, 43.3, 28.0, 24.8, 21.2. HRMS (ESI): *m/z* calcd. for $C_{24}H_{34}BrN_2O_2S$ [M + NH_4^+]: 493.1354, found 493.1362.

Ethyl (*S,E*)-5-(1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridin-4-yl)pent-4-enoate (7f). According to general procedure VII, **7f** was obtained as a white solid (23 mg, 35 % yield). M.p. 74–75 °C; $[\alpha]_D^{25}$ = +66.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.16 (d, *J* = 15.7 Hz, 1H), 5.80–5.67 (m, 1H), 5.57 (bs, 1H), 5.21 (bs, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.00 (dd, *J* = 19.0, 4.3 Hz, 1H), 3.48 (d, *J* = 19.6 Hz, 1H), 2.79 (bs, 2H), 2.53–2.39 (m, 4H), 2.31 (s, 3H), 1.41 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.1, 137.3, 136.2, 133.3, 132.7, 129.2, 127.6, 126.8, 123.4, 61.7, 60.5, 54.1, 42.9, 34.2, 28.2, 28.0, 24.8, 21.2, 14.4. HRMS (ESI): *m/z* calcd. for $C_{23}H_{39}N_2O_4S$ [M + NH_4^+]: 439.2480, found 439.2469.

(*S,E*)-4-(5-Bromopent-1-en-1-yl)-1-(*tert*-butylsulfonyl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7g). According to general procedure VII, **7g** was obtained as a colorless oil (25 mg, 36 % yield). $[\alpha]_D^{25}$ = +77.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.18 (d, *J* = 15.8 Hz, 1H), 5.76–5.62 (m, 1H), 5.58 (br, 1H), 5.22 (br, 1H), 4.01 (dd, *J* = 19.1, 4.3 Hz, 1H), 3.54–3.41 (m, 3H), 2.80 (br, 2H), 2.37–2.27 (m, 5H), 2.00 (m, 2H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.4, 136.2, 133.3, 133.0, 129.3, 127.6, 126.8, 123.3, 61.8, 54.2, 42.9, 33.3, 32.4, 31.2, 28.0, 24.8, 21.2. HRMS (ESI): *m/z* calcd. for $C_{21}H_{34}BrN_2O_4S$ [M + NH_4^+]: 457.1526, found 457.1519.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(oct-1-en-1-yl)-2-(*p*-tolyl)-1,2,3,6-tetrahydropyridine (7h). According to general procedure VII, **7h** was obtained as a colorless oil (20 mg, 32 % yield). $[\alpha]_D^{25}$ = +77.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.12 (d, *J* = 15.7 Hz, 1H), 5.83–5.66 (m, 1H), 5.55 (bs, 1H), 5.21 (t, *J* = 3.7 Hz, 1H), 3.99 (dd, *J* = 18.9, 4.3 Hz, 1H), 3.48 (d, *J* = 18.6 Hz, 1H), 2.81 (bs, 2H), 2.31 (s, 3H), 2.22–2.08 (m, 2H), 1.41 (s, *J* = 9.1 Hz, 9H), 1.40–1.24 (m, 8H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.2, 136.3, 133.6, 131.5, 129.5, 129.2, 127.6, 122.2, 61.7, 54.2, 42.9, 33.0, 31.9, 29.5, 29.1, 28.0, 24.8, 22.8, 21.2, 14.2. HRMS (ESI): *m/z* calcd. for $C_{24}H_{41}N_2O_2S$ [M + NH_4^+]: 421.2883, found 421.2883.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-(*p*-tolyl)-4-(3-(trimethylsilyl)prop-1-en-1-yl)-1,2,3,6-tetrahydropyridine (7i). According to general procedure VII, **7i** was obtained as a colorless oil (45 mg, 33 % yield); $[\alpha]_D^{25}$ = +53.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.99 (d, *J* = 15.6 Hz, 1H), 5.82–5.71 (m, 1H), 5.45 (s, 1H), 5.20 (t, *J* = 3.7 Hz, 1H), 3.99 (dd, *J* = 18.8, 4.2 Hz, 1H), 3.48 (d, *J* = 18.8 Hz, 1H), 2.79 (s, 2H), 2.31 (s, 3H), 1.60 (d, *J* = 8.1 Hz, 2H), 1.42 (s, 9H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.0, 138.1, 135.4, 132.0, 130.9, 129.4, 129.3, 127.7, 122.4, 63.5, 55.9, 44.7, 29.8, 26.5, 25.5, 22.9, 0.00. HRMS (ESI): *m/z* calcd. for $C_{22}H_{39}N_2O_2SSi$ [M + NH_4^+]: 423.2158, found 423.2163.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-styryl-1,2,3,6-tetrahydropyridine (7j). According to general procedure VII, **7j** was obtained as a white solid (43 mg, 68 % yield). M.p. 129–131 °C; $[\alpha]_D^{25}$ = +134.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.25 (m, 10H), 6.88 (d, *J* = 16.3 Hz, 1H), 6.65 (d, *J* = 16.3 Hz, 1H), 5.82 (bs, 1H), 5.33 (bs, 1H), 4.10 (dd, *J* = 19.5, 4.4 Hz, 1H), 3.57 (dd, *J* = 19.5, 2.2 Hz, 1H), 3.01 (bs, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.1, 137.1, 133.6, 130.2, 128.8, 128.6, 127.8, 127.7, 127.7, 127.1, 126.5, 125.6, 61.8, 54.3, 43.3, 27.8, 24.8. HRMS (ESI): *m/z* calcd. for $C_{23}H_{33}N_2O_2S$ [M + NH_4^+]: 401.2098, found 401.2101.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-(4-methylstyryl)-2-phenyl-1,2,3,6-tetrahydropyridine (7k). According to general procedure VII, **7k** was obtained as a white solid (20 mg, 39 % yield). M.p. 66–67 °C; $[\alpha]_D^{25}$ = +134.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.31–7.17 (m, 5H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.76 (d,

J = 16.3 Hz, 1H), 6.54 (d, *J* = 16.3 Hz, 1H), 5.71 (bs, 1H), 5.24 (bs, 1H), 4.01 (dd, *J* = 19.3, 4.5 Hz, 1H), 3.48 (dd, *J* = 19.5, 2.0 Hz, 1H), 2.92 (bs, 2H), 2.28 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.1, 137.7, 134.3, 133.7, 129.6, 129.3, 128.6, 127.7, 127.1, 126.5, 125.0, 61.8, 54.4, 43.3, 27.8, 24.8, 21.4. HRMS (ESI): *m/z* calcd. for $C_{24}H_{33}N_2O_2S$ [M + NH_4^+]: 413.2263; 413.2267.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-phenyl-4-(3-(trimethylsilyl)prop-1-en-1-yl)-1,2,3,6-tetrahydropyridine (7l). According to general procedure VII, **7l** was obtained as a white solid (40 mg, 32 % yield). $[\alpha]_D^{25}$ = +57.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 7.33–7.28 (m, 3H), 6.00 (d, *J* = 15.7 Hz, 1H), 5.83–5.72 (m, 1H), 5.47 (d, *J* = 2.7 Hz, 1H), 5.24 (t, *J* = 3.7 Hz, 1H), 4.00 (dd, *J* = 18.9, 4.3 Hz, 1H), 3.48 (d, *J* = 18.9Hz, 1H), 2.82 (s, 2H), 1.60 (d, *J* = 8.2 Hz, 2H), 1.42 (s, 9H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.1, 135.4, 131.9, 130.3, 129.4, 129.3, 127.8, 122.4, 63.5, 56.1, 44.8, 29.7, 26.5, 25.5, 0.0. HRMS (ESI): *m/z* calcd. for $C_{21}H_{37}N_2O_2SSi$ [M + NH_4^+]: 409.2340, found 409.2357.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-(4-methoxyphenyl)-4-styryl-1,2,3,6-tetrahydropyridine (7m). According to general procedure VII, **7m** was obtained as a colorless oil (24 mg, 60 % yield). $[\alpha]_D^{25}$ = +116.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.27 (m, 7H), 6.88 (d, *J* = 16.2 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 16.2 Hz, 1H), 5.83 (bs, 1H), 5.28 (bs, 1H), 4.07 (dd, *J* = 19.5, 4.6 Hz, 1H), 3.78 (s, 3H), 3.54 (dd, *J* = 19.4, 2.0 Hz, 1H), 2.97 (bs, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.7, 133.6, 124.2, 112.1, 61.4, 57.4, 43.4, 29.2, 24.6, 13.7, 5.0, 4.1. HRMS (ESI): *m/z* calcd. for $C_{24}H_{34}NO_3S$ [M + H^+]: 428.2206, found 428.2206.

(*R,E*)-1-(*tert*-Butylsulfonyl)-2-hexyl-4-styryl-1,2,3,6-tetrahydropyridine (7n). According to general procedure VII, **7n** was obtained as a colorless oil (20 mg, 49 % yield). $[\alpha]_D^{25}$ = –3.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.20 (m, 5H), 6.81 (d, *J* = 16.2 Hz, 1H), 6.50 (d, *J* = 16.2 Hz, 1H), 5.82 (bs, 1H), 4.18–3.97 (m, 2H), 3.84 (d, *J* = 19.4 Hz, 1H), 2.67 (dd, *J* = 16.7, 3.0 Hz, 1H), 2.36 (d, *J* = 16.5 Hz, 1H), 1.68–1.51 (m, 3H), 1.37 (s, 9H), 1.28 (bs, 7H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.3, 132.9, 130.9, 128.8, 127.6, 126.7, 126.5, 124.6, 61.4, 52.5, 42.8, 32.2, 31.9, 29.4, 28.6, 26.9, 24.6, 22.8, 14.2. HRMS (ESI): *m/z* calcd. for $C_{23}H_{38}NO_2S$ [M + H^+]: 392.2544, found 392.2461.

(*S,E*)-1-(*tert*-Butylsulfonyl)-2-cyclopropyl-4-styryl-1,2,3,6-tetrahydropyridine (7o). According to general procedure VII, **7o** was obtained as a yellowish oil (32 mg, 51 % yield). $[\alpha]_D^{25}$ = +4.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68–7.18 (m, 5H), 6.84 (d, *J* = 16.2 Hz, 1H), 6.53 (d, *J* = 16.2 Hz, 1H), 5.88 (bs, 1H), 4.12 (bs, 2H), 3.33 (dd, *J* = 9.0, 6.3 Hz, 1H), 2.73 (ddd, *J* = 16.5, 5.8, 2.7 Hz, 1H), 2.52 (d, *J* = 16.7 Hz, 1H), 1.35 (s, 9H), 1.22–1.03 (m, 1H), 0.78–0.65 (m, 1H), 0.64–0.49 (m, 2H), 0.40–0.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.2, 133.4, 130.8, 128.8, 127.7, 127.0, 126.5, 124.7, 61.4, 57.5, 43.7, 29.9, 24.6, 13.7, 5.1, 4.2. HRMS (ESI): *m/z* calcd. for $C_{20}H_{33}N_2O_2S$ [M + NH_4^+]: 365.2104, found 365.2101.

(*S,E*)-1-(*tert*-Butylsulfonyl)-4-styryl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (7p). According to general procedure VII, **7p** were obtained as a colorless oil (23 mg, 60 % yield). $[\alpha]_D^{25}$ = +35.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.14 (m, 5H), 6.72 (d, *J* = 16.3 Hz, 1H), 6.44 (d, *J* = 16.3 Hz, 1H), 5.81 (s, 1H), 4.62–4.57 (m, 1H), 4.26–4.19 (m, 1H), 3.90–3.84 (m, 1H), 2.79–2.58 (m, 2H), 1.34 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.99 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.8, 131.1, 129.5, 128.7, 127.8, 127.3, 126.4, 125.3 (q, $^1J_{CF}$ = 286.7 Hz, C), 123.8, 62.4, 52.7 (q, $^2J_{CF}$ = 31.2 Hz, CH), 43.9, 24.4, 23.3. HRMS (ESI): *m/z* calcd. for $C_{18}H_{26}F_3N_2O_2S$ [M + NH_4^+]: 391.1662, found 391.1658.

VIII. Standard procedure for the Diels-Alder reaction with PTAD. The corresponding diene (0.10 mmol) was dissolved in acetone (0.1 M) and cooled down to –40 °C. PTAD (0.13 mmol) was then added and the mixture was stirred at the same temperature until the reaction was complete (followed by TLC analysis, typically 2–3 h). Next, the crude mixture was concentrated under reduced pressure and the product was purified by flash column chromatography (*n*-hexane/EtOAc).

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]-pyridazine-1,3(2H)-dione (8a). According to general procedure VIII, **8a** was obtained from **6a** as a white solid (45 mg, 88 % yield). M.p. 86–87 °C; $[\alpha]_D^{25}$ = +10.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.37 (m, 5H), 7.24 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 5.95 (bs, 1H), 5.13 (t, *J* = 8.2 Hz, 1H), 4.63 (d, *J* = 14.9 Hz, 1H), 4.48 (bs, 1H), 4.32 (ddd, *J* = 16.5, 6.5, 2.7 Hz, 1H), 4.24–4.08 (m, 2H), 3.02 (dd, *J* = 14.1, 7.9 Hz, 1H), 2.57–2.45 (m, 1H), 2.38 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.2, 151.3, 138.6, 137.7, 131.3, 130.3, 129.7, 129.2, 128.2, 126.5, 125.7, 118.0, 62.0, 60.3, 56.0, 48.9, 42.4, 37.8, 24.6, 21.2. HRMS (ESI): *m/z* calcd. for $C_{26}H_{34}N_5O_4S$ [M + NH_4^+]: 512.2331, found 512.2326.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2,8-diphenyl-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8b). According to general procedure VIII, **8b** was obtained from **6b** as a white solid (1.529 g, 97 % yield). M.p. 97–99 °C; $[\alpha]_D^{25}$ = +9.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.30 (m, 10H), 5.95 (s, 1H), 5.16 (t, *J* = 8.4 Hz, 1H), 4.68 (d, *J* = 15.1 Hz, 1H), 4.49–4.47 (m, 1H), 4.36–4.13 (m, 3H), 3.03 (dd, *J* = 14.1, 8.0 Hz, 1H), 2.54–2.47 (m, 1H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.1, 151.2, 141.6, 131.2, 130.1, 129.1, 128.9, 128.1, 127.8, 126.4, 125.9, 118.0, 61.6, 60.4, 55.9, 48.7, 42.2, 37.6, 24.4. HRMS (ESI): *m/z* calcd. for $C_{25}H_{28}N_4O_4S$ [M + NH_4^+]: 498.2170, found 498.2163.

(8*S*,10a*R*)-5-(3-Bromopropyl)-9-(*tert*-butylsulfonyl)-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8c). According to general procedure VIII, **8c** was obtained from **7g** as a white solid (28 mg, 80 % yield). M.p. 85–87 °C; $[\alpha]_D^{25}$ = –67.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.34 (m, 5H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 5.95 (bs, 1H), 5.14 (t, *J* = 8.7 Hz, 1H), 4.82 (d, *J* = 15.4 Hz, 1H), 4.61 (bs, 1H), 4.36 (bs, 1H), 4.19 (dd, *J* = 15.5, 6.1 Hz, 1H), 3.53–3.41 (m, 2H), 2.95 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.43 (d, *J* = 10.6 Hz, 1H), 2.38 (s, 3H), 2.22–1.97 (m, 4H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.6, 150.1, 139.1, 137.7, 131.2, 130.2, 129.8, 129.2, 128.2, 126.4, 125.6, 122.4, 61.5, 60.2, 57.2, 51.7, 49.20, 37.9, 33.3, 31.6, 28.7, 24.6, 21.2. HRMS (ESI): *m/z* calcd. for $C_{29}H_{39}BrN_5O_4S$ [M + NH_4^+]: 632.1899, found 632.1901.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-(4-methoxyphenyl)-2,8-diphenyl-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8d). According to general procedure VIII, **8d** was obtained from **6i** as a white solid (20 mg, 67 % yield). M.p. 88–90 °C; $[\alpha]_D^{25}$ = –8.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.44 (m, 4H), 7.40–7.27 (m, 8H), 7.00–6.98 (m, 2H), 5.20 (t, *J* = 8.6 Hz, 1H), 4.87 (d, *J* = 15.0 Hz, 1H), 4.57–4.55 (m, 1H), 4.39 (m, 2H), 4.13 (dd, *J* = 15.3, 6.4 Hz, 1H), 3.86 (s, 3H), 3.08 (dd, *J* = 14.1, 8.4 Hz, 1H), 2.19–2.12 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.6, 153.2, 151.1, 141.8, 131.2, 130.7, 129.6, 129.1, 129.0, 128.9, 128.1, 127.6, 125.9, 125.6, 124.5, 114.4, 61.5, 59.8, 56.3, 55.3, 48.4, 46.6, 34.5, 29.7, 24.4. HRMS (ESI): *m/z* calcd. for $C_{32}H_{34}N_4O_5S$ [M + NH_4^+]: 604.2588, found 604.2585.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-methyl-2-phenyl-8-(*p*-tolyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]-pyridazine-1,3(2H)-dione (8e). According to general procedure VIII, **8e** was obtained from **6o** as a white solid (48 mg, 87 % yield).

M.p. 112–114 °C; $[\alpha]_D^{25}$ = –16.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.11 (m, 9H), 5.13 (t, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.34 (s, 1H), 4.12–3.96 (m, 3H), 3.19 (dd, *J* = 14.6, 8.1 Hz, 1H), 2.28 (s, 3H), 2.18 (dd, *J* = 14.2, 8.1 Hz, 1H), 1.84 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.8, 151.0, 138.8, 137.4, 131.2, 129.7, 129.1, 128.0, 125.9, 125.5, 124.5, 121.8, 61.5, 58.6, 55.7, 48.5, 46.0, 33.6, 24.4, 21.1, 16.0. HRMS (ESI): *m/z* calcd. for $C_{27}H_{32}N_4O_4S$ [M + NH_4^+]: 526.2483, found 526.2479.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-2-phenyl-8-(trifluoromethyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]-pyridazine-1,3(2H)-dione (8i). According to general procedure VIII, **8i** was obtained from **6g** as a white solid (43 mg, 91 % yield). M.p. 145–147 °C; $[\alpha]_D^{25}$ = –7.9 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61–7.33 (m, 5H), 4.87–4.73 (m, 1H), 4.42 (d, *J* = 12.0 Hz, 2H), 4.11 (dd, *J* = 16.2, 7.5 Hz, 2H), 3.91 (dd, *J* = 16.0, 7.3 Hz, 1H), 3.15 (dd, *J* = 14.5, 9.7 Hz, 1H), 2.08 (dd, *J* = 14.5, 8.2 Hz, 1H), 1.89 (s, 3H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = –73.26 (s, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.7, 150.7, 131.2, 129.1, 128.1, 127.3, 125.5, 125.3 (q, $^1J_{CF}$ = 282.7 Hz, C), 118.5, 62.9, 55.4 (q, $^2J_{CF}$ = 31.4 Hz, CH), 54.8, 49.2, 45.9, 24.6, 24.3, 15.9. HRMS (ESI): *m/z* calcd. for $C_{21}H_{25}F_3N_4O_4S$ [M + NH_4^+]: 490.1730, found 490.1728.

(8*S*,10a*R*)-9-(*tert*-Butylsulfonyl)-6-methyl-2-phenyl-8-(trifluoromethyl)-5,7,8,9,10,10a-hexahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (8j). According to general procedure VIII, **8j** was obtained from **6p** as a white solid (36 mg, 88 % yield). M.p. 145–147 °C; $[\alpha]_D^{25}$ = –16.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.11 (m, 9H), 5.13 (t, *J* = 8.1 Hz, 1H), 4.49 (d, *J* = 14.7 Hz, 1H), 4.34 (s, 1H), 4.12–3.96 (m, 3H), 3.19 (dd, *J* = 14.6, 8.1 Hz, 1H), 2.28 (s, 3H), 2.18 (dd, *J* = 14.2, 8.1 Hz, 1H), 1.84 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.8, 151.0, 138.8, 137.4, 131.2, 129.7, 129.1, 128.0, 125.9, 125.5, 124.5, 121.8, 61.5, 58.6, 55.7, 48.5, 46.0, 33.6, 24.4, 21.1, 16.0. HRMS (ESI): *m/z* calcd. for $C_{27}H_{32}N_4O_4S$ [M + NH_4^+]: 504.1887, found 504.1891.

IX. Standard procedure for the Diels-Alder reaction with tetracyanoethylene. The corresponding diene (0.10 mmol) and tetracyanoethylene (0.20 mmol) were added to a Schlenk tube, dissolved in toluene (0.1 M), and heated at 100 °C until the reaction was complete (TLC analysis, typically 2–3 h). The crude mixture was then concentrated under reduced pressure and the product was purified by flash column chromatography (*n*-hexane/EtOAc).

(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-3-phenyl-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8f). According to general procedure IX, **8f** was obtained from **6b** as a white solid (38 mg, 84 % yield). M.p. 186–188 °C; $[\alpha]_D^{25}$ = +31.0 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 5.69 (s, 1H), 4.86 (s, 1H), 4.27 (dd, *J* = 12.5, 4.9 Hz, 1H), 3.76 (t, *J* = 10.9 Hz, 1H), 3.62 (s, 1H), 3.25–3.14 (m, 3H), 2.93 (d, *J* = 13.6 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.4, 131.2, 128.6, 128.4, 128.1, 127.3, 117.2, 110.9, 110.2, 110.1, 108.5, 62.7, 48.4, 41.6, 40.8, 38.8, 37.2, 32.7, 24.4. HRMS (ESI): *m/z* calcd. for $C_{23}H_{23}N_5O_2S$ [M + NH_4^+]: 451.1576, found 451.1569.

(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-5-(4-chlorophenyl)-3-(thiophen-3-yl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8g). According to general procedure IX, **8g** was obtained from **6l** as a colorwhite solid (31 mg, 92 % yield). M.p. 137–139 °C; $[\alpha]_D^{25}$ = +20.2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.42 (m, 2H), 7.33 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.19–7.18 (m, 1H), 7.10–7.05 (m, 2H), 6.98 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.02 (s, 1H), 4.26 (dd, *J* = 11.1, 4.0 Hz, 1H), 3.85–3.78 (m, 1H), 3.70–3.67 (m, 1H), 3.40–3.20 (m, 2H), 2.87 (s, 2H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.8, 135.4, 134.8, 129.9, 129.2, 128.9, 127.3, 126.6, 126.2, 123.4, 110.4, 110.0, 109.9, 108.3, 62.9, 54.9, 46.5, 41.5, 40.7, 38.8, 38.3, 34.4, 24.6. HRMS (ESI): *m/z* calcd. for $C_{27}H_{24}ClN_5O_2S_2$ [M + NH_4^+]: 567.1060, found 567.1056.

(3*S*,10a*R*)-2-(*tert*-Butylsulfonyl)-3-(thiophen-3-yl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8h). According to general procedure IX, **8h** was obtained from **6d** as a colorless oil (46 mg, 86 % yield); $[\alpha]_D^{25}$ = +32.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.30 (m, 2H), 7.14–7.12 (m, 1H), 5.72 (s, 1H), 4.89 (s, 1H), 4.22 (d, *J* = 7.4 Hz, 1H), 3.69–3.57 (m, 2H), 3.25–3.16 (m, 3H), 2.92 (d, *J* = 15.7 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.5, 131.2, 127.4, 126.4, 124.8, 117.2, 110.9, 110.1, 110.0, 108.4, 62.7, 56.8, 41.6, 40.5, 38.6, 37.2, 32.6, 29.7, 24.3. HRMS (ESI): *m/z* calcd. for $C_{21}H_{21}N_5O_2S_2$ [M + NH_4^+]: 457.1475, found 457.1475.

(3*S*,10a*S*)-2-(*tert*-Butylsulfonyl)-3-(perfluoropropyl)-1,2,3,4,6,8a-hexahydroisoquinoline-7,7,8,8-tetracarbonitrile (8k). According to general procedure IX, **8k** was obtained from **6h** as a white solid (41 mg, 75 % yield). M.p. 172–174 °C; $[\alpha]_D^{25}$ = +40.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.73–5.71 (m, 1H), 4.87 (d, *J* = 24.6 Hz, 1H), 3.91–3.76 (m, 2H), 3.52–3.50 (m, 1H), 3.17–3.13 (m, 2H), 3.02 (d, *J* = 18.3 Hz, 1H), 2.76 (d, *J* = 18.3 Hz, 1H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = –80.70 (t, *J* = 10.7 Hz, 3F), –110.24 (d, *J* = 275.8 Hz, 1F), –119.07 (d, *J* = 275.8 Hz, 1F), –125.15 to –127.59 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 127.0, 119.4–108.9 (C_3F_7), 118.3, 110.8, 110.2, 110.1, 108.2, 64.1, 51.9, 44.6, 42.2, 39.6, 38.7, 32.7, 29.7, 24.7. HRMS (ESI): *m/z* calcd. for $C_{20}H_{18}F_7N_5O_2S$ [M + NH_4^+]: 543.1408, found 543.1407.

X. General procedure for the hydrogenation reaction. Synthesis of (8*S*,10a*R*)-9-(*tert*-butylsulfonyl)-2,8-diphenyloctahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazine-1,3(2H)-dione (9). A round-bottom flask was charged with Diels–Alder adduct **8b** (200 mg, 0.42 mmol), Pd (10 % on activated carbon) (42 mg, 0.042 mmol), and a stirrer bar, and the mixture was suspended in anhydrous methanol (10 mL). The vessel was purged three times with hydrogen gas and fitted with a gas bag containing hydrogen. The mixture was stirred for 3 h before filtering through a short pad of Celite. The filtrate was then concentrated to dryness under reduced pressure. No further purification was necessary and compound **9** was isolated as a white solid (183 mg, 91 % yield) (2:1 mixture of diastereoisomers). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.31 (m), 5.25–5.20 (m), 4.95 (d, *J* = 18.1 Hz, 1H, *minor*), 4.20–4.09 (m, 1H, *minor*), 3.98 (dt, *J* = 12.6, 4.3 Hz, 1H, *major*), 3.89–3.83 (m, 1H, *minor*), 3.79–3.72 (m), 3.66–3.55 (m), 3.08–3.01 (m, 1H, *minor*), 2.65–2.39 (m), 2.21 (dt, *J* = 13.9, 3.7 Hz, 1H, *major*), 2.12–2.05 (m, 1H, *major*), 1.94–1.83 (m), 1.46 (s, 9H, *minor*), 1.42 (s, 9H, *major*); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.0, 149.9, 145.9, 138.5, 129.1, 129.0, 128.3, 127.2, 126.7, 125.7, 108.8, 62.2, 62.0, 54.6, 54.4, 43.6, 40.7, 38.1, 31.1, 30.5, 27.4, 26.9, 26.7, 24.6. HRMS (ESI): *m/z* calcd. for $C_{21}H_{21}N_4O_2$ [M + H^+]: 483.2061, found 483.2054.

XI. General procedure for the deprotection of *tert*-butylsulfonyl. Synthesis of (8*S*,10a*R*)-1,3-dioxo-2,8-diphenyl-2,3,5,7,8,9,10,10a-octahydro-1H-pyrido[3,4-c][1,2,4]triazolo[1,2-a]pyridazin-9-ium chloride (10). Diels–Alder adduct **8b** (100 mg, 0.21 mmol) was dissolved in anhydrous 1,4-dioxane (1.8 mL), and concentrated hydrochloric acid (12 M, 0.2 mL) was added. The reaction mixture was then stirred at 110 °C for 3 h. After this time, the crude mixture was concentrated to dryness under reduced pressure, and the resulting solid was precipitated and washed with methanol and diethyl ether. No further purification was needed, affording **10** as an off-white solid (59 mg, 71 % yield). M.p. 296–298 °C; $[\alpha]_D^{25}$ = +40.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1H), 10.14 (s, 1H), 7.74–7.72 (m, 2H), 7.56–7.40 (m, 8H), 6.05 (s, 1H), 5.11 (d, *J* = 8.1 Hz, 1H), 4.38 (s, 1H), 4.27–4.06 (m, 3H), 3.21–3.15 (m, 1H), 2.99–2.83 (m, 2H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ = 152.7, 152.1, 136.7, 131.7, 129.6, 129.4, 129.3, 128.7, 128.3, 126.8, 117.9, 60.5, 50.9, 46.6, 42.9, 39.2, 36.8. HRMS (ESI): *m/z* calcd. for $C_{21}H_{21}N_4O_2$ [M + NH_4^+]: 361.1659, found 361.1659.

XII. General Procedure for the Preparation of (2*S*,5*R*,*Z*)-4-allylidene-1-(*tert*-butylsulfonyl)-5-fluoro-2-phenylpiperidine (11). Metathesis product **7l** (39 mg, 0.1 mmol) was dissolved in acetonitrile (0.1 M) and Selectfluor (46 mg, 0.13 mmol) was added, and the reaction mixture was then stirred for 16 h at room temperature. The crude mixture was concentrated under reduced pressure and purified by flash column chromatography using mixtures of *n*-hexane/EtOAc as the eluent, affording a colorless oil (20 mg, 58 % yield). $[\alpha]_D^{25}$ = +78.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 6.65–6.53 (m, 1H), 6.15 (dd, *J* = 10.9, 5.4 Hz, 1H), 5.36–5.17 (m, 3H), 4.76 (d, *J* = 48.5 Hz, 1H), 4.13–4.03 (m, 1H), 3.45–3.26 (m, 2H), 3.06–2.98 (m, 1H), 1.52 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ = –167.32 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.6, 130.6, 130.0, 128.6, 127.2, 121.9, 92.4, 90.1, 62.4, 57.7, 48.0, 28.1, 24.6. HRMS (ESI): *m/z* calcd. for $C_{18}H_{28}FN_2O_2S$ [M + NH_4^+]: 355.1850, found 355.1848.

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Metathesis Reactions

A family of chiral nitrogen-containing 1,7-enynes was used as starting materials in the preparation of a variety of enantioenriched tetrahydropyridine-based conjugated 1,3-dienes through ruthenium-catalyzed ring-closing enyne metathesis (RCEYM) and cross enyne metathesis/ring-closing metathesis (CEYM/RCM) reactions.

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