Copper-Catalyzed Ring-Opening of Heterobicyclic Alkenes with Grignard Reagents: Remarkably High *anti*-Stereocontrol

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Abstract: Unlike most of the reported protocols for the ring-opening reaction of heterobicyclic alkenes with carbon nucleophiles which typically occur with *syn* selectivity, the alkylative ring-opening reaction of [2.2.1]oxa- and azabicyclic alkenes with Grignard reagents in the presence of a catalytic amount of copper(I) takes place with very high or complete *anti*-stereocontrol under smooth reaction conditions. This new procedure proved to be wide in scope with respect to both the Grignard reagent and the bicyclic alkene. Especially noteworthy is the facile ring-opening reaction of low reactive substrates such as nonaromatic oxabicyclic alkenes and azabenzonorbornadienes under this catalyst system.

Key words: ring-opening reaction, copper catalyst, oxabicyclic alkenes, azabenzonorbornadiene, Grignard reagents, (2-py-ridyl)sulfonamides

Introduction

Development of new methods and efficient strategies for carbon–carbon bond-forming processes that efficiently create multiple stereocenters is one of the challenges in synthetic organic chemistry. Within this context, the transition-metal-catalyzed ring-opening reaction of meso heterobicyclic alkenes with nucleophiles is especially valuable since several stereocenters can be simultaneously created with high stereocontrol in one step.¹ The group of Lautens has taken the lead in exploring the possibilities of this strategy, including the development of enantioselective variants, thorough mechanistic studies and its application to the synthesis of biologically relevant products.^{1,2}

Initially, the ring-opening reaction of [2.2.1]oxabicyclic alkenes was achieved with limited success using organolithium^{1a,3} and organocuprate^{1a,4} nucleophilic reagents, affording the corresponding *syn* addition products in moderate to good yields. Grignard reagents by itself, however, were found to be unreactive species in this transformation.⁵ Later on, the use of transition metal catalysts allowed the use of softer organometallic reagents as nucleophiles such as organozincs (Pd),⁶ phenylstannane (Pd),⁷ organoaluminum (Zr or Ti),⁸ alkenylzirconium,⁹ zinc acetylides (Ni)¹⁰ and organoboron (Rh).¹¹ Additionally, the alkylative ring opening of oxabenzonorbornadienes with organic halides in the presence of palladium¹²

or nickel¹³ catalysts, and with propiolates catalyzed by nickel complexes,¹⁴ have been also reported. In all cases the ring-opening occurs with *syn* stereoselectivity, as a result of the *exo* attack of the nucleophile to the oxabicyclic unit.

To the best of our knowledge, the enantioselective rhodium-catalyzed addition of malonates to oxabenzonorbornadienes, reported by Lautens and co-workers,¹⁵ and the addition of dialkylzinc reagents catalyzed by a chiral copper-phosphoramidite in the presence of Zn(OTf)₂, by Feringa and co-workers,¹⁶ constitute the only current protocols for the *anti*-stereocontrolled ring opening of [2.2.1]oxabicyclic alkenes with carbon nucleophiles. Despite the great interest of these two procedures, especially their high enantioselectivity, the synthetic scope seems to be limited to the case of oxabenzonorbornadienes and a narrow structural diversity of carbon nucleophiles (malonate-type and primary dialkylzinc reagents).

In addition to these carbon nucleophiles, protocols for the reductive ring opening^{2a-c,17} and the addition of heteroatom nucleophiles (oxygen-,¹⁸ nitrogen-^{15,18a,e} and sulfurbased¹⁹ nucleophiles) to oxabenzonorbornadienes have also been developed, the latter being highly *anti*-stereoselective.

Compared to the widely studied oxa-bridged bicyclic alkenes, few reports have appeared in the literature on stereocontrolled ring-opening reactions of their aza analogues, even though the resulting 1-aminodihydronaphthalenes are useful scaffolds for the preparation of potentially bioactive compounds. The enantioselective Pd-catalyzed addition of arylboronic acids to azabenzonorbornadienes, reported by Lautens et al.,²⁰ and the palladium- or nickel-catalyzed ring opening of azabenzonorbornadienes with organic halides or alkynes, described by Cheng et al,^{12–14} are the existing precedents regarding the ring-opening addition of carbon-based nucleophiles to azabicycles, all of them occurring with complete syn-stereocontrol. As far as we know, prior to this work, the Rh-catalyzed reaction with amines described by Lautens^{2d} was the only reported example on *anti*-stereocontrolled ring opening of azabenzonorbornadiene derivatives.

Therefore, although a remarkable progress has been achieved in recent years in metal-catalyzed ring opening of heterobicyclic alkenes, some limitations still remain. For example, as mentioned before, the vast majority of the reported methods have been described to occur with *syn*

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selectivity. On the other hand, regarding the type of carbon nucleophiles capable of inducing this metal-catalyzed transformation, it is surprising that the highly reactive and readily available Grignard reagents have been scarcely studied. Lautens and co-workers reported the nickel-catalyzed ring opening of [2.2.1]oxabicyclic alkenes with a large excess of Grignard reagents to give mainly *syn*-substituted products.^{21,22} More recently, the group of Nakamura has described the iron-catalyzed *syn*-stereocontrolled ring opening of [2.2.1] and [3.2.1]oxabicyclic alkenes with Grignard reagents.²³

Herein, we report a very general protocol for the *anti*-stereocontrolled ring opening of oxa- and aza-bicyclic[2.2.1]alkenes with Grignard reagents in the presence of a substoichiometric amount of copper(I) catalyst.^{24,25} In

Biographical Sketches

addition to oxabenzonorbornadienes, the less reactive aza analogues and non-aromatic [2.2.1]oxabicycles do also participate in the ring opening process under smooth reaction conditions. The first *anti*-stereocontrolled alkylative ring opening of azabicyclic alkenes has been realized by means of using (2-pyridyl)sulfonyl group as the key activating group at the nitrogen atom.

Ring Opening of Oxabicyclic Alkenes

As initial experiment to explore the role of copper as catalyst, the reaction of oxabenzonorbornadiene (1a) with ethylmagnesium bromide (1.5 equiv) in the presence of a 10 mol% of CuI (toluene, rt) provided a 90:10 mixture of



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2000. His current research interests are focused on developing new stereocontrolled metal-catalyzed processes and new chiral ligands for asymmetric catalysis. the *anti/syn* ring-opened products $2b^{26}$ (60% yield), accompanied by dihydronaphthalen-1-ol (**3**, 35%) and a small amount of naphthalene (**4**). Compound **3** likely results from the reductive ring opening of **1a** caused by a β -hydride transfer from the Grignard reagent.

Encouraged by the high anti-stereoselectivity displayed by this catalytic system, the effect of several commercially available copper salts, ligands and solvents on the reactivity and selectivity in the ring opening of 1a with EtMgBr were surveyed. First, we confirmed that no reaction took place in the absence of copper salt, even under prolonged reaction times. On the other hand, the addition of Ph₃P²⁷ (10 mol%) as ligand produced a significant enhancement of both the reaction yield and the anti/syn ratio (Table 1, entry 1). With regard to the solvent, only noncoordinating solvents such as toluene and CH₂Cl₂ proved to be suitable, while coordinating solvents such as Et₂O, THF or DME led to very low conversions. Finally, among the different copper salts tested, CuTC^{28,29} (entry 8, TC = thiophene-2-carboxylate) and especially CuCl (entry 3) produced the best results in terms of reactivity and stereoselectivity in the reaction of 1a with EtMgBr. Thus, using the system CuCl/Ph₃P (10 mol%) the ring opening was very stereoselective, affording a 97:3 mixture of anti/ syn products without formation of side products.

The synthetic scope with regard to the Grignard reagent under these optimized conditions [CuCl (10 mol%),³⁰ Ph₃P (10 mol%),³¹ toluene, r.t.] is shown in Table 2.

Primary, secondary, and benzyl alkylmagnesium bromides and chlorides afforded the corresponding dihydronaphthalenols in good chemical yields and very high or complete anti selectivity.32 Particular attention deserves the easy delivery of a methyl group under these conditions (product anti-2a,³³ entry 1), which contrasts with the low reactivity displayed by Me₂Zn in the Cu-catalyzed ring opening of oxabenzonorbornadiene.¹⁶ Although in general CuTC provides poorer results than CuCl, in the case of c-C₆H₁₁MgCl a better yield was obtained in the presence of CuTC (2e, comparative entries 6 and 7). Remarkably, less reactive aryl Grignard reagents provided the ring-opened products with complete antistereoselectivity (entries 9-12). The reaction proceeded smoothly with both electron-rich and electron-poor aryl derivatives. It should be noted that, to the best of our knowledge, no previous anti ring opening arylations of oxa-bridged bicyclic alkenes had been described.

It is worth mentioning that differently substituted oxabenzonorbornadiene derivatives such as **1b–d**,³⁴ can also be successfully used in this ring opening reaction. For instance, in Scheme 1 are summarized the results with MeMgBr and 4-FC₆H₄MgBr as model examples of alkyland arylmagnesium reagents. In all cases, regardless of the electronic nature or the position of the substitutents, the corresponding 2-substituted 1,2-dihydro-1-naphthalenols **5–7** were obtained in good yields with practically complete *anti* stereocontrol.

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|----------|-----------|-----------|---------|---------|--------|----------|-------|--------------|--|
| Table I | Screening | of Copper | Sources | for the | King C | Jpening | 01 1a | with Euviger | |

| EtMgBr (1.5 equiv) CuX (10 mol%) 1a toluene, r.t. anti-2b | H H H H H H H H H H H H H H H H H H H | |
|---|---|------------------------------|
| Entry | Copper salt ^a | Ratio of anti-2b/syn-2b/3/4b |
| 1 | CuI | 69:4:10:17 |
| 2 | CuBr | 85:4:7:4 |
| 3 | CuCl | 97:3:-:- |
| 4 | (CuOTf)·C ₆ H ₆ | 80:5:4:11 |
| 5 | Cu(OTf) ₂ | 17:1:37: ^c |
| 6 | CuCl ₂ | 78:3:8:11 |
| 7 | CuCN | 36:9:-:43° |
| 8 | CuTC | 90:5:-:5 |
| 9 | Cu(MeCN) ₄ PF ₆ | 73:4:-:- ^c |

^a 10 mol%.

^b Determined by ¹H NMR from the crude reaction mixture; 3 = 1,2-dihydronaphthalen-1-ol; 4 = naphthalene.

^c Oxabenzonorbornadiene (**1a**) was also detected.

 Table 2
 Cu-Catalyzed Ring Opening of 1a with Grignard Reagents

| la la | RMgX (1.5 equiv) <u>CuCl (10 mol%)</u> PPh ₃ (10 mol%) toluene, r.t. | OH anti-2 | syn- 2 | | | |
|-----------------|--|------------------------------------|---------------|----------|--------------------------------|------------------------|
| Entry | Х | R | Product | Time (h) | Ratio of anti/syn ^a | Yield (%) ^b |
| 1 | Br | Me | 2a | 6 | >98:<2 | 92 |
| 2^c | Br | Et | 2b | 0.3 | 97:3 | 76 |
| 3 | Br | Et | 2b | 0.3 | 95:5 | 83 |
| 4 | Br | <i>i</i> -Bu | 2c | 3 | >98:<2 | 89 |
| 5 | Cl | $C_{10}H_{21}$ | 2d | 4 | 90:10 | 66 |
| 6 | Cl | $c-C_{6}H_{11}$ | 2e | 2 | >98:<2 | 51 |
| 7° | Cl | $c-C_{6}H_{11}$ | 2e | 1 | >98:<2 | 64 |
| 8 | Br | Bn | 2f | 12 | >98:<2 | 47 ^d |
| 9 | Br | Ph | 2g | 2 | >98:<2 | 90 |
| 10 ^c | Br | Ph | 2g | 4 | >98:<2 | 84 |
| 11° | Br | 4-OMeC ₆ H ₄ | 2h | 12 | >98:<2 | 92 ^e |
| 12 | Br | $4-FC_6H_4$ | 2i | 1.5 | >98:<2 | 94 |

^a Determined by ¹H NMR from the crude reaction mixture.

^b Yield of *anti*-product after chromatography.

^c 10 mol% of CuTC (copper thiophene-2-carboxylate) was used instead of CuCl.

^d Yield in converted product (10% of starting material was recovered).

^e Yield in converted product (15% of starting material was recovered).



Scheme 1

Next, less reactive bicyclic substrates such as non-aromatic oxabicyclic alkenes were examined. Despite the lower reactivity associated to alkyl-substituted [2.2.1]oxabicycles such as **8**, its reaction with a variety of alkyl Grignard reagents afforded, in moderate to good yields, the corresponding cyclohexenols **9** with complete regioselectivity and *anti* stereoselectivity³² (Table 3, entries 1–6). A small amount of diene **10**³⁵ (6–10%) was also observed in the addition of EtMgBr and c-C₆H₁₁MgCl to **8**. To the best of our knowledge, these constitute the first examples of highly regioselective *anti*-stereocontrolled ring opening of nonbenzo-fused oxa-bridged bicyclic alkenes with carbon nucleophiles.

Aryl Grignard reagents such as PhMgBr failed to react with **8** at room temperature, providing less than 10% conversion after two days. While the addition of Lewis acids such as $Zn(OTf)_2$, $ZnCl_2$, $CeCl_3$, LiI or $Yb(OTf)_3$ did not improve the reactivity, we were pleased to find that Ph-MgBr efficiently reacted with **8** when the reaction temperature was raised to 60 °C, affording cyclohexanol **9g** in 79% yield (Table 3, entry 7). At this temperature, the addition of MeMgBr was complete after 12 hours, while three days were needed at room temperature (entries 1 and 2).

Although less reactive, the unsymmetrical substrate 11,³⁶ bearing a methyl substituent at the bridgehead position, did also participate in a clean ring opening reaction with EtMgBr to give exclusively the alcohol 12b in 70% yield after 24 hours of reaction (Scheme 2). Interestingly, the reaction took place with complete regioselectivity by at-

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Table 3 Reactivity of Nonaromatic Oxabicyclic Alkene 8



 $^{\rm a}$ The syn product was not detected by $^{\rm l}{\rm H}$ NMR in the reaction mixture.

^b Yield after chromatographic purification.

^c Reaction performed at 60 °C.

^d Diene **10** was also isolated (6–10%).

^e Yield in converted product (30% of starting 8 was recovered).

tack of the ethyl Grignard reagent to the olefinic terminus distant to the methyl group.



Scheme 2

Ring Opening of Azabicyclic Alkenes

The good results obtained in the ring opening of oxabicyclic substrates prompted us to extend this protocol to azabenzonorbornadiene derivatives, alkenes that typically require harsh reaction conditions because of their low reactivity. Initially, we examined the ring-opening ability of *N*-tosylazabenzonorbornadiene (**13**) in the reaction with MeMgBr in the presence of a 10 mol% of CuCl (CH₂Cl₂,³⁷ r.t.). However, only a 20% conversion was observed after 24 hours of reaction, with formation of a 71:29 mixture of *anti*-**18a**/*syn*-**18a** products (Table 4, entry 1). In contrast to the case of oxabicyclic alkenes, the addition of Ph₃P or other commonly used ligands for copper, such as BINAP or dimethylethylenediamine, resulted in inhibition of the reaction (only traces of the product were detected).

At this point we envisaged that the nature of the functionality at nitrogen could influence the reactivity of the azabicycle, hopefully allowing us to find a more reactive and selective system. In this pursuit, we focused our attention on the carbamate **14** and, especially, the sulfonamides **15– 17**, of different electronic and coordinating nature (Table 4). The known sulfonamides **13** and **16** were prepared by straightforward deprotection of the carbamate **14** (TMSI/Et₃N), followed by treatment with the corresponding sulfonyl chloride.^{2d} On the other hand, the heteroaryl sulfonamides **15** and **17** were readily prepared in good yields by direct Diels–Alder cycloaddition between benzyne, generated in situ from anthranilic acid and isoamyl nitrite, and the corresponding N-sulfonylated pyrrole derivative.

 Table 4
 Screening of Different Activating Groups at Nitrogen in the Ring-Opening Reaction of Azabenzonorbornadiene

| 13-17 | MeMgBr (1.5 equiv) CuCl (10 mol%) CH ₂ Cl ₂ , r.t., 24 h | NHR Me + syn-18a- nti-18a-22a | 22a | | |
|-------|---|--|------------------------|------------|--------------------------------|
| Entry | R | Alkene | Conv. (%) ^a | Product | Ratio of anti/syn ^a |
| 1 | Ts | 13 | 20 | 18a | 71:29 |
| 2 | Boc | 14 | 0 | 19a | _ |
| 3 | (2-Thienyl)SO ₂ | 15 | 20 | 20a | 62:38 |
| 4 | $4-NO_2C_6H_4SO_2$ | 16 | b | 21a | - |
| 5 | (2-Pyridyl)SO ₂ | 17 | 85 | 22a | 90:10 |

^a Determined by ¹H NMR of the crude reaction mixture.

^bOnly decomposition products, together with a small amount of **16** were detected.

As shown in Table 4, the outcome of the ring opening reaction of **13–17** with MeMgBr (CH₂Cl₂, r.t.) in the presence of 10 mol% of CuCl proved to be quite dependent on the nature of the substitution at nitrogen. Thus, while no reaction was observed in the case of the *N*-Boc carbamate **14** after 24 hours, the starting material being recovered unaltered (entry 2), the 2-thienylsulfonamide **15** behaved similarly to the tosyl derivative **13** (entries 1 and 3). On the other hand, the more electrophilic *N*-*p*-nosyl derivative **16** led to a sluggish reaction, affording mainly decomposition products (entry 4). By far, the best results were obtained from the (2-pyridyl)sulfonyl³⁸ derivative **17** (entry 5). Not only did this substrate show a remarkable reactivity, but also the reaction occurred with good *anti*stereocontrol (90:10 *anti/syn*).

Having established the optimal protecting group for the azabicyclic system, a brief study of the effect of other copper salts on the reaction of **17** with MeMgBr led us to find that CuCN produced a dramatic acceleration effect compared to other copper sources (Table 5). Thus, while CuCl, CuI, CuTC or Cu(OTf)₂ led to incomplete reaction after 24 hours (entries 1–4), the reaction in the presence of CuCN reached completion in just two hours, affording **22a** in 90% yield with almost complete *anti*-stereoselectivity (entry 5).

Table 5 Effect of Copper Salts in the Reaction of 17 with MeMgBr

| | | MeMgBr (1. CuX (10 mo CH ₂ Cl ₂ , r.t. | 5 equiv) | NHSO ₂ Py | |
|-------|----------------------|--|----------|--------------------------------|--|
| Entry | Copper salt | Conv. (%) | Time (h) | Ratio of anti/syn ^a | |
| 1 | CuCl | 85 | 24 | 90:10 | |
| 2 | CuI | 85 | 24 | 90:10 | |
| 3 | Cu(OTf) ₂ | 17 | 24 | 98:2 | |
| 4 | CuTC | 55 | 24 | 97:3 | |
| 5 | CuCN | 100 | 2 | 98:2 | |

^a Determined from ¹H NMR spectra from the crude reaction mixture.

The generality of the process was next investigated. Table 6 shows the results of the addition of a variety of Grignard reagents to azabenzonorbornadiene **17** in the presence of CuCN (10 mol%) in CH₂Cl₂ at room temperature. Both alkyl and aryl Grignard reagents were able to undergo ring-opening addition, providing the corresponding 1-aminodihydronaphthalenes **22** in good to excellent chemical yields and very high *anti* selectivity. Alkyl Grignard reagents with β -hydrogen provided the best results in the presence of CuCl rather than CuCN (entries 2 and 3). Remarkably, aromatic reagents displayed very high reactivity, regardless of their electronic nature, affording the ring-opened products with complete *anti* stereocontrol at

room temperature (entries 5–11). It is also interesting to note that the presence of *ortho* or *meta* substituents on the aromatic ring does not have a detrimental effect on the reactivity (entries 9 and 10), except for the very sterically hindered *ortho*-disubstituted mesitylmagnesium bromide, which led to incomplete reaction after eight hours (entry 11). Although less reactive, heteroaryl Grignard reagents such as 2-thienylmagnesium bromide also promoted the ring opening reaction, affording product **22n** with good yield and complete *anti*-stereoselectivity (entry 12).

The *anti* stereochemistry of the ring-opened products **18–22** was assigned by ¹H NMR spectra, the signal of the olefinic proton at C-3 being of great diagnostic value. For compounds with *syn* relative configuration, such proton appears 0.1–0.2 ppm more shielded compared to that of the *anti* adducts. In addition, the coupling constant of H-1 with H-2 for *anti* products is significantly higher (about 6.0 Hz) than that for *syn* compounds (roughly 3.0 Hz). The same tendency has also been observed in the coupling constants of *syn* and *anti* ring-opened products from oxabicyclic alkenes.^{6,16}

Finally, to realize the full synthetic potential of this ring opening protocol in stereoselective amine synthesis, the deprotection of the (2-pyridyl)sulfonamide group of products anti-22 was readily achieved by treatment with magnesium under very mild reaction conditions (MeOH-THF, 0 °C).39 Desulfonylation proceeded smoothly to afford cleanly the corresponding primary amine within two hours. Thus, compound anti-22g was easily transformed into its Boc-derivative anti-14g in 83% overall yield upon deprotection with Mg and subsequent treatment of the free amine with di-tert-butyl carbonate at room temperature (Scheme 3). It should be noted that the diastereomeric product syn-14g had been previously described,²⁰ which confirmed the anti relative setereochemistry of anti-14g. In the same pursuit, compound anti-22h was converted into the known anti-1-amino-2-[(4-methoxy)phenyl]-1,2,3,4-tetrahydronaphthalene (24)⁴⁰ (a precursor in the synthesis of an inhibitor of acyl CoA-cholesterol acyltransferase), by amine deprotection and further alkene hydrogenation. These chemical correlations led us to establish unambiguously the relative anti configuration of the ring-opened products 22.



Scheme 3

Table 6 Cu-Catalyzed Ring Opening of 17 with Grignard Reagents

| $\begin{array}{c} & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$ | | | | | | | | |
|--|----|---|---------|------------|--------------------------------|------------------------|--|--|
| Entry | Х | R | Product | Time (min) | Ratio of anti/syn ^a | Yield (%) ^b | | |
| 1 | Br | Me | 22a | 120 | 98:2 | 89 | | |
| 2 ^c | Br | Et | 22b | 20 | >98:<2 | 65 | | |
| 3° | Cl | $C_{10}H_{21}$ | 22d | 20 | 85:15 | 74 | | |
| 4 | Cl | PhCH ₂ | 22f | 20 | >98:<2 | 53 | | |
| 5 | Br | Ph | 22g | 15 | >98:<2 | 93 | | |
| 6 | Cl | $4-MeOC_6H_4$ | 22h | 10 | >98:<2 | 98 | | |
| 7 | Cl | $4-FC_6H_4$ | 22i | 20 | >98:<2 | 92 | | |
| 8 | Cl | $4-MeC_6H_4$ | 22j | 10 | >98:<2 | 91 | | |
| 9 | Br | 3,5-(CF ₃) ₂ C ₆ H ₃ | 22k | 15 | >98:<2 | 97 | | |
| 10 | Br | 1-naphthyl | 221 | 30 | >98:<2 | 91 | | |
| 11 | Br | mesityl | 22m | 480 | >98:<2 | 87 ^d | | |
| 12 | Br | 2-thienyl | 22n | 120 | >98:<2 | 88 ^e | | |
| 13 | Cl | TMSCH ₂ | 220 | 95 | 93:7 | 73 ^e | | |

^a Determined by ¹H NMR from the crude reaction mixture.

^b Yield of *anti* product after chromatography.

° 10 mol% of CuCl was used instead of CuCN.

^d Yield in converted product (30% of starting material was recovered).

^e Yield in converted product (25% of starting material was recovered).

Mechanistic Considerations

Although a reaction pathway involving the participation of a (π -allyl)copper(III) intermediate I⁴¹ (Scheme 4) cannot be ruled out, it would be difficult to explain the complete regioselectivity observed in all cases, especially from the alkyl-substituted substrate 8, in which both termini of the allyl unit would have a very similar substitution. Rather, the results are more consistent with a coppercatalyzed $S_N 2'$ reaction in which the in situ formed organocuprate would react with the alkene anti with respect to the leaving group (*endo* attack). The resulting σ -allylic copper complex II would then undergo a reductive elimination to give the observed ring-opened product⁴² faster than equilibration to the regioisometric (σ -allyl)copper complex III through the $(\pi$ -allyl)copper intermediate I. The complete regioselectivity observed in the reaction of the unsymmetrical substrate 11 can also be reasoned through endo attack of the ethyl Grignard reagent to the sterically less congested terminus of the alkene moiety.





Presumably, the highly electrophilic magnesium salts present in the medium would enhance the leaving group ability of the heteroatom functionality of the bicyclic alkene through coordination to the oxygen in the case of the oxabicycles or to the nitrogen atom of the pyridine in the case of azabicycle **17**.⁴³ We speculate that this coordina-

tion, rather than merely the inductive effect due to the electron withdrawing nature of the pyridyl group, could explain the exceptionally high reactivity displayed by the N-(2-pyridyl)sulfonyl azabicyclic substrates.⁴⁴

Conclusion

In conclusion, this work demonstrates that Grignard reagents, in combination with a catalytic amount of a copper(I) salt, are highly effective for the alkylative and arylative ring opening of [2.2.1]oxa- and azabicyclic alkenes. Good yields and excellent regio- and *anti*-stereocontrol were achieved under smooth reaction conditions for a wide variety of substrates. The choice of a (2-pyridyl)sulfonyl moiety as activating group at nitrogen proved to be essential in the case of azabicycles.

All the reactions were carried out in anhyd solvents and under argon. All Grignard reagents and copper salts were purchased from commercially available sources and used as received. CuTC was prepared according to the literature procedure.²⁸ Flash column chromatography was performed using silica gel Merk-60 (230–400 mesh). ¹H NMR spectra were acquired at 200 or 300 MHz and ¹³C NMR were acquired at 50 or 75 MHz (indicated in each case). Chemical shifts (δ) are reported in ppm relative to CDCl₃ (7.26 and 77.0 ppm). For fluoro-containing compounds, the observed list of peaks is given as ¹³C NMR data. The coupling constants $J_{C,F}$ have not been determined. Mass spectra were determined at an ionizing voltage of 70 eV. The known azabicyclic substrates **13** and **16** were prepared according to literature procedures.^{2d}

Copper-Catalyzed Ring Opening of Oxabicyclic Alkenes with Grignard Reagents; $(1S^*, 2R^*)$ -2-Methyl-1,2-dihydronaphth-1-ol (*anti*-2a);¹⁶ Typical Procedure

To a solution of CuCl (2.0 mg, 0.02 mmol), Ph₃P (6.0 mg, 0.02 mmol) and **1a** (28.8 mg, 0.20 mmol), in anhyd toluene (2 mL) at r.t., was slowly added a 3 M solution of MeMgBr in Et₂O (100 μ L, 0.30 mmol). The mixture was stirred at r.t. for 6 h (TLC monitoring). Then, sat. aq NH₄Cl solution (2 mL) was added, the organic layer was separated and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 4:1) to afford **2a** (29.5 mg, 92%) as a white solid; mp 63–64 °C (Lit.¹⁶ mp 63–64 °C).

¹H NMR (300 MHz): δ = 7.41 (dd, *J* = 6.5, 2.4 Hz, 1 H), 7.31–7.22 (m, 2 H), 7.11 (dd, *J* = 6.5, 2.4 Hz, 1 H), 6.47 (d, *J* = 9.3 Hz, 1 H), 5.94 (dd, *J* = 9.3, 4.4 Hz, 1 H), 4.47 (t, *J* = 6.5 Hz, 1 H), 2.70–2.59 (m, 1 H), 1.74 (d, *J* = 6.9 Hz, 1 H), 1.07 (d, *J* = 7.3 Hz, 3 H).

(1S*,2R*)-2-Ethyl-1,2-dihydronaphth-1-ol (anti-2b)²⁶

Chromatography: *n*-hexane–EtOAc (4:1); yield: 26.5 mg (76%); white solid; mp 34–35 °C (Lit.¹⁶ mp 34–35 °C).

¹H NMR (300 MHz): δ = 7.37 (dd, *J* = 6.9, 2.0 Hz, 1 H), 7.29–7.19 (m, 2 H), 7.11 (dd, *J* = 6.9, 2.0 Hz, 1 H), 6.51 (d, *J* = 9.7 Hz, 1 H), 6.02 (dd, *J* = 9.7, 4.5 Hz, 1 H), 4.56 (d, *J* = 4.5 Hz, 1 H), 2.54–2.46 (m, 1 H), 1.70 (br s, 1 H), 1.55–1.25 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

(1S*,2R*)-2-(Isobutyl)-1,2-dihydronaphth-1-ol (anti-2c)

Chromatography: *n*-hexane–EtOAc (4:1); yield: 36.0 mg (89%); white solid; mp 84–85 °C.

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¹H NMR (200 MHz): δ = 7.36–7.19 (m, 3 H), 7.12 (dd, J = 7.0, 2.1 Hz, 1 H), 6.51 (d, J = 9.7 Hz, 1 H), 6.03 (dd, J = 9.7, 4.8 Hz, 1 H), 4.47 (t, J = 4.5 Hz, 1 H), 2.74–2.62 (m, 1 H), 1.82–1.63 (m, 2 H), 1.21–1.13 (m, 2 H), 0.93 (d, J = 4.8 Hz, 3 H), 0.90 (d, J = 4.8 Hz, 3 H).

¹³C NMR (50 MHz): δ = 135.5, 132.3, 131.0, 128.6, 128.2, 127.6, 126.5, 125.7, 72.7, 40.7, 40.2, 25.5, 23.3, 22.1.

(1S*,2R*)-2-Decyl-1,2-dihydronaphth-1-ol (anti-2d)

Chromatography: *n*-hexane–EtOAc (6:1); yield: 37.8 mg (66%); white solid; mp 49–50 °C.

¹H NMR (300 MHz): δ = 7.35 (dd, *J* = 6.9, 2.0 Hz, 1 H), 7.30–7.20 (m, 2 H), 7.11 (dd, *J* = 6.9, 2.0 Hz, 1 H), 6.50 (d, *J* = 9.7 Hz, 1 H), 6.02 (dd, *J* = 9.7, 4.8 Hz, 1 H), 4.53 (t, *J* = 4.8 Hz, 1 H), 2.60–2.51 (m, 1 H), 1.77 (d, *J* = 6.9 Hz, 1 H), 1.41–1.25 (m, 18 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

¹³C NMR (75 MHz): δ = 135.7, 132.4, 131.1, 128.5, 127.9, 127.6, 126.5, 125.8, 72.5, 42.5, 31.8, 31.6, 29.8, 29.6 (2C), 29.5, 29.3, 27.1, 22.7, 14.1.

MS (EI): *m/z* (%) = 286 (19, [M⁺]), 268 (49), 257 (27), 145 (90), 142 (75), 141 (100), 128 (21).

HRMS (EI): m/z calcd for $C_{20}H_{30}O$ (M⁺): 286.2297; found: 286.2284.

(1S*,2R*)-2-Cyclohexyl-1,2-dihydronaphth-1-ol (anti-2e)

Chromatography: *n*-hexane–EtOAc (4:1); yield: 29.2 mg (64%); white solid; mp 81–82 °C.

¹H NMR (300 MHz): δ = 7.34 (dd, *J* = 6.9, 2.0 Hz, 1 H), 7.30–7.20 (m, 2 H), 7.11 (dd, *J* = 6.9, 2.0 Hz, 1 H), 6.55 (d, *J* = 10.0 Hz, 1 H), 5.99 (dd, *J* = 10.0, 4.8 Hz, 1 H), 4.69 (dd, *J* = 6.9, 4.7 Hz, 1 H), 2.48–2.43 (m, 1 H), 1.71–1.57 (m, 7 H), 1.46–1.38 (m, 1 H), 1.18–1.01 (m, 4 H).

¹³C NMR (75 MHz): δ = 136.3, 132.5, 129.3, 128.5, 127.7, 127.6, 126.5, 126.4, 70.4, 48.4, 40.0, 30.8, 29.9, 26.5, 26.4.

MS (EI): m/z (%) = 228 (26, [M⁺]), 210 (48), 145 (93), 128 (100), 115 (34).

HRMS (EI): m/z calcd for $C_{16}H_{20}O$ (M⁺): 228.1514; found: 228.1507.

(1S*,2R*)-2-Benzyl-1,2-dihydronaphth-1-ol (anti-2f)

Chromatography: *n*-hexane–EtOAc (4:1); yield: 20.0 mg (47% in converted product, 10% of starting material was recovered); white solid; mp 115–116 $^{\circ}$ C.

¹H NMR (200 MHz): δ = 7.39–7.14 (m, 9 H), 6.54 (d, J = 9.7 Hz, 1 H), 5.94 (dd, J = 9.7, 4.8 Hz, 1 H), 4.54 (br s, 1 H), 2.98–2.84 (m, 1 H), 2.66–2.62 (m, 2 H), 1.94 (br s, 1 H).

¹³C NMR (50 MHz): δ = 139.4, 135.2, 132.2, 130.2, 129.1, 128.6, 128.3, 127.9, 127.8, 126.6, 126.3, 126.2, 71.5, 44.0, 37.6.

MS (EI): m/z (%) = 236 (3, [M⁺]), 218 (22), 145 (100), 127 (39), 115 (29), 91 (41).

HRMS (EI): m/z calcd for $C_{17}H_{16}O$ (M⁺): 236.1201; found: 236.1191.

(1*S**,2*S**)-2-Phenyl-1,2-dihydronaphth-1-ol (*anti*-2g)

Chromatography: *n*-hexane–EtOAc (6:1); yield: 40.0 mg (90%); white solid; mp 86-87 °C.

¹H NMR (300 MHz): δ = 7.42 (dd, *J* = 7.3, 2.4 Hz, 1 H), 7.34–7.24 (m, 7 H), 7.18 (dd, *J* = 7.3, 2.4 Hz, 1 H), 6.67 (dd, *J* = 9.7, 2.0 Hz, 1 H), 6.04 (dd, *J* = 9.7, 3.6 Hz, 1 H), 4.84 (dd, *J* = 7.7, 5.3 Hz, 1 H), 3.83–3.79 (m, 1 H), 1.96 (d, *J* = 5.3 Hz, 1 H).

¹³C NMR (75 MHz): δ = 140.8, 135.6, 132.6, 129.8, 128.8 (2 C), 128.4, 128.2, 128.1, 127.6, 127.2, 126.4, 74.3, 50.1.

MS (EI): m/z (%) = 222 (76, [M⁺]), 204 (65), 131 (75), 118 (100), 115 (33).

HRMS (EI): m/z calcd for $C_{16}H_{14}O$ (M⁺): 222.1045; found: 222.1038.

$(1S^*, 2S^*)$ -2-(4-Methoxyphenyl)-1,2-dihydronaphth-1-ol (*anti*-2h)

Chromatography: CH₂Cl₂; yield: 39.4 mg (92% in converted product, 15% of starting material was recovered); white solid; mp 73–74 $^\circ\text{C}.$

¹H NMR (300 MHz): δ = 7.42–7.39 (m, 1 H), 7.32–7.23 (m, 2 H), 7.19–7.14 (m, 3 H), 6.86–6.83 (m, 2 H), 6.65 (dd, *J* = 9.5, 2.0 Hz, 1 H), 6.02 (dd, *J* = 9.5, 3.8 Hz, 1 H), 4.78 (dd, *J* = 7.7, 5.2 Hz, 1 H), 3.79 (s, 3 H), 3.78–3.73 (m, 1 H), 1.98 (d, *J* = 5.5 Hz, 1 H).

¹³C NMR (75 MHz): δ = 158.7, 135.6, 132.6 (2 C), 130.1, 129.3, 128.2, 128.0, 127.4, 126.4, 114.1, 74.4, 55.2, 49.2.

MS (EI): m/z (%) = 252 (69, [M⁺]), 234 (56), 131 (62), 121 (60), 118 (100).

HRMS (EI): m/z calcd for $C_{17}H_{16}O_2$ (M⁺): 252.1150; found: 252.1138.

(1S*,2S*)-2-(4-Fluorophenyl)-1,2-dihydronaphth-1-ol (*anti-2i*) Chromatography: *n*-hexane–EtOAc (6:1); yield: 45.2 mg (94%); white solid; mp 125–126 °C.

¹H NMR (300 MHz): δ = 7.40–7.17 (m, 6 H), 7.02–6.94 (m, 2 H), 6.68 (dd, *J* = 9.7, 2.0 Hz, 1 H), 6.01 (dd, *J* = 9.7, 4.0 Hz, 1 H), 4.77 (dd, *J* = 6.8, 6.1 Hz, 1 H), 3.81–3.77 (m, 1 H), 2.00 (d, *J* = 6.1 Hz, 1 H).

¹³C NMR (75 MHz): δ = 164.6, 161.3, 136.3, 135.3, 132.4, 129.8, 129.7, 129.5, 128.4, 128.1, 127.7, 126.6, 126.5, 115.6, 115.3, 74.3, 49.2.

MS (EI): *m*/*z* (%) = 240 (54, [M⁺]), 222 (35), 131 (73), 118 (100), 90 (28).

HRMS (EI): m/z calcd for $C_{16}H_{13}FO$ (M⁺): 240.0950; found: 240.0939.

$(1S^*, 2R^*)$ -6,7-Difluoro-2-methyl-1,2-dihydronaphth-1-ol (*anti*-5a)

Chromatography: *n*-hexane–EtOAc (4:1); yield: 30.2 mg (77%); white solid; mp 110–111 $^{\circ}$ C.

¹H NMR (300 MHz): δ = 7.29–7.23 (m, 1 H), 6.90 (dd, *J* = 10.7, 7.7 Hz, 1 H), 6.35 (dd, *J* = 9.5, 1.6 Hz, 1 H), 5.92 (dd, *J* = 9.5, 4.0 Hz, 1 H), 4.41 (t, *J* = 7.1 Hz, 1 H), 2.63–2.54 (m, 1 H), 1.83 (d, *J* = 6.9 Hz, 1 H), 1.09 (d, *J* = 7.3 Hz, 3 H).

¹³C NMR (75 MHz): δ = 151.0, 150.9, 148.2, 147.8, 147.6, 133.1, 133.0, 129.4 (2 C), 129.3 (2 C), 124.3, 116.2, 116.0, 115.0, 114.8, 73.4, 37.2, 16.9.

 $\mathrm{MS}\;(\mathrm{EI}){:}\;m/z\;(\%)=196\;(55,\,[\mathrm{M}^+]),\,181\;(86),\,167\;(100),\,151\;(43).$

HRMS (EI): m/z calcd for $C_{11}H_{10}F_2O$ (M⁺): 196.0700; found: 196.0695.

$(1S^{*},\!2S^{*})$ -6,7-Difluoro-2-(4-fluorophenyl)-1,2-dihydronaphth-1-ol $(anti-5{\rm i})$

Chromatography: *n*-hexane–EtOAc (4:1); yield: 50.3 mg (91%); white solid; mp 117–118 $^{\circ}$ C.

¹H NMR (300 MHz): δ = 7.31–7.20 (m, 3 H), 7.06–6.94 (m, 3 H), 6.55 (dd, *J* = 9.7, 2.2 Hz, 1 H), 6.01 (dd, *J* = 9.7, 3.6 Hz, 1 H), 4.73 (dd, *J* = 8.7, 4.8 Hz, 1 H), 3.76–3.72 (m, 1 H), 1.92 (d, *J* = 5.5 Hz, 1 H).

¹³C NMR (75 MHz): δ = 163.7, 160.5, 151.6, 151.5, 151.3, 148.4, 148.2, 148.1, 148.0, 136.1, 136.0, 132.6, 132.5, 132.4, 130.5, 129.9,

129.8, 129.4, 129.3, 129.2, 126.2, 115.9, 115.7, 115.6, 115.5, 115.1, 114.9, 73.7, 49.0.

MS (EI): m/z (%) = 276 (64, [M⁺]), 167 (88), 154 (100), 109 (48).

HRMS (EI): m/z calcd for $C_{16}H_{11}F_3O$ (M⁺): 276.0762; found: 276.0755.

(1*S**,2*R**)-5,8-Dimethoxy-2-methyl-1,2-dihydronaphth-1-ol (*anti*-6a)

Chromatography: *n*-hexane–EtOAc (4:1); yield: 33.0 mg (75%); white solid; mp 63–64 °C.

¹H NMR (300 MHz): δ = 6.84 (d, J = 10.1 Hz, 1 H), 6.78 (part A of AB system, $J_{A,B}$ = 8.9 Hz, 1 H), 6.76 (part B of AB system, $J_{A,B}$ = 8.9 Hz, 1 H), 6.04 (dd, J = 10.1, 5.3 Hz, 1 H), 4.91 (br s, 1 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 2.76–2.66 (m, 1 H), 2.18 (d, J = 5.2 Hz, 1 H), 0.94 (d, J = 7.7 Hz, 3 H).

¹³C NMR (75 MHz): δ = 151.6, 149.4, 131.7, 123.4, 122.0, 118.5, 111.0, 110.2, 66.7, 56.0, 36.2, 17.1.

MS (EI): m/z (%) = 220 (9, [M⁺]), 202 (63), 187 (100), 157 (18), 115 (17).

HRMS (EI): m/z calcd for $C_{13}H_{16}O_3$ (M⁺): 220.1099; found: 220.1097.

(1*S**,2*S**)-2-(4-Fluorophenyl)-5,8-dimethoxy-1,2-dihydronaphth-1-ol (*anti*-6i)

Chromatography: *n*-hexane–EtOAc (4:1); yield: 51.6 mg (86%); colorless oil.

¹H NMR (300 MHz): δ = 7.14–7.08 (m, 3 H), 6.92–6.86 (m, 2 H), 6.80 (part A of AB system, $J_{A,B}$ = 8.9 Hz, 1 H), 6.74 (part B of AB system, $J_{A,B}$ = 8.9 Hz, 1 H), 6.10 (dd, J = 10.9, 5.2 Hz, 1 H), 5.12 (br s, 1 H), 3.89 (d, J = 4.8 Hz, 1 H), 3.84 (s, 3 H), 3.73 (s, 3 H), 2.45 (d, J = 4.4 Hz, 1 H).

¹³C NMR (75 MHz): δ = 163.3, 160.1, 151.2, 149.5, 135.5, 135.4, 129.5, 129.3, 127.9, 122.9, 122.2, 120.6, 115.3, 115.1, 111.3, 110.6, 67.4, 56.1, 55.9, 47.2.

MS (EI): m/z = 300 (30, [M⁺]), 282 (93), 267 (100), 224 (31), 178 (31).

HRMS (EI): m/z calcd for $C_{18}H_{17}FO_3$ (M⁺): 300.1162; found: 300.1154.

(1*S**,2*R**)-2-Methyl-6,7-methylenedioxy-1,2-dihydronaphth-1-ol (*anti*-7a)

Chromatography: *n*-hexane–EtOAc (4:1); yield: 23.3 mg (57%); white solid; mp 124–125 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 6.91$ (s, 1 H), 6.61 (s, 1 H), 6.33 (dd, J = 9.7, 1.2 Hz, 1 H), 5.94 (s, 2 H), 5.84 (dd, J = 9.7, 4.4 Hz, 1 H), 4.36 (t, J = 6.5 Hz, 1 H), 2.64–2.53 (m, 1 H), 1.75 (d, J = 6.9 Hz, 1 H), 1.03 (d, J = 7.3 Hz, 3 H).

¹³C NMR (75 MHz): δ = 147.3, 146.7, 130.4, 129.6, 126.7, 125.3, 108.5, 107.0, 100.9, 74.2, 37.4, 16.8.

MS (EI): $m/z = 186 (100, [M^+ - H_2O]), 149 (23), 128 (39), 83 (40).$

(1*S**,2*S**)-2-(4-Fluorophenyl)-6,7-methylenedioxy-1,2-dihydronaphth-1-ol (*anti*-7i)

Chromatography: *n*-hexane–EtOAc (4:1); yield: 46.6 mg (82%); white solid; mp 133–134 $^{\circ}$ C.

¹H NMR (300 MHz): δ = 7.20–7.15 (m, 2 H), 7.00–6.94 (m, 2 H), 6.87 (s, 1 H), 6.68 (s, 1 H), 6.55 (dd, *J* = 9.7, 2.0 Hz, 1 H), 5.96–5.90 (m, 3 H), 4.63 (t, *J* = 6.5 Hz, 1 H), 3.77–3.73 (m, 1 H), 1.93 (d, *J* = 6.1 Hz, 1 H).

¹³C NMR (75 MHz): δ = 163.6, 160.3, 147.2, 136.0, 129.8, 129.7, 129.3, 127.5, 127.3, 126.7, 115.6, 115.3, 108.1, 107.1, 101.1, 74.4, 49.0.

MS (IE): m/z (%) = 284 (3, [M⁺]), 266 (100), 207 (45), 103 (11).

HRMS (IE): m/z calcd for $C_{17}H_{13}FO_3$ (M⁺): 284.0849; found: 284.0849.

$(1S^{*},\!2R^{*},\!5R^{*},\!6S^{*})\!\cdot\!5,\!6\text{-Bis}(methoxymethyl)\!\cdot\!2\text{-methylcyclohex-}3\text{-en-1-ol}\ (anti-9a)^{21}$

Chromatography: *n*-hexane– Et_2O (1:3); yield: 29.6 mg (74%); colorless oil.

¹H NMR (300 MHz): $\delta = 5.60$ (dt, J = 10.1, 2.6 Hz, 1 H), 5.43 (ddd, J = 10.1, 3.0, 2.0 Hz, 1 H), 4.10 (d, J = 9.9 Hz, 1 H), 3.56 (dd, J = 9.3, 8.0 Hz, 1 H), 3.52 (dd, J = 9.3, 7.2 Hz, 1 H), 3.50–3.41 (m, 1 H), 3.34 (s, 3 H), 3.33 (s, 4 H), 3.32 (s, 1 H), 2.61–2.54 (m, 1 H), 2.43 (dq, J = 7.3, 2.6 Hz, 1 H), 2.29–2.20 (m, 1 H), 1.04 (d, J = 7.1 Hz, 3 H).

(1*S**,2*R**,5*R**,6*S**)-5,6-Bis(methoxymethyl)-2-ethylcyclohex-3en-1-ol (*anti*-9b)

Chromatography: *n*-hexane–Et₂O (1:3); yield: 26.1 mg (61%); colorless oil.

¹H NMR (300 MHz): δ = 5.72 (dt, J = 10.1, 3.4 Hz, 1 H), 5.51 (ddd, J = 10.1, 3.0, 1.8 Hz, 1 H), 4.13 (d, J = 9.7 Hz, 1 H), 3.71–3.43 (m, 4 H), 3.36 (s, 3 H), 3.35 (s, 3 H), 2.61–2.54 (m, 1 H), 2.43 (dq, J = 7.5, 2.8 Hz, 1 H), 2.11–2.03 (m, 1 H), 1.63–1.49 (m, 1 H), 1.42–1.24 (m, 1 H), 0.96 (t, J = 7.5 Hz, 3 H).

¹³C NMR (75 MHz): δ = 130.5, 126.2, 72.4, 72.2, 71.2, 59.0, 58.9, 44.3, 38.1, 37.5, 26.2, 11.4.

MS (EI): *m*/*z* (%) = 182 (9, [M⁺ – CH₄O]), 137 (22), 126 (40), 106 (56), 97 (82), 79 (100).

HRMS (EI): m/z calcd for $C_{11}H_{18}O_2$ (M⁺ – CH₄O): 182.1307; found: 182.1295.

(1*S**,2*R**,5*R**,6*S**)-5,6-Bis(methoxymethyl)-2-(isobutyl)cyclohex-3-en-1-ol (*anti*-9c)

Chromatography: n-hexane–Et₂O (1:3); yield: 37.3 mg (77%); colorless oil.

¹H NMR (300 MHz): δ = 5.75 (ddd, *J* = 10.1, 3.4, 2.4 Hz, 1 H), 5.54 (ddd, *J* = 10.1, 3.6, 1.8 Hz, 1 H), 4.30 (d, *J* = 10.1 Hz, 1 H), 3.61–3.50 (m, 3 H), 3.39 (d, *J* = 3.8 Hz, 2 H), 3.37 (s, 3 H), 3.36 (s, 3 H), 2.57–2.52 (m, 1 H), 2.42 (dq, *J* = 7.5, 2.8 Hz, 1 H), 2.28–2.19 (m, 1 H), 1.80–1.23 (m, 1 H), 1.35–1.23 (m, 1 H), 1.19–1.09 (m, 1 H), 0.92 (s, 3 H), 0.90 (s, 3 H).

¹³C NMR (75 MHz): δ = 130.8, 126.1, 72.8, 71.8, 71.1, 59.0, 58.9, 43.6, 41.0, 37.7, 37.0, 25.2, 23.2, 22.4.

MS (EI): m/z (%) = 210 (18, [M⁺ – CH₄O]), 154 (58), 147 (61), 91 (81), 57 (100).

HRMS (EI): m/z calcd for $C_{13}H_{22}O_2$ (M⁺ – CH₄O): 210.1620; found: 210.1614.

(1*S**,2*R**,5*R**,6*S**)-5,6-Bis(methoxymethyl)-2-decylcyclohex-3en-1-ol (*anti*-9d)

Chromatography: *n*-hexane– Et_2O (1:3); yield: 50.9 mg (78%); colorless oil.

¹H NMR (300 MHz): δ = 5.74–5.68 (m, 1 H), 5.49 (ddd, *J* = 10.1, 3.4, 2.4 Hz, 1 H), 5.54 (ddd, *J* = 10.1, 2.9, 1.8 Hz, 1 H), 4.16 (d, *J* = 10.1 Hz, 1 H), 3.62–3.46 (m, 4 H), 3.36 (s, 3 H), 3.35 (s, 3 H), 2.57–2.54 (m, 1 H), 2.41 (dq, *J* = 7.5, 2.6 Hz, 1 H), 2.15–2.08 (m, 1 H), 1.57–1.24 (m, 18 H), 0.86 (t, *J* = 6.5 Hz, 3 H).

¹³C NMR (75 MHz): δ = 130.8, 126.0, 72.5, 72.1, 71.3, 63.0, 59.0, 42.8, 38.0, 37.3, 33.7, 32.8, 31.9, 30.0, 29.6, 29.4, 27.0, 25.7, 22.6, 14.0.

MS (EI): *m/z* (%) = 326 (2, [M⁺]), 294 (17), 238 (39), 105 (71), 97 (100), 91 (92).

HRMS (EI): m/z calcd for $C_{20}H_{38}O_3$ (M⁺): 326.2821; found: 326.2818.

(1*S**,2*R**,5*R**,6*S**)-5,6-Bis(methoxymethyl)-2-cyclohexylcyclohex-3-en-1-ol (*anti-*9e)

Chromatography: *n*-hexane– Et_2O (1:3); yield: 22.5 mg (42%); colorless oil.

¹H NMR (300 MHz): $\delta = 5.69$ (dt, J = 10.3, 2.8 Hz, 1 H), 5.51 (dt, J = 10.3, 2.4 Hz, 1 H), 4.02 (d, J = 10.3 Hz, 1 H), 3.78–3.72 (m, 1 H), 3.64–3.50 (m, 2 H), 3.36 (s, 3 H), 3.35 (s, 3 H), 3.34 (d, J = 5.3 Hz, 1 H), 2.61–2.54 (m, 1 H), 2.42 (dq, J = 6.7, 3.0 Hz, 1 H), 2.04–1.98 (m, 1 H), 1.76–1.61 (m, 5 H), 1.54–1.48 (m, 1 H), 1.31–1.08 (m, 5 H).

$(1R^*, 2S^*, 5R^*, 6S^*)$ -5,6-Bis(methoxymethyl)-2-phenylcyclohex-3-en-1-ol (*anti*-9g)²¹

Chromatography: n-hexane–Et₂O (1:3); yield: 41.5 mg (79%); colorless oil.

¹H NMR (300 MHz): δ = 7.27–7.19 (m, 5 H), 5.90–5.85 (m, 1 H), 5.84–5.78 (m, 1 H), 4.46 (d, *J* = 9.7 Hz, 1 H), 3.77–3.72 (m, 1 H), 3.58–3.48 (m, 3 H), 3.46 (d, *J* = 5.9 Hz, 2 H), 3.42 (s, 3 H), 3.31 (s, 3 H), 2.72–2.66 (m, 1 H), 2.47–2.39 (m, 1 H).

(1S*,2R*)-2-Ethyl-4-methyl-1,2-dihydro-1-naphthol (12b)

Chromatography: *n*-hexane–EtOAc (6:1); yield: 37.6 mg (70%); white solid; mp 51-52 °C.

¹H NMR (300 MHz): δ = 7.34–7.15 (m, 5 H), 5.74 (d, J = 4.1 Hz, 1 H), 4.43 (d, J = 5.4 Hz, 1 H), 2.37–2.33 (m, 1 H), 2.03 (s, 3 H), 1.71 (br s, 1 H), 1.47–1.18 (m, 2 H), 0.89 (t, J = 7.5 Hz, 3 H).

N-(2'-Thiophenesulfonyl)pyrrole

To a solution of NaH (0.7 g, 17.5 mmol) in DMF (7 mL) at 0 °C was added a solution of pyrrole (1.0 mL, 14.3 mmol) in DMF (5 mL). The resulting suspension was stirred for 15 min at 0 °C and a solution of 2-thiophenesulfonyl chloride (3.1 g, 17.2 mmol) in DMF (4 mL) was added. The mixture was allowed to warm to r.t. and stirred at r.t. for 2 h; then brine (10 mL) was added. The aqueous layer was extracted with Et₂O (2 ×) and the combined organic phases were washed several times with H₂O, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (*n*-hexane–EtOAc 10:1) to afford the product as a white solid; yield: 2.6 g (85%); mp 101–102 °C.

¹H NMR (300 MHz): δ = 7.66 (dd, *J* = 3.8, 1.2 Hz, 1 H), 7.63 (dd, *J* = 5.0, 1.4 Hz, 1 H), 7.19–7.17 (m, 2 H), 7.06 (dd, *J* = 5.0, 3.8 Hz, 1 H), 6.32–6.31 (m, 2 H).

¹³C NMR (75 MHz): δ = 133.8, 133.4, 127.5, 120.7, 113.9.

 $\mathrm{MS}\;(\mathrm{EI}){:}\;m/z\;(\%)=213\;(60,\,[\mathrm{M}^+]),\,147\;(100),\,99\;(31),\,57\;(34).$

N-(2'-Pyridylsulfonyl)pyrrole

To a suspension of NaH (0.7 g, 17.5 mmol) in DMF (7 mL) at 0 °C was added a solution of pyrrole (1.0 mL, 14.3 mmol) in DMF (5 mL). The mixture was stirred for 15 min at 0 °C and treated with a solution of 2-pyridylsulfonyl chloride⁴⁵ (3.0 g, 17.2 mmol) in DMF (4 mL). The mixture was allowed to warm to r.t. and stirred at r.t. for 2 h; then brine (10 mL) was added. The aqueous layer was extracted with Et₂O (2 ×) and the combined organic layers were washed several times with H₂O, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (*n*-hexane–CH₂Cl₂, 1:1) to afford the product as a white solid; yield: 2.5 g (84%); mp 106–107 °C.

¹H NMR (300 MHz): $\delta = 8.66$ (d, J = 4.6 Hz, 1 H), 8.03 (dd, J = 7.9, 0.8 Hz, 1 H), 7.91 (td, J = 7.9, 1.8 Hz, 1 H), 7.50 (ddd, J = 7.7, 4.8, 1.2 Hz, 1 H), 7.23 (t, J = 2.2 Hz, 2 H), 6.31 (t, J = 2.4 Hz, 2 H).

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¹³C NMR (75 MHz): δ = 156.0, 150.4, 138.2, 127.5, 121.9, 121.5, 113.6.

MS (EI): m/z (%) = 208 (25, [M⁺]), 144 (13), 117 (83), 78 (100).

Diels–Alder Reaction between Benzyne and *N*-Sulfonylpyrrole Derivatives; *N*-(2'-Thiophenesulfonyl)-2,3-benzo-7-azabicyclo[2.2.1]hepta-2,5-diene (15); Typical Procedure

To a solution of *N*-(2'-thiophenesulfonyl)pyrrole (3.8 g, 17.8 mmol) in DME (7 mL) at 50 °C in a three-neck flask fitted with a reflux condenser and two addition funnels, was slowly (over 45 min) simultaneously and separately added a solution of anthranilic acid (2.4 g, 17.8 mmol) in DME (18 mL) and a solution of isoamyl nitrite (2.9 mL, 21.4 mmol) in DME (11 mL). The mixture was stirred at 50 °C for 2 h, and then concentrated. The residue was dissolved in Et₂O and washed with aq sat. K₂CO₃. The aqueous layer was extracted with Et₂O (2 ×) and the combined organic phases were washed with brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 20:1) to afford **15** as a white solid; yield: 3.1 g (60%); mp 179–180 °C.

¹H NMR (300 MHz): δ = 7.45 (dd, *J* = 5.0, 1.2 Hz, 1 H), 7.23 (dd, *J* = 3.8, 1.4 Hz, 1 H), 7.09 (dd, *J* = 5.3, 3.0 Hz, 2 H), 6.89 (dd, *J* = 5.0, 3.6 Hz, 1 H), 6.84 (dd, *J* = 5.0, 3.0 Hz, 2 H), 6.76 (t, *J* = 1.6 Hz, 2 H), 5.48 (t, *J* = 1.4 Hz, 2 H).

¹³C NMR (75 MHz): δ = 146.9, 141.4, 138.5, 133.3, 132.8, 127.7, 125.2, 121.2, 67.9.

N-(2'-Pyridylsulfonyl)-2,3-benzo-7-azabicyclo[2.2.1]hepta-2,5-diene (17)

Chromatography: CH₂Cl₂; yield: 2.6 g (51%); white solid; mp 178–179 $^{\circ}$ C (dec.).

¹H NMR (300 MHz): δ = 8.58 (dt, *J* = 4.8, 1.4 Hz, 1 H), 7.75–7.69 (m, 2 H), 7.39–7.29 (m, 1 H), 7.09 (dd, *J* = 5.3, 3.0 Hz, 2 H), 6.83 (t, *J* = 1.4 Hz, 2 H), 6.80 (dd, *J* = 5.3, 3.0 Hz, 2 H), 5.65 (t, *J* = 1.6 Hz, 2 H).

¹³C NMR (75 MHz): δ = 155.8, 149.9, 147.2, 142.5, 137.5, 126.1, 125.0, 123.4, 121.1, 67.9.

MS (EI): m/z (%) = 284 (5, [M⁺]), 219 (100), 142 (46), 115 (75), 78 (58).

Copper-Catalyzed Ring Opening of Azabicyclic Alkenes with Grignard reagents; (15*,2R*)-2-Methyl-*N*-tosyl-1,2-dihydro-naphthalen-1-amine (*anti*-18a); Typical Procedure

To a solution of CuCN (1.8 mg, 0.02 mmol) and **13** (59.0 mg, 0.20 mmol) in anhyd CH_2Cl_2 (2 mL), was slowly added at r.t., a 3 M solution of MeMgBr in Et₂O (100 µL, 0.30 mmol). The mixture was stirred at r.t. for 24 h (TLC monitoring). Then sat. aq NH₄Cl solution (2 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 4:1) to afford **18a** as a white solid; yield: 6.3 mg (10%); mp 129–130 °C.

¹H NMR (300 MHz): δ = 7.70 (d, *J* = 8.5 Hz, 2 H), 7.28 (d, *J* = 9.1 Hz, 2 H), 7.19 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.04–6.99 (m, 2 H), 6.77 (d, *J* = 7.9 Hz, 1 H), 6.43 (d, *J* = 9.8 Hz, 1 H), 5.92 (dd, *J* = 9.7, 6.3 Hz, 1H), 4.68 (d, *J* = 8.1 Hz, 1 H), 4.20 (dd, *J* = 8.1, 3.6 Hz, 1 H), 2.69–2.62 (m, 1 H), 2.44 (s, 3 H), 0.89 (d, *J* = 7.3 Hz, 3 H).

MS (EI): m/z (%) = 158 (25, [M⁺ – (SO₂Tol)]), 142 (100), 91 (17).

(1*S**,2*R**)-2-Methyl-*N*-[(2'-pyridyl)sulfonyl]-1,2-dihydronaphthalen-1-amine (*anti*-22a)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 53.5 mg (89%); white solid; mp 167–168 $^{\circ}$ C.

¹H NMR (300 MHz): δ = 8.53 (d, *J* = 4.6 Hz, 1 H), 7.94 (d, *J* = 7.9 Hz, 1 H), 7.85 (td, *J* = 7.9, 1.6 Hz, 1 H), 7.41 (ddd, *J* = 7.5, 4.6, 1.2

Hz, 1 H), 7.13 (td, J = 7.5, 1.4 Hz, 1 H), 6.99 (d, J = 6.7 Hz, 1 H), 6.91 (td, J = 7.5, 1.2 Hz, 1 H), 6.84 (d, J = 6.9 Hz, 1 H), 6.44 (d, J = 9.5 Hz, 1 H), 5.95 (dd, J = 9.5, 5.5 Hz, 1 H), 5.31–5.28 (m, 1 H), 4.41–4.37 (m, 1 H), 2.78–2.67 (m, 1 H), 0.91 (d, J = 7.3 Hz, 3 H).

¹³C NMR (75 MHz): δ = 158.3, 149.9, 137.7, 132.1, 131.6, 131.4, 128.6, 128.5, 127.4, 126.4, 126.2, 126.1, 121.6, 57.7, 36.2, 16.7.

MS (EI): m/z (%) = 158 (21, [M⁺ – (SO₂Py)]), 142 (100), 115 (10), 78 (12).

(1*S**,2*R**)-2-Ethyl-*N*-[(2'-pyridyl)sulfonyl]-1,2-dihydronaphthalen-1-amine (*anti*-22b)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 40.9 mg (65%); white solid; mp 117–118 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.52$ (dq, J = 4.6, 1.0 Hz, 1 H), 7.93 (dt, J = 7.9, 1.2 Hz, 1 H), 7.84 (td, J = 7.7, 1.8 Hz, 1 H), 7.40 (ddd, J = 7.5, 4.6, 1.2 Hz, 1 H), 7.12 (td, J = 7.5, 1.6 Hz, 1 H), 6.98 (dd, J = 7.5, 1.2 Hz, 1 H), 6.90 (td, J = 7.5, 1.4 Hz, 1 H), 6.84 (dd, J = 7.5, 1.0 Hz, 1 H), 6.47 (d, J = 9.7 Hz, 1 H), 6.00 (ddd, J = 9.7, 5.9, 1.2 Hz, 1 H), 5.33 (d, J = 9.1 Hz, 1 H), 4.47 (dd, J = 9.3, 3.0 Hz, 1 H), 2.56–2.48 (m, 1 H), 1.25 (pent, J = 7.3 Hz, 2 H), 0.88 (t, J = 7.3 Hz, 3 H).

¹³C NMR (75 MHz): δ = 158.4, 149.8, 137.6, 132.2, 131.6, 130.3, 128.7, 128.5, 127.4, 126.7, 126.4, 126.1, 121.6, 55.8, 42.9, 24.5, 11.6.

MS (EI): m/z (%) = 172 (20, [M⁺ – (SO₂Py)]), 156 (100), 141 (35).

$(1S^{*},\!2R^{*})$ -2-Decyl-N-[(2'-pyridyl)sulfonyl]-1,2-dihydronaphthalen-1-amine $(anti-22{\rm d})$

Chromatography: *n*-hexane–EtOAc (4:1); yield: 63.1 mg (74%); colorless oil.

¹H NMR (300 MHz): $\delta = 8.51$ (dq, J = 4.6, 0.8 Hz, 1 H), 7.93 (dt, J = 7.9, 1.0 Hz, 1 H), 7.83 (td, J = 7.7, 1.8 Hz, 1 H), 7.39 (ddd, J = 7.5, 4.6, 1.2 Hz, 1 H), 7.12 (td, J = 7.3, 1.4 Hz, 1 H), 6.97 (d, J = 7.5 Hz, 1 H), 6.90 (td, J = 7.5, 1.4 Hz, 1 H), 6.84 (dd, J = 7.5, 1.4 Hz, 1 H), 6.46 (d, J = 9.7 Hz, 1 H), 5.99 (ddd, J = 9.7, 5.9, 1.0 Hz, 1 H), 5.35 (d, J = 8.7 Hz, 1 H), 4.44 (d, J = 10.1 Hz, 1 H), 2.61–2.55 (m, 1 H), 1.32–1.12 (m, 18 H), 0.87 (t, J = 6.9 Hz, 3 H).

 ^{13}C NMR (75 MHz): δ = 158.4, 149.8, 137.6, 132.1, 131.6, 130.6, 128.8, 128.5, 127.4, 126.5, 126.4, 126.1, 121.6, 56.1, 41.2, 31.9, 31.5, 29.6, 29.4, 29.3, 27.2, 22.7, 14.1.

MS (EI): m/z (%) = 284 (35, [M⁺ – (SO₂Py)]), 268 (100), 141 (71), 79 (25).

$(1S^{\ast},\!2R^{\ast})\text{-}2\text{-}Benzyl\text{-}N\text{-}[(2'\text{-}pyridyl)\text{sulfonyl}]\text{-}1,\!2\text{-}dihydronaphtalen\text{-}1\text{-}amine}\ (anti-22f)$

Chromatography: *n*-hexane–EtOAc (2:1); yield: 39.9 mg (53%); white solid; mp 112–113 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.51$ (dq, J = 4.6, 0.8 Hz, 1 H), 7.80–7.71 (m, 2 H), 7.39 (ddd, J = 6.5, 4.6, 1.8 Hz, 1 H), 7.29–7.16 (m, 4 H), 7.06–6.97 (m, 4 H), 6.86 (dd, J = 7.5, 0.6 Hz, 1 H), 6.53 (d, J = 9.7 Hz, 1 H), 5.90 (ddd, J = 9.7, 5.9, 1.2 Hz, 1 H), 5.36 (d, J = 8.3 Hz, 1 H), 4.34 (d, J = 8.3 Hz, 1 H), 2.93–2.85 (m, 1 H), 2.53 (dd, J = 13.3, 7.5 Hz, 1 H), 2.38 (dd, J = 13.5, 8.5 Hz, 1 H).

 ^{13}C NMR (75 MHz): δ = 157.9, 149.8, 138.8, 137.6, 132.0, 131.1, 129.8, 129.0, 128.9, 128.7, 128.4, 127.7, 127.0, 126.6, 126.3, 126.1, 121.9, 55.0, 42.5, 37.3.

MS (EI): m/z (%) = 234 (4, [M⁺ – (SO₂Py)]), 218 (100), 143 (27), 78 (21).

(1*S**,2*S**)-2-Phenyl-*N*-[(2'-pyridyl)sulfonyl]-1,2-dihydronaph-thalen-1-amine (*anti*-22g)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 67.4 mg (93%); white solid; mp 136–137 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.58-8.56$ (m, 1 H), 7.96–7.93 (m, 1 H), 7.85 (td, J = 7.7, 1.6 Hz, 1 H), 7.43 (ddd, J = 7.7, 4.8, 1.2 Hz, 1 H), 7.19–7.04 (m, 7 H), 6.95 (td, J = 7.5, 1.4 Hz, 1 H), 6.78–6.73 (m, 2 H), 6.04 (ddd, J = 9.5, 5.5, 0.8 Hz, 1 H), 5.41 (d, J = 7.9 Hz, 1 H), 4.69 (dd, J = 8.3, 2.6 Hz, 1 H), 4.01 (dd, J = 5.7, 2.8 Hz, 1 H).

¹³C NMR (75 MHz): δ = 158.2, 149.9, 138.6, 137.8, 132.6, 131.2, 128.8, 128.7, 128.5, 128.3, 128.0, 127.9, 127.1, 126.5, 126.3, 121.7, 58.4, 47.7.

MS (EI): *m/z* (%) = 220 (50, [M⁺ – (SO₂Py)]), 204 (100), 115 (12), 91 (13), 78 (13).

(1*S**,2*S**)-2-(4-Methoxyphenyl)-*N*-[(2'-pyridyl)sulfonyl]-1,2-dihydronaphthalen-1-amine (*anti*-22h)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 76.9 mg (98%); white solid; mp 160–161 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.56$ (dq, J = 4.6, 1.0 Hz, 1 H), 7.93 (dt, J = 7.9, 1.0 Hz, 1 H), 7.84 (td, J = 7.7, 1.6 Hz, 1 H), 7.43 (ddd, J = 7.5, 4.6, 1.2 Hz, 1 H), 7.18 (td, J = 7.5, 1.2 Hz, 1 H), 7.10 (dd, J = 7.5, 1.4 Hz, 1 H), 6.98–6.92 (m, 3 H), 6.77 (dd, J = 7.5, 0.6 Hz, 1 H), 6.72 (d, J = 9.5 Hz, 1 H), 6.68–6.64 (m, 2 H), 6.03 (ddd, J = 9.5, 5.4, 1.0 Hz, 1 H), 5.36 (d, J = 8.5 Hz, 1 H), 4.64 (dd, J = 8.1, 2.8 Hz, 1 H), 3.96–3.93 (m, 1 H), 3.70 (s, 3 H).

¹³C NMR (75 MHz): δ = 158.6, 158.2, 149.9, 137.7, 132.6, 131.3, 130.5, 129.0, 128.8, 128.7, 127.9, 127.8, 126.5, 126.3, 121.7, 114.0, 113.9, 58.6, 55.1, 46.9.

MS (EI): m/z (%) = 250 (33, [M⁺ – (SO₂Py)]), 234 (100), 219 (13), 78 (11).

(1*S**,2*S**)-2-(4-Fluorophenyl)-*N*-[(2'-pyridyl)sulfonyl]-1,2-dihydronaphthalen-1-amine (*anti*-22i)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 70.0 mg (92%); white solid; mp 183–184 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.54-8.52$ (m, 1 H), 7.89 (dt, J = 7.9, 1.0 Hz, 1 H), 7.82 (td, J = 7.7, 1.8 Hz, 1 H), 7.41 (ddd, J = 7.5, 4.6, 1.2 Hz, 1 H), 7.17 (td, J = 7.5, 1.4 Hz, 1 H), 7.08 (dd, J = 7.3, 1.2 Hz, 1 H), 7.02–6.97 (m, 2 H), 6.93 (dd, J = 7.5, 1.4 Hz, 1 H), 6.80–6.73 (m, 3 H), 6.70 (d, J = 9.7 Hz, 1 H), 5.99 (ddd, J = 9.5, 4.8, 1.2 Hz, 1 H), 5.34 (d, J = 8.3 Hz, 1 H), 4.62 (dd, J = 8.3, 3.2 Hz, 1 H), 3.99–3.96 (m, 1 H).

¹³C NMR (75 MHz): δ = 161.9 (d, $J_{C,F}$ = 244.0 Hz), 158.2, 149.9, 137.7, 134.3 (d, $J_{C,F}$ = 3.0 Hz), 132.5, 131.1, 129.6 (d, $J_{C,F}$ = 8.4 Hz), 128.9, 128.7, 128.3, 128.2, 128.1, 126.6, 126.4, 121.7, 115.3 (d, $J_{C,F}$ = 20.9 Hz), 58.6, 46.9.

MS (EI): m/z = 238 (52, $[M^+ - (SO_2Py)]$), 222 (100), 109 (13), 78 (15).

$(1S^*,\!2S^*)\text{-}2\text{-}(4\text{-}Methylphenyl)\text{-}N\text{-}[(2'\text{-}pyridyl)\text{sulfonyl}]\text{-}1,\!2\text{-}dihydronaphthalen\text{-}1\text{-}amine}\ (anti-22j)$

Chromatography: *n*-hexane–EtOAc (2:1); yield: 68.5 mg (91%); white solid; mp 183–184 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.57$ (dq, J = 4.8, 1.0 Hz, 1 H), 7.94 (dt, J = 7.9, 1.0 Hz, 1 H), 7.84 (td, J = 7.7, 1.6 Hz, 1 H), 7.43 (ddd, J = 7.5, 4.6, 1.2 Hz, 1 H), 7.18 (td, J = 7.5, 1.4 Hz, 1 H), 7.10 (dd, J = 7.5, 1.4 Hz, 1 H), 6.97–6.91 (m, 5 H), 6.77–6.71 (m, 2 H), 6.03 (ddd, J = 9.5, 5.5, 1.0 Hz, 1 H), 5.30 (d, J = 8.1 Hz, 1 H), 4.65 (dd, J = 8.1, 3.0 Hz, 1 H), 3.96 (ddd, J = 5.5, 2.8, 1.0 Hz, 1 H), 2.22 (s, 3 H).

¹³C NMR (75 MHz): δ = 158.2, 149.9, 137.7, 136.7, 135.4, 132.6, 131.3, 129.2, 128.8, 128.6, 127.9, 127.8, 126.5, 126.3, 121.8, 58.5, 47.3, 20.9.

MS (EI): m/z (%) = 234 (38, [M⁺ – (SO₂Py)]), 218 (100), 202 (11), 78 (13).

(1*S**,2*S**)-2-[3′,5′-Bis(trifluoromethyl)phenyl]-*N*-[(2′-pyrid-yl)sulfonyl]-1,2-dihydronaphthalen-1-amine (*anti*-22k)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 96.7 mg (97%); white solid; mp 218–219 °C.

¹H NMR (300 MHz): $\delta = 8.61$ (d, J = 4.9 Hz, 1 H), 7.98 (d, J = 7.7 Hz, 1 H), 7.90 (td, J = 7.5, 1.6 Hz, 1 H), 7.67 (s, 1 H), 7.57 (s, 2 H), 7.49 (ddd, J = 7.5, 4.6, 1.2 Hz, 1 H), 7.29 (td, J = 7.1, 1.0 Hz, 1 H), 7.21 (d, J = 6.5 Hz, 1 H), 7.09 (dt, J = 7.5, 1.4 Hz, 1 H), 6.93 (d, J = 7.1 Hz, 1 H), 6.88 (d, J = 9.5 Hz, 1 H), 6.04 (dd, J = 9.7, 5.3 Hz, 1 H), 5.51 (d, J = 7.9 Hz, 1 H), 4.75 (dd, J = 7.9, 3.4 Hz, 1 H), 4.22 (t, J = 4.4 Hz, 1 H).

¹³C NMR (75 MHz): δ = 158.1, 150.0, 141.8, 138.0, 132.1, 131.8 (q, $J_{C,F}$ = 33.0 Hz), 130.4, 129.7, 129.4, 128.8, 128.7, 128.4 (m), 126.9, 126.6, 126.4, 124.9, 121.7, 121.3 (m), 58.2, 47.1.

MS (EI): m/z (%) = 356 (46, [M⁺ – (SO₂Py)]), 340 (100), 79 (17).

(1*S**,2*S**)-2-(1'-Naphthyl)-*N*-[(2'-pyridyl)sulfonyl]-1,2-dihydronaphthalen-1-amine (*anti*-22l)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 75.1 mg (91%); white solid; mp 132–133 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.46-8.41$ (m, 2 H), 7.87 (dt, J = 7.7, 1.0 Hz, 1 H), 7.82 (dd, J = 7.8, 1.2 Hz, 1 H), 7.75 (td, J = 7.7, 1.6 Hz, 1 H), 7.64–7.58 (m, 2 H), 7.53–7.48 (m, 1 H), 7.35 (ddd, J = 7.7, 4.6, 1.2 Hz, 1 H), 7.20–7.11 (m, 3 H), 7.05 (dd, J = 7.3, 1.4 Hz, 1 H), 6.89–6.83 (m, 2 H), 6.57 (d, J = 7.3 Hz, 1 H), 6.13 (dd, J = 9.5, 6.5 Hz, 1 H), 5.58 (d, J = 8.1 Hz, 1 H), 4.86–4.81 (m, 2 H).

¹³C NMR (75 MHz): δ = 157.9, 149.8, 137.5, 134.2, 132.8, 132.3, 131.9, 131.5, 129.0, 128.9, 128.7, 128.6, 128.5, 127.9, 127.8, 126.7, 126.5, 126.2, 125.6, 125.3, 125.1, 123.6, 121.7, 57.1, 43.3.

MS (EI): *m/z* (%) = 270 (27, [M⁺ – (SO₂Py)]), 254 (100), 253 (56), 126 (13), 78 (15).

(1*S**,2*S**)-2-(2',4',6'-Trimethylphenyl)-*N*-[(2'-pyridyl)sulfonyl]-1,2-dihydronaphthalen-1-amine (*anti*-22m)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 49.3 mg (87% in converted product, 30% of starting material was recovered); white solid; mp 152–153 °C.

¹H NMR (300 MHz): $\delta = 8.44$ (d, J = 4.2 Hz, 1 H), 7.67 (d, J = 6.1 Hz, 1 H), 7.57 (td, J = 7.9, 1.6 Hz, 1 H), 7.38 (d, J = 7.7 Hz, 1 H), 7.32-7.25 (m, 3 H), 7.11–7.08 (m, 1 H), 6.48–6.44 (m, 3 H), 5.76 (dd, J = 9.7, 2.4 Hz, 1 H), 5.47 (dd, J = 13.7, 9.5 Hz, 1 H), 5.00 (d, J = 9.7 Hz, 1 H), 4.23 (dt, J = 13.9, 2.6 Hz, 1 H), 2.22 (s, 6 H), 2.13 (s, 3 H).

 ^{13}C NMR (75 MHz): δ = 157.7, 149.6, 137.3, 137.2, 137.0, 135.7, 134.1, 133.6, 131.9, 130.0, 128.2, 128.1, 126.8, 126.5, 125.9, 125.4, 120.1, 57.4, 43.2, 21.8, 20.7.

MS (EI): m/z (%) = 262 (61, [M⁺ – (SO₂Py)]), 246 (100), 231 (33), 78 (21).

$(1S^*,2R^*)-N\-[(2'-Pyridyl)sulfonyl]-2-(2'-thienyl)-1,2-dihydronaphthalen-1-amine~(anti-22n)$

Chromatography: *n*-hexane–EtOAc (2:1); yield: 48.6 mg (88% in converted product, 25% of starting material was recovered); white solid; mp 153–154 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.59-8.56$ (m, 1 H), 7.98 (d, J = 6.9 Hz, 1 H), 7.89 (td, J = 7.7, 1.8 Hz, 1 H), 7.44 (ddd, J = 7.7, 4.8, 1.2 Hz, 1 H), 7.20 (td, J = 7.5, 1.2 Hz, 1 H), 7.10 (d, J = 6.3 Hz, 1 H), 7.01–6.95 (m, 2 H), 6.83–6.73 (m, 3 H), 6.67 (d, J = 9.7 Hz, 1 H), 6.11 (ddd, J = 9.5, 5.9, 1.0 Hz, 1 H), 5.46 (d, J = 8.3 Hz, 1 H), 4.75 (dd, J = 8.1, 2.2 Hz, 1 H), 4.26 (dd, J = 5.6, 2.4 Hz, 1 H).

¹³C NMR (75 MHz): δ = 158.1, 149.9, 141.8, 137.8, 132.0, 131.1, 129.0, 128.9, 128.1, 128.0, 127.8, 126.7, 126.6, 126.4, 125.2, 124.2, 121.8, 58.3, 42.4.

MS (EI): m/z (%) = 226 (37, [M⁺ – (SO₂Py)]), 210 (100), 142 (11), 78 (12).

(1*S**,2*R**)-*N*-[(2'-Pyridyl)sulfonyl]-2-[(1'-trimethylsilyl)methyl]-1,2-dihydronaphthalen-1-amine (*anti*-220)

Chromatography: *n*-hexane–EtOAc (2:1); yield: 54.4 mg (73%); white solid; mp 126–127 $^{\circ}$ C.

¹H NMR (300 MHz): $\delta = 8.51-8.49$ (m, 1 H), 7.93 (dt, J = 7.9, 1.0 Hz, 1 H), 7.83 (td, J = 7.7, 1.6 Hz, 1 H), 7.39 (ddd, J = 7.7, 4.6, 1.2 Hz, 1 H), 7.13 (td, J = 7.3, 1.4 Hz, 1 H), 6.99 (d, J = 6.5 Hz, 1 H), 6.91 (td, J = 7.5, 1.4 Hz, 1 H), 6.82 (d, J = 7.3 Hz, 1 H), 6.41 (d, J = 7.7 Hz, 1 H), 5.98 (ddd, J = 9.7, 5.9, 1.0 Hz, 1 H), 5.36 (d, J = 8.5 Hz, 1 H), 4.38 (d, J = 8.5 Hz, 1 H), 2.74–2.66 (m, 1 H), 0.54 (dd, J = 14.3, 5.9 Hz, 1 H), 0.43 (dd, J = 14.3, 9.7 Hz, 1 H), -0.02 (s, 9 H).

¹³C NMR (75 MHz): δ = 158.4, 149.8, 137.6, 132.1, 132.0, 131.4, 129.0, 128.5, 127.3, 126.4, 126.1, 125.6, 121.6, 58.8, 37.6, 19.6, -0.8.

MS (EI): m/z (%) = 230 (27, [M⁺ – (SO₂Py)]), 214 (64), 141 (18), 73 (100).

(15*,25*)-(2-Phenyl-1,2-dihydronaphthalen-1-yl)carbamic Acid *tert*-Butyl Ester (*anti*-14g)

A solution of *anti*-**22g** (70 mg, 0.19 mmol) in a 1:2 mixture of anhyd THF–MeOH (2 mL) was added to Mg powder (46.5 mg, 1.9 mmol) at 0 °C. The mixture was stirred for 2 h, then equal volumes of Et₂O and sat. aq NH₄Cl were added and the resulting mixture was stirred for 2 h. The aqueous layer was extracted with Et₂O (2 × 10 mL) and the combined organic layers were dried (MgSO₄) and concentrated to give the pure amine. Subsequently, the amine was dissolved in CH₂Cl₂ (2 mL) and treated with di-*tert*-butyl carbonate (0.6 mmol). The mixture was stirred at r.t. overnight and concentrated in vacuo. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 5:1) to afford *anti*-**14g** as a white solid; yield: 52 mg (83%); mp 121–122 °C.

¹H NMR (300 MHz): δ = 7.21–7.14 (m, 9 H), 6.71 (d, J = 9.5 Hz, 1 H), 6.06 (dd, J = 9.1, 4.2 Hz, 1 H), 4.91–4.85 (m, 2 H), 3.86 (br s, 1 H), 1.41 (s, 9 H).

¹³C NMR (75 MHz): δ = 155.0, 132.9, 129.5, 128.4, 128.2, 128.1, 127.9, 126.8, 126.4, 79.4, 55.0, 47.5, 28.4.

MS (EI): $m/z = 220 (20, [M^+ - (Boc)]), 204 (100), 57 (33).$

$(1S^*, 2S^*)$ -2-(4-Methoxyphenyl)-1,2-dihydronaphthalen-1-amine (23)

A solution of *anti*-**22h** (140 mg, 0.36 mmol) in a 1:2 mixture of anhyd THF–MeOH (2 mL) was added to Mg powder (87.8 mg, 3.6 mmol) at 0 °C. The mixture was stirred for 2 h, then equal volumes of Et₂O and sat. aq NH₄Cl were added and stirred for 2 h. The aqueous layer was extracted with Et₂O (2 × 10 mL) and the combined organic layers were dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (EtOAc–MeOH, 9:1) to give the pure amine **23** as a colorless oil; yield: 68 mg (86%).

¹H NMR (300 MHz): δ = 7.41–7.38 (m, 1 H), 7.32–7.25 (m, 2 H), 7.22–7.17 (m, 3 H), 6.90–6.85 (m, 2 H), 6.67 (dd, *J* = 9.5, 1.8 Hz, 1 H), 6.05 (dd, *J* = 9.7, 4.0 Hz, 1 H), 4.06 (d, *J* = 7.7 Hz, 1 H), 3.83 (s, 3 H), 3.60–3.55 (m, 1 H), 1.71 (br s, 2 H).

¹³C NMR (75 MHz): δ = 158.5, 138.0, 134.0, 132.5, 130.7, 129.1, 127.9, 127.4, 127.3, 126.3, 126.0, 114.0, 56.4, 55.2, 49.9.

$(1S^{*},\!2S^{*})\text{-}2\text{-}(4\text{-}Methoxyphenyl)\text{-}1,\!2,\!3,\!4\text{-}tetrahydronaphthalen-1-amine}\ (24)^{40}$

A suspension of **23** (50 mg, 0.20 mmol) and 10% Pd/C (21 mg, 0.02 mmol) in anhyd MeOH (2 mL) was stirred at r.t. under a H_2 atmo-

sphere (1 atm) overnight. The mixture was filtered through Celite and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (EtOAc–MeOH, 9:1) to afford **24** as a yellow solid; yield: 45.5 mg (90%); mp 62–63 °C.

¹H NMR (300 MHz): δ = 7.68 (d, *J* = 7.1 Hz, 1 H), 7.28–7.14 (m, 5 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 4.06 (d, *J* = 9.7 Hz, 1 H), 3.84 (s, 3 H), 3.08–2.97 (m, 1 H), 2.90 (dt, *J* = 16.8, 4.0 Hz, 1 H), 2.68–2.60 (m, 1 H), 2.10–2.03 (m, 2 H), 1.47 (br s, 2 H).

(1*S**,2*S**)-2-Ethyl-*N*-[(2′-pyridyl)sulfonyl]-1,2-dihydronaph-thalen-1-amine (*syn*-22b)

To a solution of **17** (58 mg, 0.20 mmol) and Cu(OTf)₂ (7.2 mg, 0.02 mmol) in 1,2-dichloroethane (3 mL), heated at reflux, was added a 1 M solution of Et₂Zn in hexanes (400 μ L, 0.4 mmol). The mixture was stirred at reflux for 48 h, then H₂O (0.5 mL) was added and the mixture was stirred at r.t. for further 45 min. Then EtOAc (5 mL) was added, the aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic phases were dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 2:1) to afford *syn*-**22b** as a colorless oil; yield: 7.7 mg (12%).

¹H NMR (300 MHz): $\delta = 8.36$ (dq, J = 4.6, 1.0 Hz, 1 H), 7.90 (dt, J = 7.9, 1.2 Hz, 1 H), 7.79 (td, J = 7.7, 1.8 Hz, 1 H), 7.33 (ddd, J = 7.7, 4.6, 1.2 Hz, 1 H), 7.06 (td, J = 6.7, 2.0 Hz, 1 H), 6.97 (d, J = 7.3 Hz, 1 H), 6.77 (dd, J = 7.5, 1.4 Hz, 1 H), 6.73–6.70 (m, 1 H), 6.51 (dd, J = 9.7, 2.8 Hz, 1 H), 5.81 (dd, J = 9.7, 2.8 Hz, 1 H), 5.37 (d, J = 9.7 Hz, 1 H), 4.51 (dd, J = 10.1, 4.8 Hz, 1 H), 2.46–2.38 (m, 1 H), 1.82 (sept, J = 7.5 Hz, 1 H), 1.61 (sept, J = 7.5 Hz, 1 H), 1.03 (t, J = 7.5 Hz, 3 H).

¹³C NMR (75 MHz): δ = 158.2, 149.7, 137.4, 133.7, 132.6, 130.9, 128.1, 127.8, 126.9, 126.7, 126.4, 125.9, 121.5, 54.9, 41.1, 22.5, 11.4.

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