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N-Sulfinyl Amines as a Nitrogen Source in the Asymmetric Intramolecular Aza-Michael Reaction: Total Synthesis of (−)-Pinidinol

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Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Abstract: *N*-Sulfinyl amines have been successfully employed as nitrogen nucleophiles for the asymmetric intramolecular aza-Michael reaction. The synthetic strategy involves a cross-metathesis reaction followed by the Michael-type cyclization, either in a base-catalyzed two-step procedure or in a tandem fashion. The developed methodology allows access to chiral substituted pyrrolidines and piperidines bearing one or two stereocenters and it has been applied to the synthesis of the piperidine alkaloid (−)-pinidinol.

Keywords: aza-Michael reaction · cross metathesis · sulfinylamines · piperidines · pyrrolidines

Introduction

β-Amino carbonyl derivatives bearing a heterocyclic nitrogen atom are especially valuable, since they are versatile synthetic intermediates for the preparation of a wide variety of heterocycles.[1] Among them, pyrrolidine and piperidine substructures are worth mentioning due to their ubiquitous presence in the skeleton of several naturally occurring alkaloids[2] and their utility as chiral auxiliaries and chiral ligands in asymmetric catalysis.[3]

Among the traditional methodologies for generating chiral β-amino carbonyl compounds, asymmetric Mannich- and aza-Michael-type reactions are the most powerful strategies for the synthesis of these moieties. However, owing to simplicity and atom economy, 1,4-addition of a nitrogen-centered nucleophile to an α,β-unsaturated functionality, that is, the aza-Michael reaction, probably is the most direct way for selectively creating a carbon–nitrogen bond at the β-position of activated olefins. A plethora of nitrogen-based nucleophiles (such as amines, oximes, carbamates, amides, azides, hydrazones, or nitrogen-containing heterocycles) and an ample range of different acceptors (such as α,β-unsaturated aldehydes, ketones, esters, amides, nitroolefins, and vinyl sulfones) readily participate in this reaction in many different ways. Additionally, the possibility of performing acid or basic catalysis, or even uncatalyzed processes, offers to synthetic organic chemists a vast array of alternatives to carry out the aza-Michael reaction.

The impressive achievements made to date in the asymmetric version of this transformation rely on the use of chiral auxiliaries as the main stereochemical controllers,[4] whereas the catalytic enantioselective aza-Michael reaction remained undeveloped until very recently.[5] Among the two major ways to induce asymmetry, by using chiral amines or chiral Michael acceptors, the conjugated addition of lithium amides as homochiral ammonia equivalents is the most popular approach, and it has been extensively used and studied.[6] However, most of the work with these chiral amines is related to intermolecular aza-Michael reactions. The asymmetric intramolecular version, which represents a straightforward way to access nitrogen heterocycles, relies on the use of enantiomerically pure starting materials and, until very recently, only a few reports involving enantioselective organocatalytic processes have been published.[7]

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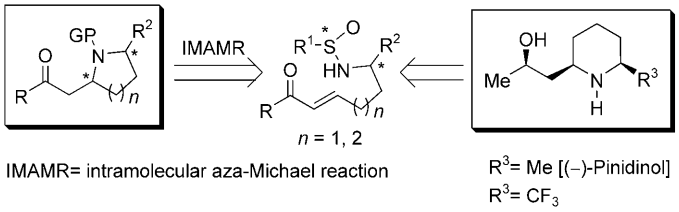
On the other hand, *N*-sulfinyl imines are among the most popular and efficient substrates reported to date for the stereoselective addition of organometallic reagents to chiral imines.[8] This is, in fact, a highly reliable method for the asymmetric construction of chiral amines since the sulfinyl group is readily cleaved by acidic treatment. However, the use of *N*-sulfinyl amines as nitrogen-centered nucleophiles is very scarce.[9] Once the sulfinyl group has exerted its directing effect, it is usually removed and the free amino group employed for further transformations. We envisioned the possibility of using *N*-sulfinyl amines both as a nitrogen source and chiral inducers in the intramolecular aza-Michael reaction, which would allow for the preparation of chiral substituted pyrrolidines and piperidines bearing one or two stereocenters (Scheme 1). In addition, the utility of this methodology will be illustrated by the synthesis of the piperidine natural product (−)-pinidinol.

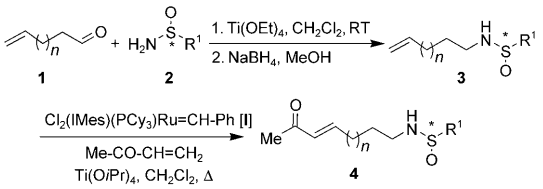


Scheme 1. Synthetic strategy.

Results and Discussion

Intramolecular Aza-Michael reaction with *N*-sulfinyl amines 4 and 9: Our initial efforts were directed at the study of the intramolecular aza-Michael reaction (IMAMR) on unsubstituted sulfinyl amines **4** bearing an α,β-unsaturated ketone moiety. Following our recent results in this field,[7b,d] Michael acceptors **4** were assembled by means of a cross-metathesis (CM) reaction between unsaturated *N*-sulfinyl amines **3** and an appropriate α,β-unsaturated compound. The CM counterparts **3** were in turn prepared by reductive amination of unsaturated aldehydes **1** and sulfinyl amines **2** (Table 1). Metathesis reactions involving a sulfinyl group are very scarce in the literature and most of them are related to ring-closing metathesis (RCM) processes.[10] After several attempts, we were delighted to find out that the reaction of amines **3** with methyl vinyl ketone in the presence of second-generation Grubbs catalyst **I** and Ti(O*i*Pr)$_4$ led to the formation of the desired CM compounds **4** in good to excellent yields in 2 h (Table 1).[11] It is worth mentioning that when substrate **3a** was subjected to the optimized CM conditions, the corresponding diastereoisomeric pyrrolidines arising from an intramolecular cyclization were isolated in 12% yield together with the desired product **4a**. This result prompted us to explore this CM aza-Michael tandem process independently (see later).

Table 1. Preparation of Michael acceptors **4**.



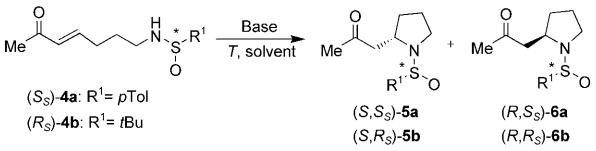
	1	n	2 (R^1)	3 (yield [%])[a]	4 (yield [%])[a,b]
1	**1a**	1	(S_S)-**2a** (*p*Tol)	(S_S)-**3a** (90)	(S_S)-**4a** (70)[c]
2	**1a**	1	(R_S)-**2b** (*t*Bu)	(R_S)-**3b** (67)	(R_S)-**4b** (>99)
3	**1b**	2	(S_S)-**2a** (*p*Tol)	(S_S)-**3c** (69)	(S_S)-**4c** (72)
4	**1b**	2	(R_S)-**2b** (*t*Bu)	(R_S)-**3d** (65)	(R_S)-**4d** (>99)

[a] Isolated yields after column chromatography. [b] Only the *E* isomer was detected in all cases. [c] A mixture of diastereoisomeric pyrrolidines **5a** and **6a** was also obtained in 12% yield.

To find the optimum conditions for the IMAMR we decided to examine the process with sulfinyl amine (S_S)-**4a** as a model substrate. The initial attempt was carried out with a catalytic amount of *t*BuOK (0.3 equiv) in THF at room temperature. After 30 min, the formation of diastereoisomeric pyrrolidines (*S*,S_S)-**5a** and (*R*,S_S)-**6a** was detected in 87% yield and in a 21:79 ratio (Table 2, entry 1). When the same reaction was performed at −40 °C, we observed an inverted selectivity, since compounds **5a**/**6a** were isolated in a 77:23 ratio (Table 2, entry 2). When the base was added at −40 °C and the reaction mixture was allowed to reach room temperature in 12 h, the 23:77 (**5a**/**6a**) ratio was obtained again (Table 2, entry 3), which proved the reversibility of the process, with pyrrolidine (*R*, S_S)-**6a** as the thermodynamic product and (*S*, S_S)-**5a** as the kinetic one. The use of other bases, such as lithium/potassium hexamethyl disilazide (LiHMDS and KHMDS) led to comparable results, that is, **6a** was the major product at room temperature (Table 2, entries 4 and 6), whereas an inverted selectivity was yet again observed at −40 °C and kinetic product **5a** was formed in a major extent (Table 2, entries 5 and 7). A slight influence of the counterion was also detected, the lithium salt gave a 36:64 (**5a**/**6a**) ratio at room temperature, whereas the potassium salt afforded a 21:79 proportion (Table 2, entries 4 and 6), thus indicating that an increased basicity improved the selectivity.[12] The same effect was observed at low temperature. The influence of the solvent was evaluated in the reaction with Cs_2CO_3 as a base. In these experiments, we found quite simi-

Abstract in Spanish: *En este trabajo se han utilizado* N-*sulfinilaminas como nucleófilos nitrogenados para la reacción aza-Michael intramolecular asimétrica. La estrategia sintética implica una reacción de metátesis cruzada seguida de la ciclación tipo Michael, bien en un proceso en dos pasos catalizado por una base, o bien de manera tándem. La metodología desarrollada permite la obtención de pirrolidinas y piperidinas sustituídas quirales con uno o dos estereocentros y se ha aplicado a la síntesis del alcaloide derivado de piperidina (−)-pinidinol.*

Table 2. IMAMR of *N*-sulfinyl amines **4a**,**b**.



(S_S)-**4a**: R^1= *p*Tol
(R_S)-**4b**: R^1= *t*Bu

(S,S_S)-**5a**
(S,R_S)-**5b**

(R,S_S)-**6a**
(R,R_S)-**6b**

	4	Base [equiv]	*T* [°C]	Solvent	*t*	**5+6** (yield [%])[a]	d.r. **5/6**[b]
1	**4a**	*t*BuOK (0.3)	RT	THF	30 min	**5a+6a** (87)	21:79
2	**4a**	*t*BuOK (0.3)	−40	THF	60 min	**5a+6a** (70)	77:23
3	**4a**	*t*BuOK (0.3)	−40 to RT	THF	12 h	**5a+6a** (78)	23:77
4	**4a**	LiHMDS (0.3)	RT	THF	10 min	**5a+6a** (95)	36:64
5	**4a**	LiHMDS (0.3)	−40	THF	10 min	**5a+6a** (98)	63:37
6	**4a**	KHMDS (0.3)	RT	THF	10 min	**5a+6a** (85)	21:79
7	**4a**	KHMDS (0.3)	−40	THF	10 min	**5a+6a** (82)	77:23
8	**4a**	Cs_2CO_3 (1)	RT	THF	90 min	**5a+6a** (87)	69:31
9	**4a**	Cs_2CO_3 (1)	RT	MeOH	30 min	**5a+6a** (90)	75:25
10	**4a**	Cs_2CO_3 (1)	RT	CH_2Cl_2	5 h	**5a+6a** (86)	72:28
11	**4a**	Cs_2CO_3 (1)	RT	DMF	90 min	**5a+6a** (68)	73:27
12	**4b**	*t*BuOK (0.3)	RT	THF	30 min	**5b+6b** (74)	85:15
13	**4b**	*t*BuOK (0.3)	−40	THF	60 min	**5b+6b** (69)	20:80
14	**4b**	*t*BuOK (0.3)	−40 to RT	THF	12 h	**5b+6b** (64)	81:19
15	**4b**	LiHMDS (0.3)	−40	THF	40 min	**5b+6b** (68)	78:22
16	**4b**	KHMDS (0.3)	−40	THF	40 min	**5b+6b** (64)	15:85

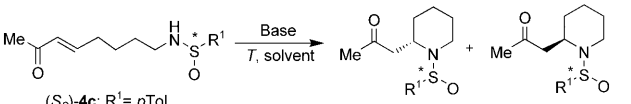
[a] Isolated yields after column chromatography. [b] Ratio determined by ^{1}H NMR spectroscopic integration in the crude reaction mixture.

lar selectivities independent from the solvent employed (THF, MeOH, CH_2Cl_2, and DMF; Table 2, entries 8–11).

Next, our study was extended to the *tert*-butyl sulfinyl amine (R_S)-**4b**. The reaction with *t*BuOK at room temperature gave a 85:15 ratio of pyrrolidines (S,R_S)-**5b** and (R,R_S)-**6b** and, yet again, an inversion of the selectivity was observed at low temperature (Table 2, entries 12 and 13). The reversibility of the process was confirmed when the reaction was allowed to reach room temperature after adding the base at −40 °C (Table 2, entry 14). The influence of the counterion was bigger than in the reaction on (S_S)-**4a**, to such an extent that an inversion of selectivity took place when the base changed from LiHMDS to KHMDS (Table 2, entries 15 and 16). It is worth mentioning that the IMAMR turned out to be more synthetically useful for substrate (R_S)-**4b** relative to (S_S)-**4a**, since the products (S,R_S)-**5b** and (R,R_S)-**6b** could be easily separated by means of column chromatography, whereas (S,S_S)-**5a** and (R,S_S)-**6a** were impossible to separate. In addition, better selectivities were achieved in the reaction on (R_S)-**4b**.

Next, the extension of this protocol to the synthesis of the corresponding piperidine-derived adducts **7** and **8** was examined. Thus, compounds (S_S)-**4c** and (R_S)-**4d** were subjected to the conditions mentioned above. When compound **4c** was treated with *t*BuOK in THF at room temperature, piperidine (R, S_S)-**8a** was obtained in 85% yield as a single diastereoisomer (Table 3, entry 1). When the reaction was performed at −40 °C it led to the formation of the same compound **8a** as the major product (Table 3, entry 2). Therefore, unlike the pyrrolidine formation, in the case of the six-membered rings, no inversion of the selectivity took place at low temperature. Even at lower temperatures (−78 °C), the thermodynamic product was mainly obtained (Table 3, entry 3) even with other bases, such as LiHMDS or Cs_2CO_3 (Table 3, entries 4 and 5). However, when substrate (R_S)-**4d** was subjected to the IMAMR, a mixture of piperidines (S,R_S)-**7b** and (R,R_S)-**8b**, with predominance of **7b**, was obtained in all conditions tested either at different temperatures or with different bases or solvents (Table 3, entries 6–9).

Table 3. IMAMR on *N*-sulfinyl amines **4c**,**d**.



(S_S)-**4c**: R^1= *p*Tol
(R_S)-**4d**: R^1= *t*Bu

(S,S_S)-**7a**
(S,R_S)-**7b**

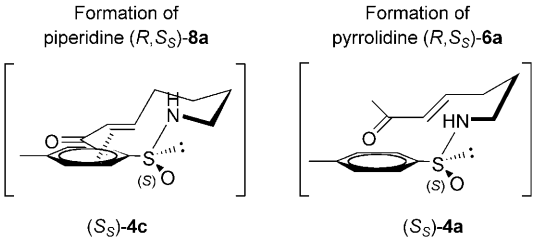
(R,S_S)-**8a**
(R,R_S)-**8b**

	4	Base [equiv]	*T* [°C]	Solvent	*t*	**7+8** (yield [%])[a]	d.r. **7/8**[b]
1	**4c**	*t*BuOK (0.3)	RT	THF	30 min	**8a** (85)	>1:99
2	**4c**	*t*BuOK (0.3)	−40	THF	30 min	**7a+8a** (80)	5:95
3	**4c**	*t*BuOK (0.3)	−78	THF	50 min	**7a+8a** (81)	11:89
4	**4c**	LiHMDS (0.3)	−78	THF	60 min	**7a+8a** (82)	12:88
5	**4c**	Cs_2CO_3 (1)	RT	MeOH	12 h	**7a+8a** (66)	5:95
6	**4d**	*t*BuOK (0.3)	RT	THF	30 min	**7b+8b** (78)	88:12
7	**4d**	*t*BuOK (0.3)	−40	THF	2 h	**7b+8b** (71)	87:13
8	**4d**	LiHMDS (0.3)	−40	THF	60 min	**7b+8b** (68)	87:13
9	**4d**	Cs_2CO_3 (1)	RT	MeOH	12 h	**7b+8b** (60)	87:13

[a] Isolated yields after column chromatography. [b] Ratio determined by ^{1}H NMR spectroscopic integration in the crude reaction mixture.

With these results in hand, it became apparent that complete stereocontrol can be achieved in the formation of piperidine (R,S_S)-**8a** from substrate (S_S)-**4c**, which contains a *p*-tolyl group attached to the sulfoxide unit. However, the formation of the analogous pyrrolidine (R,S_S)-**6a** from the *N*-*p*-tolyl sulfinyl Michael acceptor (S_S)-**4a** took place with a low level of diastereodifferentiation (see Table 2, entry 1). The selectivity achieved in both cases could be attributed to a stacked geometry of the arene and enone moieties, which would direct the addition of the amide nitrogen to the α,β-unsaturated ketone. Thus, the presence of an additional carbon atom between the nitrogen and the carbon acceptor in (S_S)-**4c**, relative to (S_S)-**4a**, seems crucial to gain an effec-

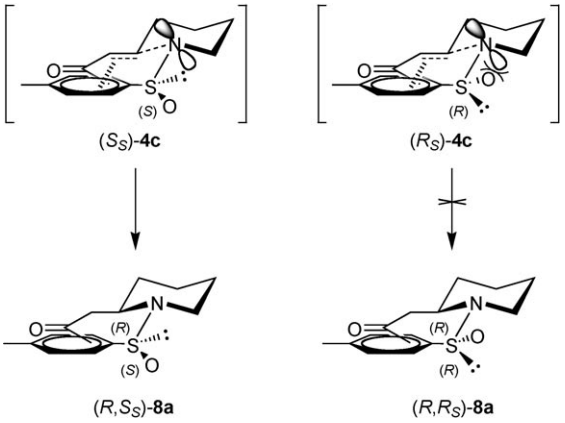
tive π-stacking, hence giving a better facial selectivity in the formation of piperidine **8a** (Scheme 2).[13] Additionally, this interaction would also explain the difference in selectivity



Scheme 2. The π-stacking interaction between the *p*-tolyl group and the α,β-unsaturated ketone.

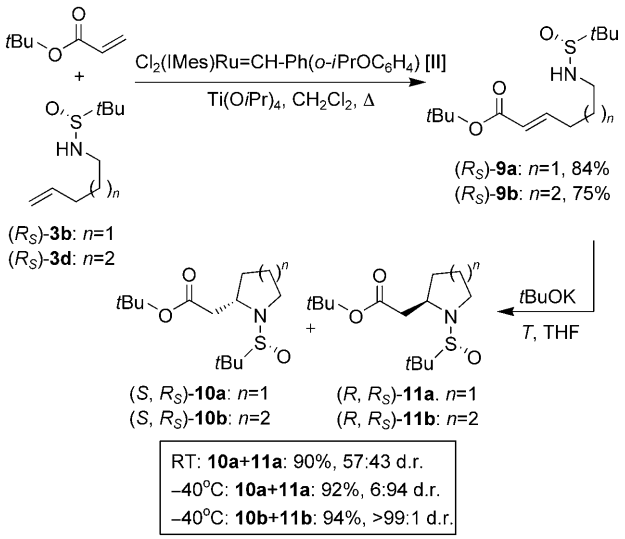
found between substrate (S_S)-**4c** (Table 3, entry 1) and (R_S)-**4d** (Table 3, entry 6), which contains a *t*Bu group attached to the sulfoxide, since in this case only steric effects are operating.

The stereochemical outcome of the overall process could also be rationalized on the basis of this stacked geometry. The addition of the amide nitrogen may be predicted to proceed through a chairlike transition state. Therefore, in the transition state leading to the cyclized product (*R*,S_S)-**8a**, the sulfoxide oxygen and the amide nitrogen atom should be located in an *anti* relationship thus yielding the final piperidine *R*. The same disposition with the *R* enantiomer of the starting sulfoxide is not favored in terms of electronic and steric effects (Scheme 3).



Scheme 3. Rationalization of the stereochemical outcome

The next step of our study was focused on the use of other Michael acceptors distinct from ketones. With this purpose, compounds (R_S)-**9a,b** bearing an α,β-unsaturated ester moiety were synthesized by a CM reaction of sulfinyl amines (R_S)-**3b,d** with *tert*-butyl acrylate. It was necessary to use second-generation Hoveyda–Grubbs catalyst **II** to obtain good yields in the CM reaction (Scheme 4). When compound **9a** was treated with *t*BuOK at room temperature,



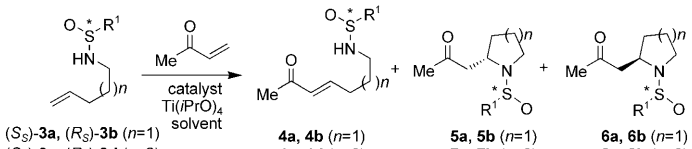
Scheme 4. CM and IMAMR with *tert*-butyl acrylate.

equimolecular amounts of the diastereoisomeric pyrrolidines (*S*,R_S)-**10a** and (*R*,R_S)-**11a** were obtained in 90% yield. However, the same reaction performed at −40°C led to the almost exclusive formation of compound **11a** (6:94 diastereomeric ratio (d.r.)) in very good yield. In the case of Michael acceptor (R_S)-**9b**, the same reaction at −40°C afforded the piperidine (*S*,R_S)-**10b** as a single diastereoisomer in 94% yield.[14] Therefore, this two-step methodology allows for the preparation of homoproline and homopipecolic acid derivatives in very good yields and with excellent diastereoselectivity.

Tandem CM–IMAMR with *N*-sulfinyl amines 3: As mentioned above, in the CM reaction of substrate (S_S)-**3a** with methyl vinyl ketone, the formation of the corresponding pyrrolidine coming from an intramolecular cyclization was detected to a small extent.[15] We then decided to optimize the conditions of this CM–IMAMR tandem process to obtain the final nitrogen heterocycles in a single step.

Since the CM between (S_S)-**3a** and methyl vinyl ketone in the presence of second-generation Grubbs catalyst **I** gave **5a**+**6a** in 12% yield after 2 h in refluxing CH_2Cl_2 (Table 1, entry 1) our first attempt was to increase the reaction time. Thus, when a solution of (S_S)-**3a** in CH_2Cl_2 was heated in the presence of ruthenium catalyst **I** for 6 h, the corresponding pyrrolidine was obtained in 28% yield as a mixture of diastereoisomers **5a**/**6a** (85:15 d.r.) (Table 4, entry 1). After 48 h, the yield of the tandem process increased to 70% and only 10% of the CM product (S_S)-**4a** remained uncyclized (Table 4, entry 2). To our delight, when using second-generation Hoveyda–Grubbs catalyst **II** the tandem sequence took place almost quantitatively (Table 4, entry 3). Noteworthy is that the major product in these tandem reactions was the kinetic pyrrolidine (*S*,S_S)-**5a**, contrasting with the reaction on (S_S)-**4a** under basic conditions at room temperature, for which the major product was (*R*,S_S)-**6a** (see Table 2,

Table 4. Tandem CM–IMAMR on *N*-sulfinyl amines **3**.



(S_S)-**3a**, (R_S)-**3b** (*n*=1)
(S_S)-**3c**, (R_S)-**3d** (*n*=2)

4a, **4b** (*n*=1)
4c, **4d** (*n*=2)

5a, **5b** (*n*=1)
7a, **7b** (*n*=2)

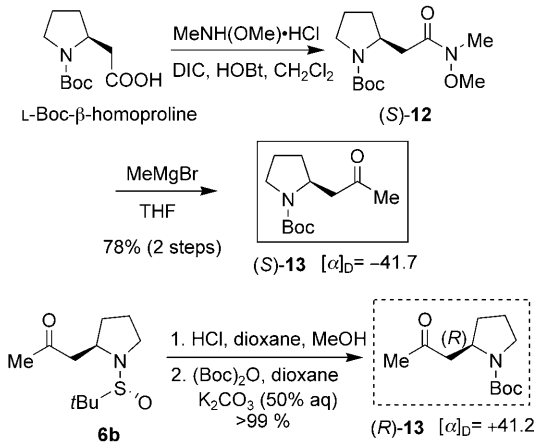
6a, **6b** (*n*=1)
8a, **8b** (*n*=2)

	3	Catalyst[a]	Conditions	**4** (yield [%])[b]	**5**+**6** or **7**+**8** (yield [%])[b]	d.r. **5**/**6** or **7**/**8**[c]
1	**3a**	[Ru]-**I**	CH_2Cl_2/reflux/6 h	**4a** (50)	**5a**+**6a** (28)	**5a**/**6a** (85:15)
2	**3a**	[Ru]-**I**	CH_2Cl_2/reflux/48 h	**4a** (10)	**5a**+**6a** (70)	**5a**/**6a** (88:12)
3	**3a**	[Ru]-**II**	CH_2Cl_2/reflux/48 h	**4a** (0)	**5a**+**6a** (95)	**5a**/**6a** (89:11)
4	**3a**	[Ru]-**II**	toluene/reflux/12 h	**4a** (23)	**5a**+**6a** (10)	**5a**/**6a** (80:20)
5	**3a**	[Ru]-**II**	CH_2Cl_2/microwaves/1 h/100 °C	**4a** (21)	**5a**+**6a** (20)	**5a**/**6a** (81:19)
6	**3a**	[Ru]-**II**	CH_2Cl_2/microwaves/7 h/60 °C	**4a** (14)	**5a**+**6a** (60)	**5a**/**6a** (88:12)
7	**3b**	[Ru]-**I**	CH_2Cl_2/reflux/48 h	**4b** (9)	**5b**+**6b** (74)	**5b**/**6b** (9:91)
8	**3b**	[Ru]-**II**	CH_2Cl_2/reflux/48 h	**4b** (0)	**5b**+**6b** (92)	**5b**/**6b** (8:92)
9	**3c**	[Ru]-**II**	CH_2Cl_2/reflux/48 h	**4c** (54)	**7a**+**8a** (30)	**7a**/**8a** (70:30)
10	**3c**	[Ru]-**II**	$ClCH_2CH_2Cl$/reflux/48 h	**4c** (41)	**7a**+**8a** (25)	**7a**/**8a** (71:29)
11	**3d**	[Ru]-**II**	CH_2Cl_2/reflux/48 h	**4d** (63)	**7b**+**8b** (22)	**7b**/:**8b** (24:76)
12	**3d**	[Ru]-**II**	$ClCH_2CH_2Cl$/reflux/48 h	**4d** (77)	**7b**+**8b** (15)	**7b**/**8b** (24:76)

[a] [Ru]-**I**: Cl_2(Imes)(PCy_3)Ru=CH-Ph. [Ru]-**II**: Cl_2(Imes)Ru=CH-Ph(*o*-*i*PrOC_6H_4). [b] Isolated yields after column chromatography. [c] Ratio determined by ^{1}H NMR spectroscopic integration in the crude reaction mixture.

entry 1).[16] To evaluate the influence of the temperature, (S_S)-**3a** was heated with catalyst **II** in refluxing toluene for 12 h. Unfortunately, in this case the yield dropped to 10%, and only 23% of the CM product (S_S)-**4a** could be isolated (Table 4, entry 4). From this result, it can be deduced that increasing the temperature has a negative influence on the tandem process. Bearing in mind our recent results in the tandem process CM–IMAMR with carbamates,[15] we decided to carry out the reaction under microwave irradiation since it dramatically decreases the reaction time. In this case, under microwave irradiation of (S_S)-**3a** in the presence of catalyst **II** no improvement over the regular heating conditions was observed, which yet showed again the negative effect of the temperature on the tandem protocol (Table 4, entries 5 and 6). At this point, the optimum conditions (catalyst **II**, refluxing CH_2Cl_2 for 48 h) were applied to substrates **3b–d**. Thus, (R_S)-**3b** gave the kinetic pyrrolidine (*R*,R_S)-**6b** in 92% yield and in a 8:92 (**5b**/**6b**) ratio (Table 4, entry 8). This result demonstrated again the better diastereodifferentiation induced by the *tert*-butyl sulfinyl group relative to the *p*-tolyl sulfinyl group, likewise in the formation of these pyrrolidines under basic catalysis. Different results were obtained with substrates **3c**,**d** since the corresponding piperidines **7a**,**b** and **8a**,**b** were obtained in both cases as the minor reaction products relative to the CM adducts. Nevertheless, kinetic products (*S*,S_S)-**7a** and (*R*,R_S)-**8b** were once again the major diastereoisomers (Table 4, entries 9–12). These results highlighted the difficult formation of piperidines, similarly to what occurred under basic conditions. Finally, all attempts performed to carry out the tandem process with alkyl acrylates **9** as Michael acceptors were unsuccessful, and products coming from the CM reaction were obtained instead.

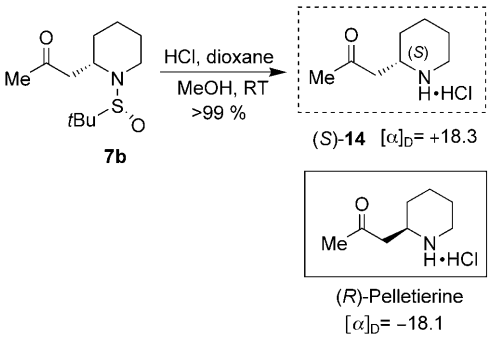
Determination of the absolute configuration of compounds 5–8: The absolute configuration of the newly created stereocenter in pyrrolidines **5**,**6** and piperidines **7**,**8** was determined by chemical correlation. Thus, commercially available L-Boc-β-homoproline (Boc = *tert*-butoxycarbonyl) was transformed into the corresponding Weinreb amide (*S*)-**12**, which was in turn treated with methyl magnesium bromide to render compound (*S*)-**13**. On the other hand, **6b**, the kinetic product obtained in the tandem cyclization of (R_S)-**3b**, was treated with HCl to remove the *t*Bu sulfinyl group and the nitrogen atom was protected as an *N*-Boc group to afford once again compound **13** (Scheme 5). Comparing the optical rotation of derivatives **13** obtained



Scheme 5. Determination of the absolute configuration of pyrrolidines **6**. DIC = *N*,*N*′-diisopropylcarbodiimide; HOBt = *N*-hydroxybenzotriazole.

through both routes, we realized that the value found for the product derived from **6b** had an opposite sign to that obtained from the commercially available homoproline derivative. Consequently, this result allowed us to assign the absolute configuration *R*,*Rs* to pyrrolidine **6b**.

The total synthesis of the natural product Pelletierine[17] was employed to determine the absolute configuration of the piperidine family. Thus, removal of the chiral auxiliary of **7b** afforded piperidine **14**, which contains the complete skeleton of the natural product (Scheme 6). The optical de-



Scheme 6. Determination of the absolute configuration of piperidines **7**.

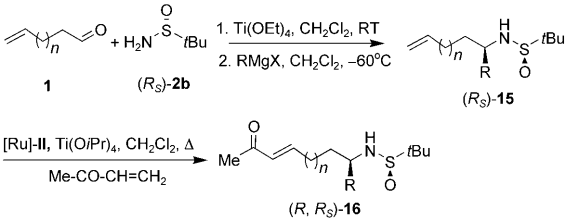
viation value showed that **14** displayed the opposite configuration of the natural product. Therefore, the absolute configuration *S*,*Rs* could be assigned to the IMAMR product **7b**. We assumed the same stereochemical outcome for the cyclization of all products reported herein.

Evaluation of double asymmetric induction in the IMAMR: At this point of our study, we were curious about the influence of a second stereocenter in the IMAMR substrate in the selectivity of the process. Accordingly, to investigate a double asymmetric induction in the cyclization, a set of enantiomerically pure *N*-sulfinyl amines **16** bearing two stereocenters was synthesized. The most direct way to access these amines was the addition of organometallic reagents to the corresponding sulfinyl imines. Since this reaction was described to be more favorable in terms of selectivity with *tert*-butyl sulfinyl imines (when compared with *p*Tol sulfinyl imines), we decided to employ sulfinyl amine (R_S)-**2b** as the chiral starting sulfoxide.[18]

After condensation of **2b** with aldehydes **1a**,**b**, the addition of Grignard reagents to the intermediate *N*-sulfinyl imines at −60°C afforded the desired amines (R_S)-**15** in good yields and with excellent selectivities. The best conditions to perform the CM reaction were found to involve the use of ruthenium catalyst **II**, thus rendering Michael acceptors (R,R_S)-**16** in excellent yields as single diastereoisomers (Table 5).

The intramolecular aza-Michael addition on substrates (R,R_S)-**16a–d** was carried out in THF with *t*BuOK. At room temperature, **16a** furnished a mixture of diastereoisomeric pyrrolidines (2*S*,5*R*,R_S)-**17a** and (2*R*,5*R*,R_S)-**18a** in 93% yield and with a 86:14 ratio (Table 6, entry 1). Following the

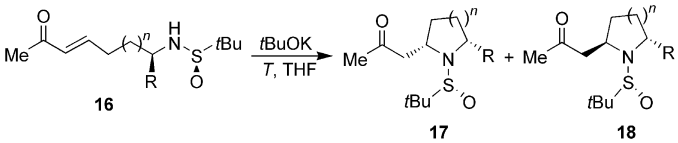
Table 5. Synthesis of Michael acceptors **16**.



	1	*n*	RMgX	15 (yield [%], d.r)[a]	16 (yield [%])[a][b]
1	**1a**	1	*i*PrMgCl	**15a** (83, >99:1)	**16a** (>99)
2	**1a**	1	PhMgCl	**15b** (70, 30:1)	**16b** (82)
3	**1b**	2	*i*PrMgCl	**15c** (76, >99:1)	**16c** (93)
4	**1b**	2	PhMgCl	**15d** (63, >99:1)	**16d** (84)

[a] Isolated yields after column chromatography. [b] Only the *E* isomer was detected in all cases.

Table 6. IMAMR on *N*-sulfinyl amines **16a–d**.



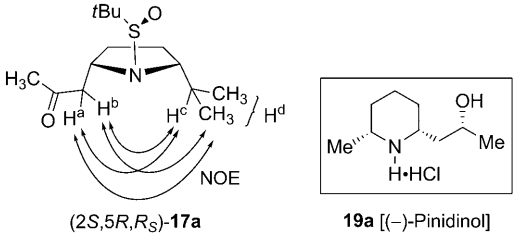
	16	*n*	R	*T* [°C]	*t* [min]	17+18 (yield [%])[a]	d.r. 17/18[b]
1	**16a**	1	*i*Pr	RT	30	**17a+18a** (93)	86:14
2	**16a**	1	*i*Pr	−40	60	**17a+18a** (87)	21:79
3	**16b**	1	Ph	RT	30	**17b** (96)	>99:1
4	**16b**	1	Ph	−40	60	**17b** (88)	>99:1
5	**16c**	2	*i*Pr	RT	60	**17c** (40)	>99:1
6	**16c**	2	*i*Pr	−40	90	**17c+18c** (70)	85:15
7	**16c**	2	*i*Pr	−40 to RT	150	**17c** (68)	>99:1
8	**16d**	2	Ph	RT	60	**17d+18d** (48)	92:8
9	**16d**	2	Ph	−40	90	**17d+18d** (76)	74:26
10	**16d**	2	Ph	−40 to RT	150	**17d+18d** (80)	92:8

[a] Isolated yields after column chromatography. [b] Ratio determined by ^{1}H NMR spectroscopic integration in the crude reaction mixture.

tendency shown by other substrates, when the reaction was performed at −40°C, the kinetic product **18a** was formed to a major extent (Table 6, entry 2). On the other hand, **16b** displayed a different behavior since it resulted, either at room temperature or at −40°C, in the pyrrolidine (2*S*,5*R*,R_S)-**17b** as a single diastereoisomer (Table 6, entries 3 and 4). From substrate **16c**, the piperidine (2*S*,6*R*,R_S)-**17c** was obtained as a single product although in a moderate 40% yield at room temperature (Table 6, entry 5). At −40°C, the final product was obtained in 70% yield although the selectivity dropped to (**17c**/**18c**) 85:15 (Table 6, entry 6). Combining these last results (good selectivity at room temperature and good yield at low temperature) and taking advantage of the reversibility of the process, piperidine **17c** was obtained as a single product in 68% yield when, after the addition of the base at −40°C, the reaction was allowed to reach room temperature (Table 6, entry 7). Likewise, substrate (R,R_S)-**16d** afforded (2*S*,6*R*,R_S)-**17d** with good selectivity (**17d**/**18d** 92:8) and moderate yield (48%) at room temperature (Table 6, entry 8), and in good yield

(76%) and poor selectivity (**17d**/**18d** 74:26) at −40°C (Table 6, entry 9). Again, by adding the base at low temperature and removing the cooling bath until the reaction reached room temperature, it was possible to obtain **17d**+**18d** in a 92:8 ratio and with 80% combined yield (Table 6, entry 10).

The relative configuration of the newly created stereocenter in the disubstituted pyrrolidines was determined by NOESY experiments on substrate **17a**. We observed positive NOE effects between protons H^a,H^b and H^c,H^d, clearly indicating that both substituents of the pyrrolidine ring (at the 2- and 5-positions) are oriented towards the same direction. These results allowed us to assign the configuration (2*S*,5*R*,R_S) to pyrrolidine **17a** (Scheme 7), which showed that the stereochemical control in the process was exerted by the sulfinyl group.

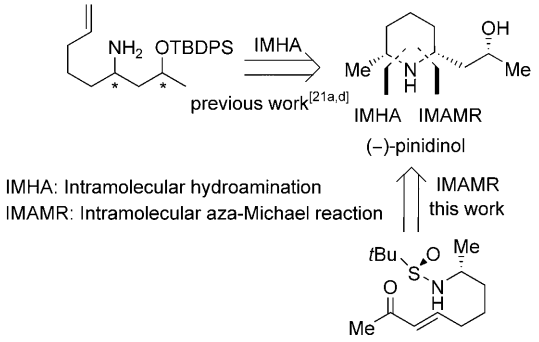


Scheme 7. Determination of the relative configuration of the disubstituted pyrrolidines and piperidines.

As mentioned before, the last part of our work was related to the total synthesis of the natural product (−)-pinidinol **19a**. Accordingly, the preparation of this alkaloid allowed us to indirectly confirm the absolute configuration of the chiral center generated in the formation of the 2, 6-disubstituted piperidines **17c**,**d** bearing both substituents in a *cis* relative disposition (Scheme 7).

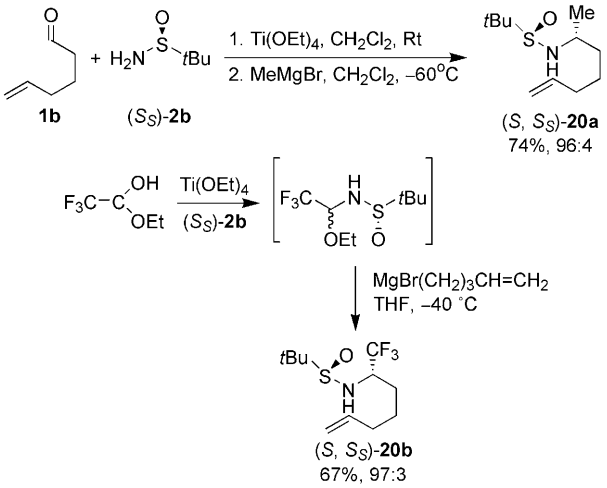
Total synthesis of (−)-pinidinol 19a and its fluorinated analogue 19b: The last step of our study was focused on the application of the developed methodology for the preparation of *cis* 2,5-disubstituted pyrrolidines and 2,6-disubstituted piperidines to the total synthesis of the natural product (−)-pinidinol[19] and its trifluoromethyl analogue. Although these substructures are present in several families of compounds with interesting biological properties,[20] the choice of (−)-pinidinol was based on the fact that only five asymmetric syntheses of this compound have been reported to date.[21] Only those reported by Davis[21a] and Molander[21d] were consistent in reaching the final product in 16 and 19% yield, respectively. In both cases, their synthetic strategy was based on an intramolecular hydroamination (IMHA) of a 1,3-amino alcohol bearing a remote olefin (Scheme 8). Our approach will allow us to generate the complete skeleton of the natural product through the IMAMR of the Michael acceptor depicted in Scheme 8.

The first step of our synthetic strategy was the preparation of the starting *N*-sulfinyl amines **20a** and the trifluoro-



Scheme 8. Retrosynthesis of (−)-pinidinol.

methyl analogue **20b**. Amine **20a** was assembled by following the strategy described before for the preparation of compounds **15**, that is, by addition of methyl magnesium bromide to the *N*-sulfinyl imine generated by condensation of aldehyde **1b** and (S_S)-**2b**. To obtain the stereochemistry of the natural product, it was necessary to use the sulfoxide (S_S)-**2b**, which is the enantiomer of the starting *tert*-butyl sulfinyl amine employed throughout the study. Thus, the desired compound (*R*,S_S)-**20a** was obtained in good yield (74%) and with excellent selectivity (96:4 d.r.) with the appropriate absolute configuration at the methyl-containing stereocenter (Scheme 9). Substrate **20b** bearing the

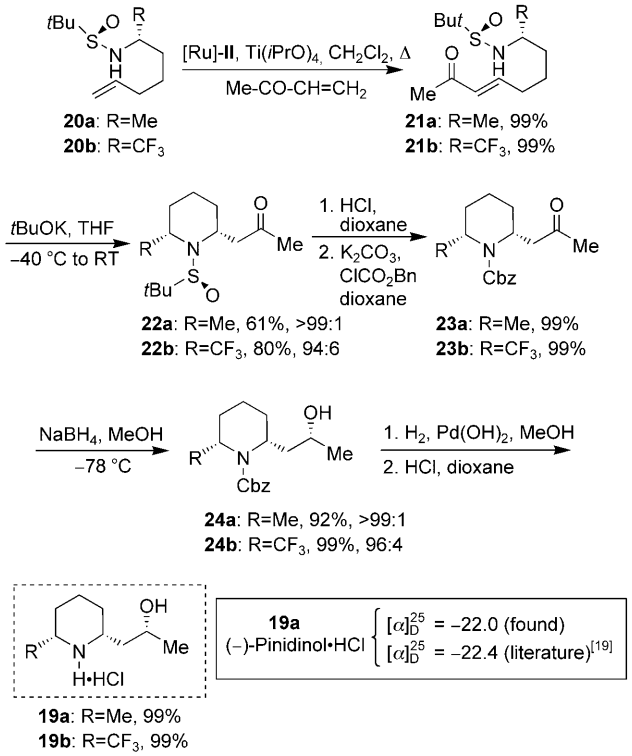


Scheme 9. Synthesis of sulfinyl amines **20a** and **20b**.

trifluoromethyl group was assembled through a slightly different strategy, according to a previously described procedure.[22] Trifluoroacetaldehyde ethyl hemiacetal was condensed with (S_S)-**2b** to afford a mixture of diastereoisomeric sulfinyl amines. Without purification, these amines were treated with an excess of 4-pentenylmagnesium chloride in THF at −40°C, and (*S*, S_S)-**20b** was obtained with excellent selectivity (97:3 d.r.) in 67% yield (Scheme 9).

Michael acceptors **21a**,**b** were prepared in excellent yields by the CM reaction of amines **20a**,**b** with methyl vinyl

ketone in the presence of ruthenium catalyst **II**. These CM products were then subjected to the cyclization conditions that involved the addition of *t*BuOK at −40 °C allowing the reaction mixture to reach room temperature within 2 h. In this way, piperidines (2*R*,6*R*,S_S)-**22a** and (2*R*,6*S*,S_S)-**22b** were obtained in good yields and with excellent diastereoselectivities. Reduction of the carbonyl group followed by removal of the sulfoxide chiral auxiliary would lead to the natural product. However, the reduction of the ketone in the presence of the sulfoxide moiety was troublesome. All attempts performed by using different reducing agents, that is, $LiEt_3BH$, $Li(tBuO)_3AlH/LiCl$, $NaBH_4/ZnI_2$, diisobutylaluminum hydride, Bu_4NBH_4, and $NaBH_4$, different solvents, such as CH_2Cl_2, Et_2O, toluene, THF, and MeOH, and different temperatures led to the formation of the desired alcohol in poor yield (25–30%) and selectivity.[23] These difficulties prompted us to modify the strategy, and we decided to change the nitrogen protecting group. Removal of the sulfoxide group with HCl in dioxane and subsequent nitrogen protection afforded Cbz-piperidines (2*R*,6*R*)-**23a** and (2*R*,6*S*)-**23b** in almost quantitative yields. At this point, after various attempts to reduce the ketone functionality, we found that the reaction with $NaBH_4$ in MeOH at −78 °C took place in excellent yield and diastereoselectivity. Finally, the hydrogenolysis of alcohols (2*R*,2*R*′,6*R*)-**24a** and (2*R*,2*R*’,6*S*)-**24b** followed by acidic treatment gave rise to the formation of (−)-pinidinol **19a** and its fluorinated analogue **19b** again in excellent yields (Scheme 10). It is worth mentioning that the overall yield of the total synthesis of (−)-pinidinol was 40% (from **1b** and (*S*)-**2b**), which is the highest yield reported to date in the literature. The trifluoromethyl analogue was obtained in 47% overall yield.



Scheme 10. Synthesis of pinidinol and its trifluoromethyl analogue.

Conclusion

The use of *N*-sulfinyl amines as the nitrogen source in the asymmetric intramolecular aza-Michael reaction has been reported for the first time. Following a CM–IMAMR sequence, either in a stepwise or in a tandem process, it was possible to synthesize 2-substituted pyrrolidines and piperidines with good yields and excellent selectivities. Pyrrolidine (*R*,R_S)-**6b** was obtained with 92:8 d.r. and 92% yield by means of the tandem protocol starting from *tert*-butyl sulfinyl amine (R_S)-**3b** (see Table 4, entry 8). Regarding the piperidine family, (*R*,S_S)-**8a** was achieved in 85% yield with complete diastereoselectivity (>99:1) through the base-mediated IMAMR (see Table 3, entry 1). An inversion of the selectivity was observed when the reactions performed under base catalysis or in a tandem fashion (Lewis acid catalysis) were compared.

In addition, 2,5-and 2,6-disubstituted pyrrolidines and piperidines, respectively, were also synthesized in very good yields and with excellent diastereoselectivities by taking advantage of the double asymmetric induction concept. Finally, the utility of the developed methodology was demonstrated by the highly efficient synthesis of the natural product (−)-pinidinol and its fluorinated analogue.

Experimental Section

General methods: Reactions were carried out under a nitrogen atmosphere unless otherwise indicated. Solvents were purified prior to use: THF and PhMe were distilled from sodium and CH_2Cl_2 from calcium hydride. The reactions were monitored with the aid of TLC on 0.25 mm precoated silica-gel plates. Visualization was carried out with UV light and aqueous ceric ammonium molybdate solution or potassium permanganate 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. Chemical shifts are given in ppm (δ), referenced to the residual proton resonances of the solvents or fluorotrichloromethane in ^{19}F NMR spectroscopic experiments. Coupling constants (J) are given in Hertz (Hz). The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The letters br indicate that the signal is broad.

General procedure for the cross-metathesis reaction: **synthesis of sulfinyl amines 4, 9, 16, and 21**: Methyl vinyl ketone or *tert*-butyl acrylate (5.0 equiv) and second-generation Grubbs catalyst **I** or second-generation Hoveyda–Grubbs catalyst **II** (10 mol%) were successively added to a stirred solution of the corresponding sulfinyl amine (1.0 equiv) and Ti(O*i*Pr)$_4$ (10 mol%) in dichloromethane (0.1 M). The mixture was heated under reflux for 2 (for compounds **4**, **9**, and **21**) or 12 h (for compounds **16**) and then concentrated to dryness and purified by means of flash chromatography on silica gel by using mixtures of dichloromethane/ethyl acetate as the eluents.

(*E*)-7-*N*-[(S_S)-*p*-Tolylsulfinyl]-3-hepten-2-one (4a): Compound (S_S)-**4a** (105 mg) was synthesized by following the general procedure described above by starting from 150 mg of (S_S)-**3a** (0.67 mmol) as a light-brown oil (70% yield). $[\alpha]_D^{25} = +86.9$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (300 MHz,

$CDCl_3$): $\delta = 1.60$–1.67 (m, 2H), 2.14 (s, 3H), 2.20 (m, 2H), 2.38 (s, 3H), 2.76–2.81 (m, 1H), 2.99–3.10 (m, 1H), 4.26 (t, $J = 3.2$ Hz, 1H), 5.97 (d, $J = 16.0$ Hz, 1H), 6.66 (dt, $J_1 = 16.0$, $J_2 = 6.9$ Hz, 1H), 7.28 (d, $J = 8.1$ Hz, 2H), 7.53 ppm (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta =$ 21.1, 26.6, 29.0, 29.5, 40.3, 125.8, 129.5, 131.7, 141.3, 141.6 146.8, 198.0 ppm; HRMS (EI): m/z: calcd for $C_{14}H_{20}NO_2S$: 266.1214 [M^++1]; found: 266.1222.

(*E*)-*tert*-Butyl 6-*N*-[(R_S)-*tert*-butylsulfinyl]-2-hexenoate (9a): Compound (R_S)-**9a** (129 mg) was synthesized by following the general procedure described above by starting from 100 mg of (R_S)-**3b** (0.53 mmol) as a light-brown oil (84% yield). $[\alpha]_D^{25} = -46.7$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (s, 9H), 1.44 (s, 9H), 1.65–1.74 (m, 2H), 2.18–2.25 (m, 2H), 3.03–3.22 (m, 3H), 5.72 (dt, $J_1 = 15.6$, $J_2 = 1.5$ Hz, 1H), 6.79 ppm (dt, $J_1 = 15.6$, $J_2 = 6.9$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 22.5$, 28.0, 29.1, 29.3, 44.9, 55.5, 80.1, 123.7, 146.4, 165.7 ppm; HRMS (EI): m/z: calcd for $C_{14}H_{27}NO_3S$: 289.1712 [M^+]; found: 289.1187.

(*E*)-7-*N*-[(R_S)-*tert*-Butylsulfinyl][(7*R*)-isopropyl]-3-hepten-2-one (16a): Compound (R,R_S)-**16a** (141 mg) was synthesized by following the general procedure described above by starting from 120 mg of (R,R_S)-**15a** (0.52 mmol) as a light-brown oil (>99% yield). $[\alpha]_D^{25} = +3.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.91$ (dd, $J_1 = 8.1$, $J_2 = 7.1$ Hz, 6H) 1.19 (s, 9H), 1.40–1.68 (m, 2H), 1.87–2.08 (m, 1H), 2.10–2.21 (m, 1H), 2.13 (s, 3H), 2.29–2.45 (m, 1H), 3.00–3.08 (m, 1H), 3.14 (d, $J =$ 7.5 Hz, 1H), 6.05 (d, $J = 15.9$ Hz, 1H), 6.75 ppm (dt, $J_1 = 15.9$, $J_2 = 7.1$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 17.6$, 18.4, 22.6, 26.8, 29.0, 30.3, 32.3, 56.0, 61.4, 131.4, 147.3, 198.4 ppm; HRMS (FAB): m/z: calcd for $C_{14}H_{28}NO_2S$: 274.1840 [M^++1]; found: 274.1834.

(*E*)-8-*N*-[(S_S)-*tert*-Butylsulfinyl][(8*R*)-methyl]-3-octen-2-one (21a): Compound (R,S_S)-**21a** (353 mg) was synthesized by following the general procedure described above by starting from 300 mg of sulfinyl amine (R,S_S)-**20a** (1.38 mmol) as a light-brown oil (>99% yield). $[\alpha]_D^{25} = +33.4$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.17$ (s, 9H), 1.24 (d, $J =$ 6.6 Hz, 3H), 1.39–1.58 (m, 4H), 2.17–2.22 (m, 2H), 2.22 (s, 3H), 2.87 (d, $J = 6.9$ Hz, 1H), 3.33 (m, 1H), 6.04 (d, $J = 15.9$ Hz, 1H), 6.75 ppm (dt, $J_1 = 15.9$, $J_2 = 7.1$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 22.5$, 23.1, 24.2 26.9, 32.1, 37.4, 52.1, 55.5, 131.4, 147.6, 198.5 ppm; HRMS (FAB): m/z: calcd for $C_{13}H_{26}NO_2S$: 260.1684 [M^++1]; found: 260.1686.

Synthesis of cyclic β-amino carbonyl derivatives through the IMAMR

Method A: General procedure for the anionic cyclization: The corresponding base (0.3–1 equiv) was added to a solution of sulfinyl amine (1.0 equiv) in an appropriate solvent (0.1 M), and the resulting mixture was stirred until TLC revealed the disappearance of the starting material (see Tables 2, 3, and 6 and Schemes 4 and 10). The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and the solvents were removed under reduced pressure. Finally, the crude mixtures were purified by means of flash chromatography on silica gel by using mixtures of dichloromethane/ethyl acetate as the eluents.

Method B: General procedure for tandem protocol: The corresponding sulfinyl amine **3** (1.0 equiv) was dissolved in dichloromethane (0.1 M) and $Ti(OiPr)_4$ (10 mol%) was added dropwise. Methyl vinyl ketone (5.0 equiv) and second-generation ruthenium alkylidene catalyst I or II (10 mol%) were successively added. The resulting solution was heated under the conditions indicated in Table 4 and then it was concentrated to dryness and purified by means of flash chromatography on silica gel by using mixtures of dichloromethane/ethyl acetate as the eluents.

***N*-[(R_S)-*tert*-Butylsulfinyl]-2*R*-(2-oxopropyl)pyrrolidine (6b)**: Compound (R,R_S)-**6b** was synthesized by following the general procedure described above (method B) by starting from 50 mg of sulfinyl amine (R_S)-**3b** (0.26 mmol) and methyl vinyl ketone to afford 51 mg of a light-yellow oil (84% yield). $[\alpha]_D^{25} = -26.5$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$ (s, 9H), 1.55 (m,1H), 1.70 (m, 2H), 1.88 (m, 1H), 2.17 (s, 3H), 2.60 (dd, $J_1 = 16.8$, $J_2 = 8.8$ Hz, 1H), 2.95–2.05 (m, 2H), 3.55 (dt, $J_1 = 7.9$, $J_2 = 5.2$ Hz, 1H), 4.06 ppm (m, 1H);. ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 23.6$, 23.8, 30.6, 31.6, 44.8, 47.7, 56.7, 57.7, 206.8 ppm; HRMS (EI): m/z: calcd for $C_{11}H_{22}NO_2S$: 232.1371 [M^++1]; found: 232.1381.

***N*-[(S_S)-*p*-Tolylsulfinyl]-2*R*-(2-oxopropyl)piperidine (8a)**: Compound (R,S_S)-**8a** was synthesized by following the general procedure described above (method A) at room temperature by starting from 50 mg of enone (S_S)-**4c** (0.18 mmol) to afford 42 mg of a white solid (85% yield). M.p. = 81–83 °C; $[\alpha]_D^{25} = +76.6$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.40$–1.81 (m, 6H), 2.16 (s, 3H), 2.38 (s, 3H), 2.72 (dd, $J_1 = 16.5$, $J_2 =$ 7.2 Hz, 1H), 2.95–3.10 (m, 2H), 3.15 (dd, $J_1 = 16.5$, $J_2 = 6.0$ Hz, 1H), 3.91–3.98 (m, 1H), 7.26 (d, $J = 8.1$ Hz, 2H), 7.46 ppm (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 20.5$, 21.3, 26.2, 30.5, 30.8, 43.0, 46.2, 52.9, 126.2, 129.5, 140.5, 140.9, 206.1 ppm; HRMS (EI): m/z: calcd for $C_{15}H_{21}NO_2S$: 279.1293 [M^+]; found: 279.1286.

***N*-[(R_S)-*tert*-Butylsulfinyl]-2*S*-(2-oxopropyl)-5*R*-isopropylpyrrolidine (17a)**: Compound (2*S*,5*R*,R_S)-**17a** was synthesized by following the general procedure described above (method A) at room temperature by starting from 25 mg of enone (R,R_S)-**16a** (0.09 mmol) to afford 20 mg of a light-yellow oil (80% yield). $[\alpha]_D^{25} = -14.7$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (dd, $J_1 = 8.1$, $J_2 = 7.1$ Hz, 6H), 1.18 (s, 9H), 1.34–1.46 (m,1H), 1.65–1.72 (m, 2H), 1.78–1.89 (m, 1H), 2.03–2.15 (m, 1H), 2.10 (s, 3H), 2.51 (dd, $J_1 = 16.8$, $J_2 = 9.4$ Hz, 1H), 2.97 (dd, $J_1 = 16.8$, $J_2 = 4.7$ Hz, 1H), 3.58–3.64 (m, 1H), 4.10–4.19 ppm (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 17.5$, 20.2, 23.5, 26.5, 30.3, 31.3, 31.4, 51.4, 57.3, 61.0, 61.2, 206.7 ppm; HRMS (FAB): m/z: calcd for $C_{14}H_{28}NO_2S$: 274.1840 [M^++1]; found: 274.1845.

***N*-[(S_S)-*tert*-Butylsulfinyl]-2*R*-(2-oxopropyl)-6*R*-methylpiperidine (22a)**: Compound (2*R*,6*R*,S_S)-**22a** was synthesized by following the general procedure described above (method A) from −40 °C to room temperature by starting from 150 mg of enone (R,S_S)-**21a** (0.59 mmol) to afford 92 mg of a light-yellow oil (61% yield). $[\alpha]_D^{25} = +1.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H and ^{13}C NMR spectra show the presence of rotamers in a 1:1.2 ratio; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.14$ (s, 9H), 1.24 (d, $J = 7.5$ Hz, 3H), 1.34–1.51 (m, 2H), 1.59–1.69 (m, 4H), 2.15 (s, 3H), 2.56–2.63 (m, 1H), 2.85 (d, $J = 6.6$ Hz, 1H), 3.67–3.70 (m, 1H), 4.06–4.08 ppm (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.8$, 19.8, 21.1, 23.1, 23.9, 28.7, 30.5, 30.6, 30.7, 49.4, 58.0, 58.1, 205.8, 206.7 ppm; HRMS (FAB): m/z: calcd for $C_{13}H_{26}NO_2S$: 260.1690 [M^++1]; found: 260.1692.

General procedure for the synthesis of enantioenriched amines 15 and 20a: $Ti(OEt)_4$ (5.0 equiv) and 4-pentenal or 5-hexenal (1.1 equiv) were added dropwise to a solution of *tert*-butylsulfinamide **2b** (1.0 equiv) in dichloromethane (0.25 M). The solution was stirred at room temperature for 20 h. At this time, saturated aqueous $NaHCO_3$ was added until white titanium salts precipitated. The suspension was filtered through a short pad of Celite washing with small portions of ethyl acetate. The filtrate was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude mixture was then dissolved in dichloromethane (0.25 M) and cooled down to −60 °C. The appropriate Grignard reagent (2.0 equiv) was slowly added at this temperature. After 1.5 h, the reaction was quenched with saturated NH_4Cl and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under vacuum, and purified by means of flash chromatography on silica gel by using *n*-hexane/ethyl acetate as the eluents. The absolute configuration for amines **15** was assigned according to previous results described by Ellman of Grignard additions to *tert*-butylsulfinimines.

***N*-[(R_S)-*tert*-Butylsulfinyl][(2*R*)-isopropyl]-6-hepten-1-amine (15c)**: Compound (R,R_S)-**15c** (746 mg) was synthesized by following the general procedure described above by starting from 485 mg of (*R*)-(+)-*tert*-butylsulfinamide **2b** (4.00 mmol) as a colorless oil (76% yield). $[\alpha]_D^{25} = -35.6$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (dd, $J_1 = 8.1$, $J_2 = 7.1$ Hz, 6H), 1.19 (s, 9H), 1.30–1.40 (m,2H), 1.40–1.56 (m, 2H), 1.89–1.98 (m, 1H), 1.98–2.10 (m, 2H), 3.04 (m, 1H), 3.06 (m, 1H) 4.93 (ddt, $J_1 = 9.8$, $J_2 = 3.4$, $J_3 = 1.3$ Hz, 1H), 4.98 (ddt, $J_1 = 16.8$, $J_2 = 3.4$, $J_3 = 1.6$ Hz, 1H), 5.78 ppm (ddt, $J_1 = 16.8$, $J_2 = 9.8$, $J_3 = 3.2$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 17.7$, 18.2, 22.6, 25.3, 31.1, 32.3, 33.5, 55.9, 61.8, 144.6, 138.4 ppm; HRMS (FAB): m/z: calcd for $C_{13}H_{28}NOS$: 246.1891 [M^++1]; found: 246.1893.

***N*-[(S_S)-*tert*-Butylsulfinyl][(2*R*)-methyl]-6-hepten-1-amine (20a)**: Compound (R,S_S)-**20a** (640 mg) was synthesized by following the general pro-

cedure described above by starting from 500 mg of (*S*)-(−)-*tert*-butylsulfinamide (4.12 mmol) as a colorless oil (71% yield). $[\alpha]_D^{25}=+41.8$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.17$ (s, 9H), 1.24 (d, $J=6.5$ Hz, 3H), 1.39–1.49 (m, 4H), 1.98–2.05 (m, 2H), 2.84 (d, $J=7.2$ Hz, 1H), 3.32 (m, 1H), 4.93 (ddt, $J_1=9.8$, $J_2=3.4$, $J_3=1.3$ Hz, 1H), 4.98 (ddt, $J_1=16.8$, $J_2=3.4$, $J_3=1.6$ Hz, 1H), 5.76 ppm (ddt, $J_1=16.8$, $J_2=9.8$, $J_3=3.2$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=22.5$, 23.2, 24.9, 33.4, 37.4, 52.4, 55.5, 114.6, 138.4 ppm; HRMS (FAB): *m*/*z*: calcd for $C_{11}H_{24}NOS$: 218.1578 [M^++1]; found: 218.1574.

General procedure for the synthesis of *N*-Cbz-protected amines 23: Hydrogen chloride (5.0 equiv, 4 M solution in 1,4-dioxane) was added at room temperature to a solution of the corresponding *N*-*tert*-butylsulfinyl piperidine **22** (1.0 equiv) in MeOH (0.1 M). After 30 min, the deprotection was completed and the solution was concentrated to dryness. The amine hydrochloride was taken up in 1,4-dioxane (0.1 M) and then K_2CO_3 50% water solution (2.0 equiv) and benzyl chloroformate (2.5 equiv) were consecutively added. The solution was stirred for 30 min at room temperature and concentrated under vacuum. The mixture was poured into a separating funnel over water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under vacuum, and purified by means of flash chromatography on silica gel by using *n*-hexane/diethyl ether as the eluents.

***N*-Benzyloxycarbonyl-2*R*-(2-oxopropyl)-6*R*-methylpiperidine (23a)**: Compound (2*R*,6*R*)-**23a** was synthesized by following the general procedure described above by starting from 50 mg of piperidine (2*R*,6*R*,S_S)-**22a** (0.19 mmol) to afford 55 mg of a colorless oil (>99% yield). $[\alpha]_D^{25}=-7.1$ ($c=1.0$ in $CHCl_3$); ^{1}H and ^{13}C NMR spectra show the presence of rotamers about the carbamate bond in an 1:4.5 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.16$ (d, $J=7.2$ Hz, 0.5H), 1.25 (d, $J=6.6$ Hz, 2.5H), 1.52–1.81 (m, 6H), 2.08 (s, 3H), 2.56 (dd, $J_1=15.9$, $J_2=8.4$ Hz, 1H), 2.75 (dd, $J_1=15.6$, $J_2=10.5$ Hz, 0.2H), 2.95 (dd, $J_1=16.4$, $J_2=4.8$ Hz, 0.8H), 4.13–4.20 (m, 0.8H), 4.21–4.29 (m, 0.8H), 4.31–4.42 (m, 0.2H), 4.62–4.68 (m, 0.2H), 5.04–5.51 (m, 2H), 7.26–7.37 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=13.4$, 14.3, 19.7, 25.4, 27.0, 27.6, 29.7, 29.8, 29.9, 45.9, 46.2, 47.5, 47.7, 48.2, 48.4, 66.6, 66.8, 127.7, 127.8, 128.3, 136.7. 136.8, 155.3, 206.8 ppm; HRMS (FAB): *m*/*z*: calcd for $C_{17}H_{24}NO_3$: 290.1756 [M^++1]; found: 290.1767.

General procedure for the synthesis of γ-amino alcohols 24: $NaBH_4$ (1.5 equiv) was added at −78 °C to a solution of the corresponding piperidine **23** (1.0 equiv) in MeOH (0.05 M). The mixture was stirred at this temperature for 10 h and then it was quenched with aqueous saturated NH_4Cl and extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, concentrated under vacuum, and purified by means of flash chromatography on silica gel by using *n*-hexane/ethyl acetate as the eluents.

***N*-Benzyloxycarbonyl-2*R*-(2*R*-hydroxypropyl)-6*R*-methylpiperidine (24a)**: Compound (2*R*,2*R*′,6*R*)-**24a** was synthesized by following the general procedure described above by starting from 46 mg of piperidine (2*R*,6*R*)-**23a** (0.16 mmol) to afford 45 mg of a colorless oil (92% yield). $[\alpha]_D^{25}=-28.8$ ($c=1.0$ in $CHCl_3$); ^{1}H and ^{13}C NMR spectra show the presence of rotamers about the carbamate bond in an 1:1.1 ratio; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.16$ (d, $J=6.2$ Hz, 3H), 1.24 (d, $J=6.5$ Hz, 3H), 1.37–1.97 (m, 8H), 3.66–3.83 (m, 1H), 3.96–4.07 (m, 1.6H), 4.24 (m, 0.2H), 3.35 (m, 0.1H), 5.07–5.19 (m, 2H), 7.28–7.36 ppm (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=12.7$, 20.6, 23.7, 24.3, 26.3, 45.8, 47.2, 49.5, 66.1, 66.9, 127.8, 127.9, 128.4, 136.6, 156.1 ppm; HRMS (EI): *m*/*z*: calcd for $C_{17}H_{25}NO_3$: 291.1834 [M^+]; found: 291.1822.

General procedure for the synthesis of (−)-pinidinol (19a) and its fluorinated analogue 19b: 20% $Pd(OH)_2$ (10 mol%) was added to a solution of the corresponding *N*-Cbz-protected piperidine **24** (1.0 equiv) in MeOH (0.05 M) and the suspension was stirred under H_2 (1 atm) for 2 h. The reaction mixture was then filtered through a short pad of Celite washing with diethyl ether. Hydrogen chloride (5.0 equiv, 4 M solution in 1,4-dioxane) was added to the filtrate and, after stirring for 30 min, solvents were removed under reduced pressure. Finally, the crude mixture was washed with diethyl ether to afford the piperidine hydrochlorides **19**.

(−)-Pinidinol·HCl (19a): Compound (2*R*,2*R*′,6*R*)-**19a** was synthesized by following the general procedure described above by starting from 30 mg of piperidine (2*R*,2*R*′,6*R*)-**24a** (0.10 mmol) to afford 17 mg of a white solid (>99% yield). $[\alpha]_D^{25}=-21.4$ ($c=0.3$ in $CHCl_3$). All spectroscopic data were corroborated by values found in literature.[21d]

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[1] a) D. O'Hagan, *Nat. Prod. Res.* **2000**, *17*, 435; b) P. M. Weintraub, J. S. Sabor, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953; c) S. Laschat, T. Dickner, *Synthesis* **2000**, 1781.

[2] a) C. Escolano, M. Amat, J. Bosch, *Chem. Eur. J.* **2006**, *12*, 8198; b) J. W. Daly, T. F. Spande, H. M. Garraffo, *J. Nat. Prod.* **2005**, *68*, 1556; c) M. G. P. Buffat, *Tetrahedron* **2004**, *60*, 1701; d) P. M. Weintraub, J. S. Sabor, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953; e) M. D. Groaning, A. I. Meyers, *Tetrahedron* **2000**, *56*, 9843; f) S. Leclercq, J. C. Braekman, D. Daloze, J. M. Pasteels, *Prog. Chem. Org. Nat. Prod.* **2000**, *79*, 115; g) J. W. Daly, H. M. Garraffo, T. F. Spende in *Alkaloids: Chemical and Biological Perspectives, Vol. 13* (Ed.: S. W. Pelletier), Pergamon, New York, **1999**, Chapter 1; h) M. Schneider in *Alkaloids: Chemical and Biological Perspectives, Vol. 10* (Ed.: S. W. Pelletier), Pergamon, Oxford, **1996**, p. 55.

[3] a) B. H. Kim, H. B. Lee, J. K. Hwang, Y. G. Kim, *Tetrahedron: Asymmetry* **2005**, *16*, 1215; b) M. Nyerges, D. Bendell, A. Arany, D. E. Hibbs, S. J. Coles, M. D. Hursthouse, P. W. Groundwater, O. Meth-Cohn, *Synlett* **2003**, 0947; c) F. Fache, E. Schultz, M. L. Tomasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159; d) J. A. Sweet, J. M. Cavallari, W. A. Price, J. W. Ziller, D. V. McGrath, *Tetrahedron: Asymmetry* **1997**, *8*, 207; e) J. K. Whitesell, *Chem. Rev.* **1989**, *89*, 1581.

[4] For recent reviews, see: a) P. R. Krishna, A. Sreesailam, R. Srinivas, *Tetrahedron* **2009**, *65*, 9657; b) J. L. Vicario, D. Badía, L. Carrillo, J. Etxebarría, E. Reyes, N. Ruiz, *Org. Prep. Proced* **2005**, *37*, 513.

[5] a) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J.* **2009**, *15*, 11058; b) J. L. Vicario, D. Badia, L. Carrillo, *Synthesis* **2007**, 2065; c) L.-W. Xu, C.-G. Xia, *Eur. J. Org. Chem.* **2005**, 633.

[6] For a recent review, see: S. G. Davies, A. D. Smith, P. D. Price, *Tetrahedron: Asymmetry* **2005**, *16*, 2833.

[7] a) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem.* **2008**, *120*, 3282; *Angew. Chem. Int. Ed.* **2008**, *47*, 3238; b) S. Fustero, J. Moscardó, D. Jiménez, M. D. Pérez-Carrión, M. Sánchez-Roselló, C. del Pozo, *Chem. Eur. J.* **2008**, *14*, 9868; c) E. C. Carlson, L. K. Rathbone, H. Yang, N. D. Collett, R. G. Carter, *J. Org. Chem.* **2008**, *73*, 5155; d) S. Fustero, D. Jiménez, J. Moscardó, S. Catalán, C. del Pozo, *Org. Lett.* **2007**, *9*, 5283; e) K. Takasu, S. Maiti, M. Ihara, *Heterocycles* **2003**, *59*, 51.

[8] For recent reviews, see: a) G.-Q. Lin, M.-H. Xu, Y.-W. Zhong, X.-W. Sun, *Acc. Chem. Res.* **2008**, *41*, 831; b) F. A. Davis, *J. Org. Chem.* **2006**, *71*, 8993; c) P. Zhou, B.-C. Chen, F. A. Davis, *Tetrahedron* **2004**, *60*, 8003; d) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651; e) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984.

[9] For some representative examples, see: a) F. A. Davis, J. Deng, *Org. Lett.* **2007**, *9*, 1707; b) F. A. Davis, Y. Wu, H. Yan, W. McCoull, K. R. Prasad, *J. Org. Chem.* **2003**, *68*, 2410; c) F. A. Davis, Y. Wu, H. Yan, K. R. Prasad, W. McCoull, *Org. Lett.* **2002**, *4*, 655; d) T. P. Tang, J. A. Ellman, *J. Org. Chem.* **2002**, *67*, 7819.

[10] To the best of our knowledge, only one example of a CM reaction involving sulfinyl amines was reported in the literature: J. C. González-Gómez, F. Foubelo, M. Yus, *Synlett* **2008**, 2702.
[11] In the absence of the Lewis acid the reaction did not proceed. Other Lewis acids, such as $BF_3{\cdot}OEt_2$, gave the CM product **4b** in only 21% yield.
[12] A recent study of the intramolecular aza-Michael reaction under basic conditions showed a similar influence of the base in the selectivity: C. Enkisch, C. Schneider, *Eur. J. Org. Chem.* **2009**, 5549.
[13] An analogue π-stacking interaction was previously invoked to explain the selectivity found in the intermolecular aza-Michael reaction of amines to 8-phenylmenthol-derived enoates: F. Dumas, B. Mezrhab, J. d'Angelo, *J. Org. Chem.* **1996**, *61*, 2293.
[14] Although under basic conditions the formation of piperidine derivatives were more favorable with *p*-tolyl sulfinyl amines, the corresponding CM reaction to obtain the Michael acceptor took place in only 5% yield, and we decided to use the *tert*-butyl sulfinyl amine in the process.
[15] We have previously described in a preliminary communication the synergistic effect of second-generation Hoveyda–Grubbs catalyst with boron trifluoride in an analogous tandem process with carbamates as the source of the nucleophilic nitrogen: S. Fustero, D. Jiménez, M. Sánchez-Roselló, C. del Pozo, *J. Am. Chem. Soc.* **2007**, *129*, 6700.
[16] The inversion of selectivity in an intramolecular aza-Michael process under base or Lewis acid catalysis has previously been observed: S. Sukemoto, M. Oshige, M. Sato, K. Mimura, H. Nishioka, H. Abe, T. Harayama, Y. Takeuchi, *Synthesis* **2008**, 3081.
[17] a) H. Takahata, M. Kubota, S. Takahashi, T. Momose, *Tetrahedron: Asymmetry* **1996**, *7*, 3047; b) F. Galinovsky, F. Bianchetti, O. Vogel, *Monatsh. Chem.* **1953**, *84*, 1221. For a recent synthesis, see reference [7c].
[18] G. Liu, D. A. Cogan, J. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913.
[19] a) M. J. Schneider, J. A. Montali, D. Hazen, C. E. Stanton, *J. Nat. Prod.* **1991**, *54*, 905; b) M. J. Schneider, F. R. Stermitz, *Phytochemistry* **1990**, *29*, 1811.
[20] a) L. V. Nechev, I. Kozedov, T. M. Harris, *Chem. Res. Toxicol.* **2001**, *14*, 1506; b) P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.* **1998**, 633.
[21] a) F. A. Davis, P. M. Gaspari, B. Nolt, P. Xu, *J. Org. Chem.* **2008**, *73*, 9619; b) J. Gebauer, D. Rost, S. Blechert, *Heterocycles* **2006**, *68*, 2129; c) S. Fréville, P. Delbecq, V. M. Thuy, H. Petit, J. P. Célérier, G. Lhommet, *Tetrahedron Lett.* **2001**, *42*, 4609; d) G. A. Molander, E. D. Dowdy, S. D. Pack, *J. Org. Chem.* **2001**, *66*, 4344; e) H. Takahata, Y. Yotsui, T. Momose, *Tetrahedron* **1998**, *54*, 13505.
[22] S. C. Kuduk, C. N. Di Marco, S. M. Pitzenberger, N. Tsou, *Tetrahedron Lett.* **2006**, *47*, 2377.
[23] Only the reduction with $LiEt_3BH$ in CH_2Cl_2 at −78 °C furnished the desired diastereoisomer although in a modest 30% yield.

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