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Organocatalytic Enantioselective Synthesis of Trifluoromethyl-Containing Tetralin Derivatives by Sequential (Hetero)Michael Reaction-Intramolecular Nitrone Cycloaddition

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Dedicated to Prof. Dr. Günter Haufe on the occasion of his retirement

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Abstract. The enantioselective synthesis of tetralin derivatives bearing a trifluoromethylated all-carbon quaternary stereocenter has been accomplished through a synthetic sequence comprising an organocatalytic β-functionalization of *ortho*-1-trifluoromethylvinyl (hetero)aromatic conjugated aldehydes followed by intramolecular nitrone 1,3-cycloaddition reaction (INCR). Both nitromethane and *N*-Cbz-hydroxylamine were employed as nucleophiles in the initial organocatalytic conjugate addition step, which provided the chiral information required for the subsequent diastereoselective INCR. Although diastereoselectivity was moderate, good yields and enantioselectivities were, in general, obtained. Interestingly, an inversion of the selectivity in the intramolecular cycloaddition step was observed when either nitromethane or *N*-Cbz-hydroxylamine were employed. This outcome was studied by means of theoretical calculations, which were in agreement with the experimental results. In addition, the ring opening of the isoxazolidine moiety rendered the corresponding fluorinated diamino alcohols in a very efficient manner.

Keywords: fluorinated tetralins; organocatalysis, quaternary stereocenter, nitro-Michael addition; aza-Michael addition; fluorinated amino alcohols

Introduction

The tetralin or 1,2,3,4-tetrahydronaphthalene core is present in a great variety of natural products and drugs,[1] therefore being classified as a privileged structural motif for the construction of drug-like molecules.[2] Consequently, synthetic efforts to access these valuable building blocks, especially in enantiomerically enriched form, are always of high interest.

Nowadays, the introduction of fluorinated groups into biologically active compounds has become a powerful strategy in order to modulate their biological properties.[3] In particular, the occurrence of the CF_3 group in pharmaceuticals is remarkable since it can enhance the lipophilicity and metabolic stability of the non-fluorinated parent molecules.[4] For that reason, the development of methodologies that enable the synthesis of novel CF_3-containing scaffolds has attracted growing attention.[5] However, the incorporation of fluorinated moieties in the carbon skeleton of chiral tetralins has been scarcely explored to date.[6]

On the other hand, nitrones are the most widely used types of dipoles in 1,3-dipolar cycloadditions.[7] They are easy to prepare from readily available starting materials and show high stability in comparison with other types of dipoles.[8] They react with a large variety of dipolarophiles, generating either isoxazole or isoxazolidine scaffolds in a very simple manner.[9]

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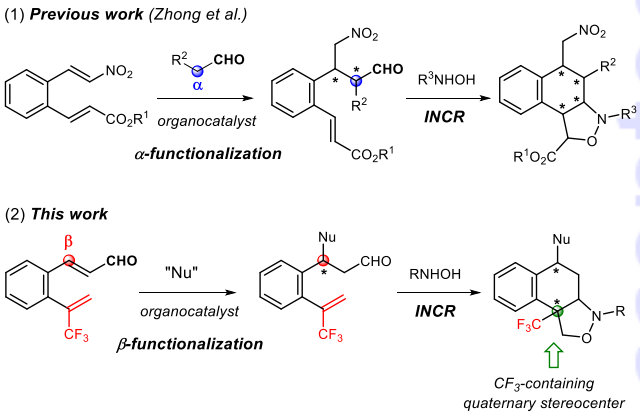
Considering the ubiquitous presence of these heterocycles in biologically relevant compounds, examples of its preparation by using this [3+2] cycloaddition reaction are widespread in the literature.[10] Additionally, isoxazoles and isoxazolidines are versatile synthetic intermediates, easily transformed to β-amino acids, β-lactams, or β-amino alcohols.[11] Also, other heterocyclic systems can be accessed through different reactions, including Mannich-type,[12] and Kinugasa[13] reactions as well as less common transformations.[14]

The asymmetric version of this 1,3-dipolar cycloaddition reaction of nitrones has received significant attention as it allows the generation of those interesting derivatives in enantiomerically enriched manner.[15] Early examples relied on the use of chiral starting materials, mainly based on chiral nitrones derived from amino acids[16] and sugars.[17] With the development of enantioselective catalysis, a large number of reports have appeared in the literature that take advantage of both transition metal catalysis[18] and organocatalysis,[19] reaching a high degree of control in the diastereo- and enantioselectivity of the process.

Despite this exponential growth, recently highlighted by Maruoka,[15b] the intramolecular version of those reactions is still a big challenge[20] and, as far as we know, no examples of enantioselective intramolecular [3+2] cycloadditions of nitrones have been described to date.[21] The main difficulty for achieving this transformation is to design the correct system in which the cycloaddition is favored once the nitrone is generated *in situ*. Generation of nitrones is usually made by either condensation or oxidation processes,[8] which should be compatible with the presence of the catalyst whether it is a chiral Lewis acid[22] or an organocatalyst.[23] The electronic nature of the reaction[24] and the spontaneous cyclization that may take place once the nitrone is generated in the presence of the dipolarophile (background reactivity) pose additional inherent difficulties.

In order to incorporate the chiral information for the asymmetric intramolecular cycloaddition of nitrones, a successfully employed strategy is the combination of this process with a previous organocatalytic event. In this manner, the enantioselectivity induced in the organocatalytic step is transferred to the final products in the subsequent cyclization step. In this context, the organocatalytic α-functionalization of aldehydes is a well established methodology, using enamine catalysis with chiral secondary amines such as Jørgensen-Hayashi or MacMillan catalysts.[25] Most examples that merge organocatalytic processes with intramolecular nitrone cycloaddition reactions (INCR) rely on this strategy, usually by means of an enantioselective conjugated addition reaction of aldehydes to nitroalkenes or α,β-unsaturated systems.[26] For example, Zhong described this reaction on β-nitrostyrenes bearing a suitable dipolarophile in the *ortho* position for the synthesis of highly substituted enantiomerically pure tetralins (Scheme 1, eq. 1).[26c] To date, only one example of β-functionalization of aldehydes has been reported in combination with an INCR, taking advantage of iminium catalysis.[27] With these precedents, and inspired by our interest in organofluorine chemistry, we envisioned the possibility of employing cinnamaldehydes, substituted at the *ortho* position with a 1-trifluoromethyl alkene moiety, as starting substrates to carry out an organocatalytic nucleophilic conjugate addition followed by INCR. By means of this sequence, that employs the almost unprecedented 1-trifluoromethyl alkene as dipolarophile,[28] a novel family of fluorinated tetralins bearing an all-carbon CF_3-containing quaternary stereocenter will be obtained (Scheme 1, eq. 2). It is worth mentioning that the development of new synthetic strategies for the enantioselective construction of all-carbon quaternary chiral centers bearing a CF_3 group represents an important challenge in organic synthesis. In fact, few examples have recently been reported in the literature, and all of them concern intermolecular processes.[29]

Finally, ring opening of the isoxazolidine cycle would render valuable fluorinated 1,3-amino alcohols as precursors of the corresponding fluorinated β-amino acids.[30]



Scheme 1. Synthetic strategies towards chiral tetralines.

Results and Discussion

Very recently we disclosed the utility of α-trifluoromethyl styrenes as suitable dipolarophiles for the intramolecular nitrone cycloaddition reaction (INCR). In this work, we found that the CF_3 acts as a directing group in controlling the regiochemistry of the cyclization process, affording preferential or exclusively the corresponding fused tricyclic

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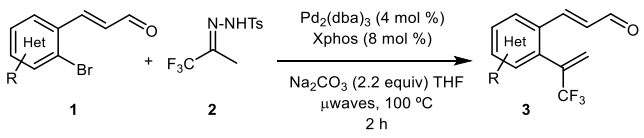
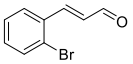
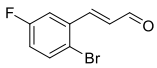
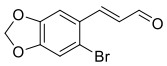
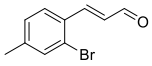
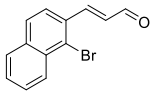
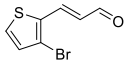
cycloadducts.[28] The next step in our study was directed towards the enantioselective version of this transformation. Following an analogous methodology, the preparation of the starting *ortho*-substituted cinnamaldehydes **3a-d** and related compounds **3e,f** was performed by means of a palladium-catalyzed cross-coupling reaction of 1,1,1-trifluoroacetone tosylhydrazone **2** with several *ortho*-bromo cinnamaldehydes or derivatives **1**.[31] Under optimized reaction conditions, good to excellent yields of conveniently functionalized (trifluoromethyl)styrenes **3** were obtained, as depicted in Table 1.

Table 1. Synthesis of the starting CF_3-containing α,β-unsaturated aldehydes **3**



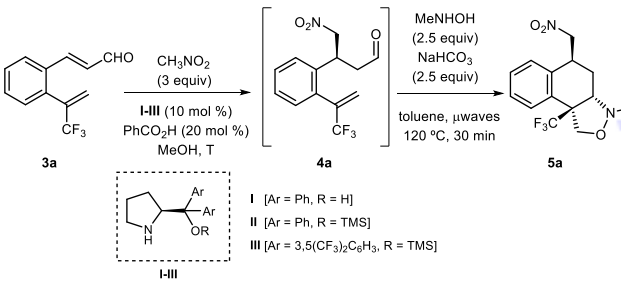
Entry	1	3	Yield [%][a]
1	 **1a**	**3a**	89
2	 **1b**	**3b**	88
3	 **1c**	**3c**	81
4	 **1d**	**3d**	99
5	 **1e**	**3e**	82
6	 **1f**	**3f**	90

[a] Isolated yields after flash column chromatography.

With the starting materials in hand, the organocatalytic β-functionalization of the aldehyde moiety was examined next. Iminium catalysis is well known to enable the enantioselective functionalization at the β-position of enals by means of a Michael-type nucleophilic addition. In this manner, we would generate suitable precursors of the nitrone functionality, bearing a stereodefined center at the β position, able to undergo the INCR in a diastereoselective fashion.

The first Michael donor we chose was nitromethane since its addition to cinnamaldehydes was successfully reported by Hayashi in 2007.[32] The enantioselective synthesis of chiral pharmaceuticals such as *baclofen* or *pregabalin* in the cited work illustrates how useful nitromethane is as an aminomethylation reagent. Bearing this precedent in mind, a slight optimization of the reaction conditions was carried out on fluorinated cinnamaldehyde **3a** as a model substrate (Table 2). Following the conditions previously described for the organocatalytic conjugate addition of nitroalkanes to enals,[32] a first attempt was made with nitromethane, employing diphenylprolinol (**I**) as the catalyst in methanol at room temperature. The complete consumption of the starting aldehyde **3a** was observed after 7 days, when solvents were removed under reduced pressure. After standard aqueous work-up, the crude mixture was re-dissolved in toluene and subjected to the INCR in the presence of *N*-methylhydroxyl amine hydrochloride and sodium bicarbonate. Heating the reaction mixture under microwave irradiation at 120ºC for 30 min gave rise to a 4:1 mixture of diastereomeric tetrahydronaphthalene isoxazolidines in 29% overall yield. Both diastereoisomers were separated by column chromatography and the major one **5a** was obtained in 82% ee (Table 2, entry 1). When diphenylprolinol silyl ether (**II**) was employed as the chiral catalyst, the disappearance of the starting material was observed after 16 hours at room temperature. Upon condensation with *N*-methylhydroxyl amine, the INCR took place efficiently affording again a 4:1 mixture of diastereoisomers in 46% yield and complete enantioselection in favor of compound **5a** (Table 2, entry 2). Trying to improve the diastereoselectivity of the process, lower temperatures in the organocatalytic Michael addition step were tested. However, neither at 0ºC nor at 10ºC the reaction progressed after 16h (Table 2, entries 3, 4). Finally, bis(trifluoromethyl) substituted catalyst **III** was also tested, resulting in product **5a** in 39% yield and 86% ee (Table 2, entry 5).

Table 2. Optimization of the sequence nitro-Michael addition/INCR



entry	Catalyst	T [ºC]	Time	Yield [%][a],[b]	ee [%][c]
1	**I**	25	7d	29	82
2	**II**	25	16h	46	>99
3	**II**	0	16h	-[d]	-
4	**II**	10	16h	-[d]	-
5	**III**	25	10d	39	86

[a] Isolated yield after flash column chromatography (from **3a**, without purifying intermediate **4a**).
[b] The INCR gave a 4:1 mixture of diastereoisomers, as determined by ^{19}F-NMR of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase; see Supporting Information for details.
[d] No conversion in the organocatalytic step.

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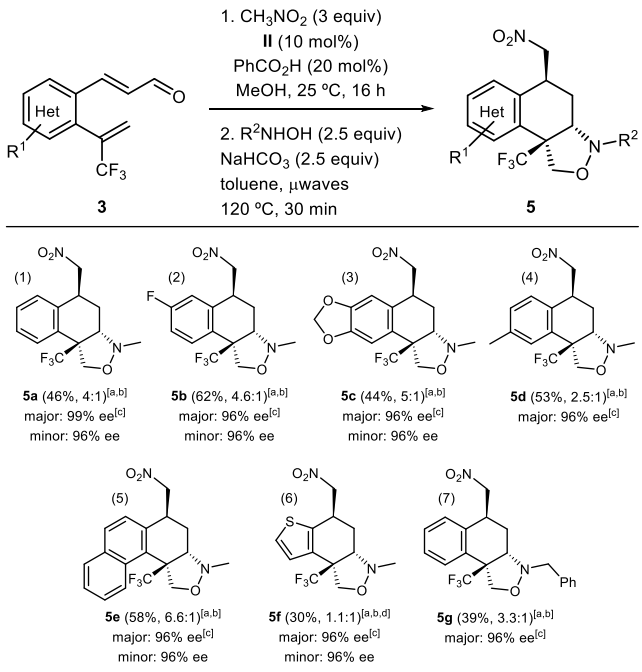
Having identified the optimal conditions for the sequential Michael addition/condensation/INCR (Table 2, entry 2), this synthetic method was examined regarding its generality with the rest of trifluoromethylstyrenes 3. The results obtained are shown in Table 3.

Starting cinnamaldehydes **3a-d**, with electronically different substitution patterns on the aromatic ring, afforded the corresponding enantiomerically enriched isoxazolidines **5a-d** in good yields, moderate diastereoselectivities and excellent enantioselectivities (Table 3, entries 1-4). Additionally, other aromatic linkers between the α,β-unsaturated aldehyde and the fluorinated dipolarophile were compatible with the reaction system, including a naphthyl and a thienyl groups (Table 3, entries 5,6). It should be mentioned that, in the case of the thienyl derivative (Table 3, entry 6), the bridged regioisomer was formed in the INCR together with the fused one **5f**. Structural variability could also be introduced by changing the *N*-alkylhydroxylamine employed in the cyclization step. Thus, the process was also performed with *N*-benzylhydroxylamine to yield isoxazolidine **5g** with moderate diastereoselectivity and excellent enantioselectivity in the major diastereoisomer (Table 3, entry 7). In this manner, a family of enantiomerically enriched tetraline derivatives bearing a CF_3-containing quaternary stereocenter were efficiently synthesized.

Table 3. Scope of the sequence nitro-Michael addition/INCR



[a] Isolated yield after flash column chromatography.
[b] Diastereomeric ratio determined by ^{19}F-NMR analysis of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereoisomer determined by HPLC methods. The ee value of the minor diastereoisomer is given when purification and chiral resolution were possible.
[d] The bridged regioisomer was also formed in 14% yield; see Supporting Information.

The absolute configuration of the products was inferred from X-ray analysis of an appropriate crystal of compound **5c**,[33] which displays a *cis* relative relationship of the trifluoromethyl and the nitromethyl groups. The same stereochemistry was assumed for all compounds **5.**

A second type of organocatalytic conjugate addition we attempted for the enantioselective β-functionalization of enals **3** was the aza-Michael reaction,[34] because of our ongoing interest in this field. A preliminary screening of nitrogen nucleophiles was carried out employing **3a** as a model substrate. Several heterocyclic amine derivatives such as pyrrole, indole, phtalimide or isatin were tested unsuccessfully as no conjugate addition was observed. Apparently, the retro-aza-Michael reaction is faster for these systems and the steric requirements for the addition to an *ortho*-substituted cinnamaldehyde could not be disregarded. Another commonly used nucleophile for enantioselective aza-Michael reactions is *O*-TBS-protected *N*-Cbz-hydroxylamine.[35] Unfortunately, in our reaction no conversion was detected again. Nevertheless, when the hydroxyl group was unprotected, *i.e*. when using *N*-Cbz-hydroxylamine,[36] the aza-Michael reaction took place in the presence of diphenylprolinol silyl ether (**II**) and yielded hemiacetal derivative **6a** (Table 4). Its formation in a tandem fashion seems to be the driving force of the process. This reaction was driven to full conversion in chloroform at room temperature. Then, the reaction mixture was evaporated to dryness and the crude mixture was re-dissolved in toluene for the cyclization step. The subsequent domino condensation with *N*-methylhydroxyl amine /INCR took place under microwave irradiation at 120 ºC for 30 min, rendering a 3:1 mixture of diastereoisomers in 42% yield overall yield. The enantiomeric excess of the major diastereoisomer was found to be 22% (Table 4, entry 1). It is worth mentioning that aqueous work-up or isolation of the intermediate hemiacetal **6a** did not improve the yield or the enantioselectivity of the process.

Once identified a compatible nitrogen nucleophile partner for the reaction with **3a**, an optimization of the reaction conditions was performed next.

In order to improve the selectivity of the sequential protocol, lower temperatures in the organocatalytic conjugate addition step were tested. We found that temperature has a dramatic effect on enantioselectivity. While the reaction at -20 ºC did not proceed at all (Table 4, entry 2), at 5 ºC, after the INCR, final tetrahydronaphthalene product **7a** was obtained with 96% ee and 51% global yield (Table 4, entry 3). On the other hand, organocatalytic reactions with diarylprolinol derivatives as the catalysts usually require an acidic co-catalyst such as benzoic acid. However in our case, the incorporation of this

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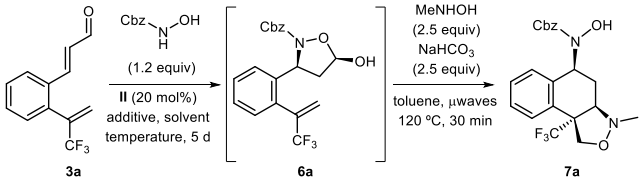
additive entailed lower enantioselectivity in the formation of compound **7a** (Table 4, entry 4). Fluorinated Jørgensen-Hayashi catalyst **III** was no effective in the aza-Michael reaction in $CHCl_3$ at 25 ºC (Table 4, entry 5). Finally, changing the solvent to toluene gave slightly lower yield and enantioselectivity (Table 4, entry 6).

Again in this sequence the INCR was completely regioselective, although the fused regioisomer **7a** was obtained with moderate diastereoselection (3:1 dr).

Table 4. Optimization of the sequence aza-Michael addition/INCR

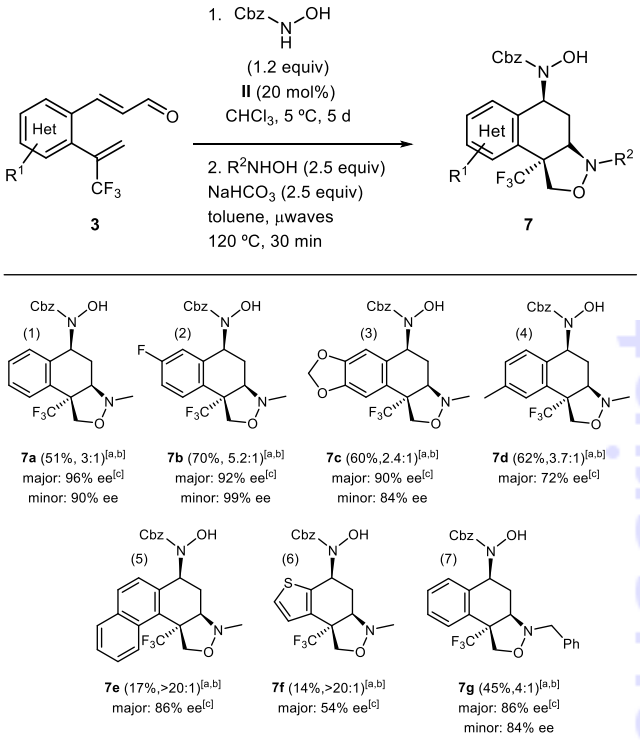


Ent.	Cat.	Solv.	Additive	T [ºC]	Yield [%][a],[b]	ee [%][c]
1	**II**	$CHCl_3$	-	25	42	22
2[c]	**II**	$CHCl_3$	-	-20	-[d]	-
3	**II**	$CHCl_3$	-	5	51	96
4	**II**	$CHCl_3$	$PhCO_2H$	5	49	80
5[c]	**III**	$CHCl_3$	-	25	-[d]	-
6	**II**	Tol.	-	5	50	94

[a] Isolated yield after flash column chromatography (from **3a**, without purifying intermediate **6a**).
[b] The INCR gave a 3:1 mixture of diastereoisomers, as determined by ^{19}F-NMR of the crude reaction mixture.
[c] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase; see Supporting Information for details.
[d] No conversion in the organocatalytic step.

With the optimized reaction conditions in hand (Table 4, entry 3), the scope of the sequential process was evaluated on substrates trifluoromethylstyrenes **3**. The results are summarized in Table 5.
Electron-withdrawing, electron-donating and electron neutral substituents on the aromatic backbone of the starting cinnamaldehydes **3a-d** were compatible with this process. The corresponding trifluoromethylated products **7a-d** were obtained in good yields but moderate diastereoselectivities; whereas enantioselectivities ranged from good to excellent (Table 5, entries 1-4). The change in the nature of the aromatic linker between the trifluoromethyl alkene and the enal, *i.e.* when this is a naphthyl or a thienyl moiety, resulted in a drop in chemical yield and enantioselectivity. However, isoxazolidines **7e** and **7f** were isolated practically as single diastereoisomers (Table 5, entries 5, 6). Finally, the use of *N*-benzylhydroxylamine afforded the corresponding product **7g** with comparable diastereoselectivity and slightly lower enantioselectivity (Table 5, entry 7).

Table 5. Scope of the sequence aza-Michael addition/INCR



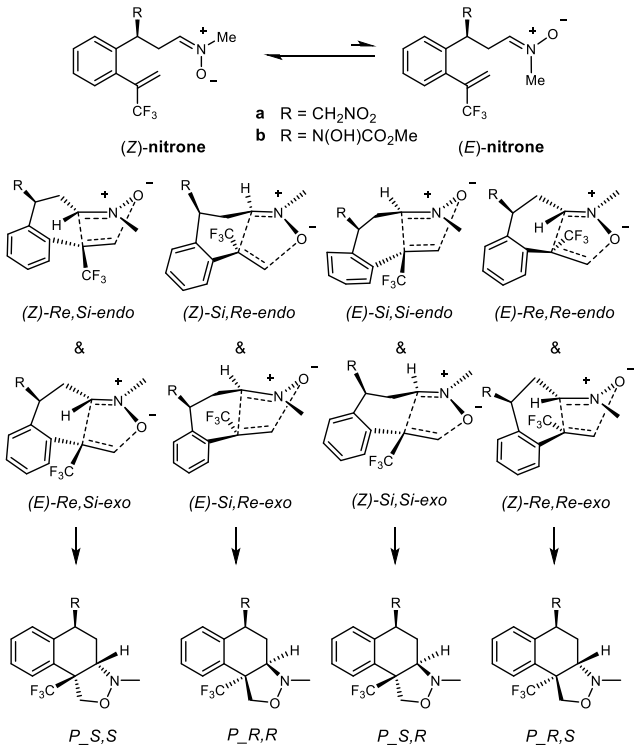
[a] Isolated yield after flash column chromatography.
[b] Diastereoisomeric ratio determined by ^{19}F-NMR of the crude mixture.
[c] Enantiomeric excess of the major diastereoisomer. The ee value of the minor diastereoisomer is given when purification and chiral resolution were possible.

The absolute configuration of this family of tetralin-derived isoxazolidines **7** was determined by X-ray diffraction of a suitable crystal of the major diastereoisomer of compound **7b**.[37] Surprisingly, the trifluoromethyl and the hydroxycarbamate groups lay *trans* to each other in this case, suggesting that different stereoelectronic factors in the transition state play a role in the preference of the *in situ* formed nitrone for the opposed face of the dipolarophile when compared to the nitromethane derivatives.

Computational calculations were carried out in the hope to shed light on this interesting finding. The cycloaddition reaction was studied at B3LYP-D3BJ/Def2SVP level of theory to calculate geometries and then single point calculations at B3LYP-D3BJ/Def2TZVP/PCM=toluene level of theory were performed (for details see Supporting Information). *E*/*Z* isomerization of nitrones has been considered since the difference was in the range of 20-30 kcal/mol,[38] compatible with the reaction conditions. Four approaches can be defined for each nitrone, thus a total of eight approaches leading to four different compounds have been studied (Scheme 2).

Diastereotopic faces correspond to nitrone (first) and alkene (second). The corresponding orientation of diastereotopic faces defines the *endo*/*exo* approach in

each case. Moreover, even though the formation of 3,4-regioisomers was not observed experimentally, it was also computed. In the case of 3,4-regioisomers only four approaches are possible due to steric constraints imposed by the intramolecularity of the reaction.



Scheme 2. Approaches corresponding to the intramolecular 1,3-dipolar cycloadditions (those leading to 3,4 regioisomers are not shown)

R = CH_2NO_2 (**a** series) and R = $N(OH)CO_2Me$ (**b** series) were compared as substituents. A total of 24 transition structures were located. (*Z*)-*Endo* approaches were the most stable ones in all cases. The remaining approaches showed considerable higher energies due to steric constraints imposed by the intramolecularity of the process.

For R = CH_2NO_2 (**a** series) the most stable transition structure (by 2.9 Kcal/mol) corresponds to the (*Z*)-*Re*,*Si-endo* approach leading to the *S*,*S* adduct. The lowest energy barrier corresponding to those approaches was 12.3 kcal/mol for the **a** series. On the contrary, for R = N(OH)CO2Me (**b** series) the most stable transition structure (although only by 0.7 kcal/mol) corresponds to the (*Z*)-*Si*,*Re-endo* (energy barrier of 18.9 kcal/mol) approach leading to *R*,*R* adducts, in good agreement with the experimental results (Figure 1).

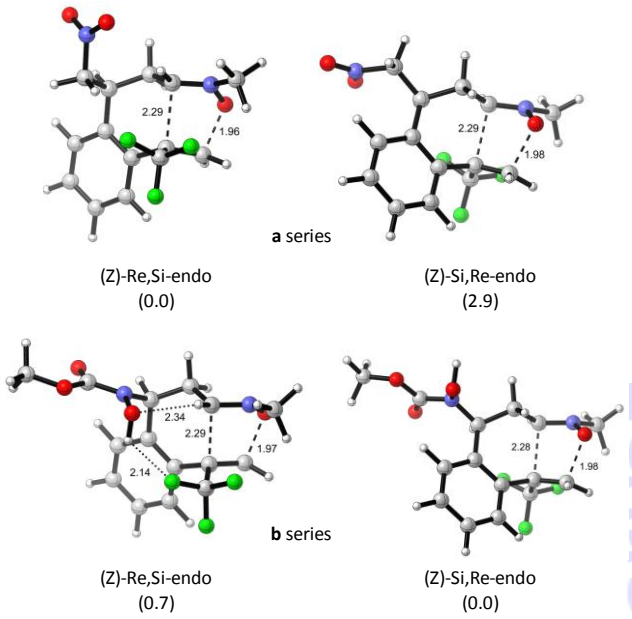


Figure 1. Transition structures corresponding to the most stable (*Z*)-*endo* approaches for the **a** and **b** series. (Relative energies are given in kcal/mol).

Although the energy difference is only 0.7 kcal/mol being in the range of DFT error,[39] there is a clear trend from the **a** to **b** series towards inverting the diastereotopicity. Since the geometries of the transition structures are relativity similar for the different R substituents considered, there is no clear difference between steric requirements. However, some interactions are present in the (*Z*)-*Re*,*Si-endo* approach for the **b** series that cannot be found in the other models. The interaction between the N(OH) group and a fluorine atom is weak and might reinforce this transition structure minimizing the difference with (*Z*)-*Si*,*Re-endo*. On the other hand, the interaction between the N(OH) group and the azomethine proton of the nitrone affects the electronic system of the dipole. Since the reaction is a normal-demand process in which the nitrone moiety acts as a nucleophile, any interaction affecting such nucleophilicity will contribute to lowering the stability. Consequently, the (*Z*)-*Si*,*Re-endo* approach in which such interaction is not present becomes the most stable TS. These non-covalent interactions (NCI) can be visualized through a topological NCI analysis,[40] in which interactions are visualized as isosurfaces. Figure 2 illustrates the presence of interactions in the less favored (*Z*)-*Re*,*Si-endo* approach which are not present in the preferred (*Z*)-*Si*,*Re-endo* approach.

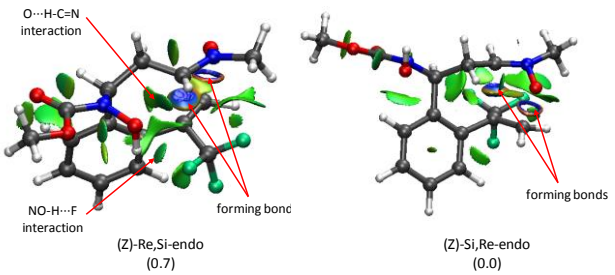


Figure 2. NCI analysis for the (*Z*)-*Re*,*Si*-*endo* and (*Z*)-*Si*,*Re*-*endo* approaches for the **b** series showing interactions in the former that are not present in the latter. (green for weak attractive interactions, blue for strong attractive interactions and red for repulsive interactions)

A (*Z*)-*Si*,*Re*-*endo* approach in which an H-bond interaction is present with the nitrone oxygen (Figure 3) was also calculated, being 2.8 kcal/mol less stable than the most stable conformation of the (*Z*)-*Si*,*Re*-*endo* approach (shown in Figure 1). Alternative routes considering intermediate hydroxyamino anions were also considered but higher barriers were found in all cases (see Supporting Information).

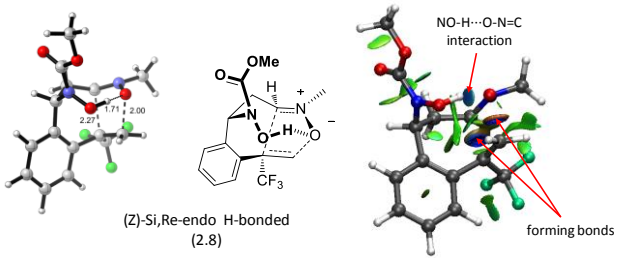
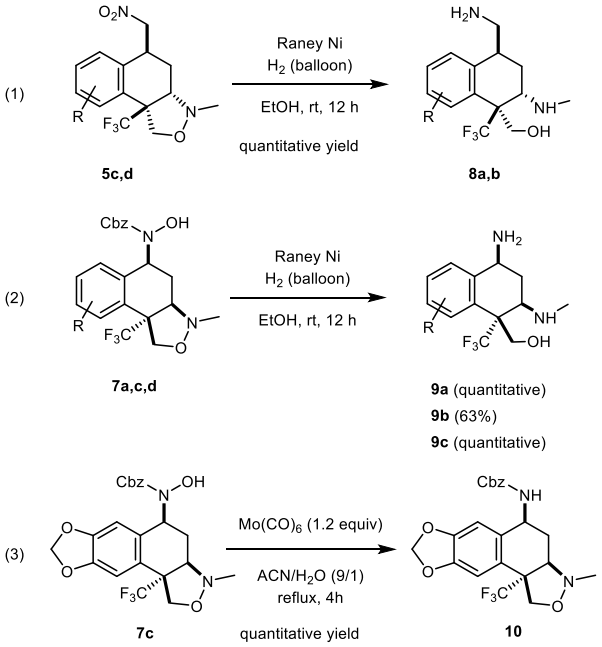


Figure 3. (*Z*)-*Si*,*Re*-*endo* approach for the **b** series showing H-bond interaction between the N(OH) group and the nitrone moiety. Confirmation of interactions through NCI analysis (right) (Relative energy is given in kcal/mol and referred to (*Z*)-*Si*,*Re*-*endo* corresponding to the **b** series shown in Figure 1).

In order to verify that the diastereofacial inversion was due to the exclusive presence of the hydroxyamino group, calculations were carried out with R = $NHCO_2Me$ (see Supporting Information). In this case, the same diastereoisomeric preference by a (*Z*)-*Re*,*Si*-*endo* approach, which was found for R = CH_2NO_2, was observed, confirming that the additional OH group is responsible for the above-mentioned interactions, explaining the diastereofacial inversion. For comparative purposes, calculations replacing the trifluoromethyl group by a methyl group were also carried out (see Supporting Information).

The nitromethane-derived isoxazolidines **5c** and **5d** could then be easily transformed into the corresponding 1,3-amino alcohols by cleavage of the O-N bond with Raney Ni under hydrogen atmosphere in ethanol. This reaction proceeded with concomitant reduction of the nitro group to afford trifluoromethylated diamino alcohols **8a** and **8b** in quantitative yield (Scheme 3, eq. 1). The same hydrogenation conditions were applied to compounds **7**, rendering diaminoalcohols **9** bearing an amino group directly attached to the tetralin skeleton (Scheme 3, eq. 2). Moreover, the selective cleavage of the *N*(Cbz)-OH bond in product **7c** was achieved with $Mo(CO)_6$, leaving the *N*(Me)-*O* bond of the isoxazolidine untouched (Scheme 3, eq, 3).



Scheme 3. Transformations on tetrahydronaphthalene isoxazolidinones **5** and **7**.

Conclusion

In conclusion, we have developed an enantioselective synthesis of two new families of tetrahydronaphthalene derivatives containing a trifluoromethyl all-carbon quaternary stereocenter. Our synthetic approach to these interesting chiral building blocks begins with an organocatalytic conjugate addition reaction on conveniently functionalized cinnamaldehydes and related aromatic compounds bearing a 1-trifluoromethyl alkene group at the *ortho* position. Once introduced the chirality at the β-position of the aldehyde, the *in situ* condensation with an hydroxylamine followed by intramolecular nitrone [3+2] cycloaddition gives rise to the desired tetralin derivatives fused with an isoxazolidine moiety, with three stereogenic centers in good yields and excellent enantioselectivities, in general.

We observed that the diastereofacial selectivity in the cycloaddition step was reversed when nitromethane or *N*-Cbz-hydroxylamine were employed as the nucleophiles in the initial organocatalytic step. Theoretical calculations determined that this inversion is due to unfavorable interactions lowering the stability of the (*Z*)-*Re*,*Si*-

endo approach in the second case (*N*-Cbz-hydroxylamine as nucleophile), being the (*Z*)-*Si*,*Re*-endo approach the most stable one.

Experimental Section

General procedure for the synthesis of fluorinated cinnamaldehydes. A 10 mL microwave glass vial was charged with $Pd_2(dba)_3$ (4 mol %, 0.06 mmol), Xphos (8 mol %, 0.12 mmol), Na_2CO_3 (2.2 equiv, 3.3 mmol) and *N*-tosylhydrazone **2** (1.5 equiv, 2.25 mmol), previously prepared from 1,1,1−trifluoroacetone (1 equiv, 22 mmol) and *N*-tosylhydrazine (1 equiv, 22 mmol) by heating at 70 °C in EtOH (0.5 M) for 5 h and then filtering the precipitate solid at room temperature as a crystalline white solid. The solid reagents were dried together under reduced pressure before being used. 2-Bromocinnamaldehyde **1a** (1.0 equiv, 1.5 mmol), prepared from the corresponding 2-bromobenzaldehyde by a literature procedure,[41] was dissolved in THF (0.3 M) and then added to the vial, which was subsequently sealed and heated by microwave irradiation at 100 °C for 2 h. The reaction mixture was cooled to room temperature, opened, filtered through Celite and concentrated under reduced pressure. The residue obtained was purified by flash chromatography [*n*-hexane-EtOAc (20:1)]. The product obtained was used immediately in the next step.[42]

(*E*)-3-(2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl)acrylaldehyde (3a): Starting from **1a** and following the general procedure indicated above, **3a** was obtained as a yellow oil in 89% yield (302 mg). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.69 (d, *J* = 7.7 Hz, 1H), 7.77-7.72 (m, 1H), 7.61 (d, *J* = 15.9 Hz, 1H), 7.52 – 7.34 (m, 3H), 6.70 (dd, *J* = 15.9, 7.7 Hz, 1H), 6.27 (q, *J* = 1.4 Hz, 1H), 5.57 (q, *J* = 1.3 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -67.35 (s, 3F).

General procedure for the synthesis of nitromethane-derived isoxazolidines. To a solution of the corresponding fluorinated cinnamaldehyde derivative **3** (1.0 equiv, 0.5 mmol), Jørgensen-Hayashi catalyst (10 mol%, 0.05 mmol) and benzoic acid (20 mol%, 0.10 mmol) in methanol (0.05 M), nitromethane (3.0 equiv, 1.5 mmol) was added. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched by addition of 20 mL of water and extracted with DCM (15 mL x 3). The organic layer was washed with brine (15 mL x 2), dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. The crude aldehyde was then used without further purification. To a solution of the corresponding intermediate fluorinated aldehyde in toluene (0.1 M) in a 10 mL microwave glass vial, *N*-alkylhydroxylamine hydrochloride (2.5 equiv, 1.25 mmol) and sodium bicarbonate (2.5 equiv, 1.25 mmol) were added. The vial was sealed and the mixture was heated by microwave irradiation at 120 °C for 30 min. The reaction mixture was cooled to room temperature, opened and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography [*n*-hexane-EtOAc (20:1)] to purify and/or separate the formed diastereoisomeric isoxazolidines. When complete separation of the minor diastereoisomer was not possible, the ^{1}H and ^{19}F-NMR data were extracted from the spectra of the mixture.

(3a*S*,5*S*,9b*S*)-3-methyl-5-(nitromethyl)-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazole (5a): Starting from **3a** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **5a** (46% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=4/1), which were separated by flash chromatography [*n*-hexane-EtOAc (20:1)]. Major diasteroisomer (58 mg, colorless oil): $[\alpha]_D^{25}$ = +69.6° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.23 (m, 4H), 4.75 (dd, *J*=12.3, 5.6 Hz, 1H), 4.69 – 4.57 (m, 2H), 3.91 (d, *J* = 10.8 Hz, 1H), 3.84-3.75 (m, 1H), 3.40-3.25 (m, 1H), 2.83 (s, 1H), 2.19 (ddd, *J* = 14.0, 5.6, 5.6 Hz, 1H), 1.93 (ddd, *J* = 13.9, 8.6, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 135.6, 131.9, 129.8, 129.0, 128.6, 128.0, 127.1 (CF_3, q, *J* = 282.4 Hz), 79.0, 73.7, 64.6 (d, *J* = 2.6 Hz), 58.8 (C-CF_3, q, *J* = 22.5 Hz), 43.7, 35.4, 27.9. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -70.69 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{16}F_3N_2O_3$ 317.1108; found 317.1115. HPLC (Phenomenex Amylose 1, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 7.60 min, t_R(minor) = 12.32 min. Minor diasteroisomer (14 mg, colorless oil): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 – 7.16 (m, 4H), 4.89 (dd, *J* = 12.3, 10.0 Hz, 1H), 4.70 – 4.59 (m, 2H), 3.90 (dq, *J* = 9.1, 1.7 Hz, 1H), 3.81-3.73 (m, 1H), 3.20 (t, *J* = 4.9, 1H), 2.80 (s, 3H), 2.26 (dt, *J* = 14.8, 4.9 Hz, 1H), 1.92 (dt, *J* = 14.8, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 135.0, 132.4, 129.8, 128.9, 128.4, 127.7, 127.1 (CF_3, q, *J* = 282.2 Hz), 80.7, 74.1, 67.4, 58.3 (C-CF_3, q, *J* = 24.0 Hz), 43.2, 35.4, 25.0. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.58 (s). HPLC (Phenomenex Amylose 1, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 6.92 min, t_R(minor) = 7.33 min.

General procedure for the synthesis of aza-derived isoxazolidines. To a solution of the corresponding fluorinated cinnamaldehyde **3** (1.0 equiv, 0.5 mmol), Jørgensen-Hayashi catalyst (20 mol%, 0.1 mmol) in chloroform (0.05 M), *N*-(benzyloxycarbonyl) hydroxylamine (1.2 equiv, 0.6 mmol) was added at 0-5 ºC. The resulting mixture was stirred at this temperature for 3-5 d until disappearance of the starting material (TLC analysis). The reaction mixture was then concentrated to dryness under reduced pressure. The crude hemiaminal was then used without further purification. To a solution of the corresponding intermediate fluorinated hemiaminal in toluene (0.1 M) in a 10 mL microwave glass vial, *N*-alkylhydroxylamine hydrochloride (2.5 equiv, 1.25 mmol) and sodium bicarbonate (2.5 equiv, 1.25 mmol) were added. The vial was sealed and the mixture was heated by microwave irradiation at 120 °C for 30 min. The reaction mixture was cooled to room temperature, opened and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)] to purify and/or separate the formed diastereoisomeric isoxazolidines. When complete separation of the minor diastereoisomer was not possible, the ^{1}H and ^{19}F-NMR data were extracted from the spectra of the mixture.

Benzyl hydroxy((3a*R*,5*S*,9b*R*)-3-methyl-9b-(trifluoromethyl)-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazol-5-yl)carbamate (7a): Starting from **3a** and *N*-methylhydroxylamine hydrochloride and following the general procedure indicated above, **7a** (51% overall yield) was obtained as a mixture of its diastereoisomers (d.r.=3/1), which were separated by flash chromatography [*n*-hexane-EtOAc (10:1 to 4:1)]. Major diasteroisomer (81 mg, colorless oil): $[\alpha]_D^{25}$ = -103.3° (c 1.0; $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.24 (br s, 1H), 7.60 – 7.24 (m, 9H), 5.65-5.57 (m, 1H), 5.28 (d, *J* = 12.3 Hz, 1H), 5.22 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 9.3 Hz, 1H), 3.92 (dq, *J* = 9.3, 1.6 Hz, 1H), 3.21 (t, *J* = 3.9 Hz, 1H), 2.72 (s, 3H), 2.37 (dt, *J* = 15.6, 4.7 Hz, 1H), 2.27 – 2.17 (m, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 156.2 (C=O), 136.4, 132.9, 132.6, 129.8, 129.3, 129.1, 128.7, 128.6, 128.6, 128.4, 127.0 (CF_3, q, *J* = 282.4 Hz), 74.5, 67.9, 65.6, 57.5 (C-CF_3, q, *J* = 24.5 Hz), 53.6, 42.3, 27.4. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -71.41 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{22}F_3N_2O_4$ 423.1526; found 423.1534. HPLC (Chiralcel IC, 85:15 hexane/ iPrOH, 1 mL/min) t_R(major) = 8.39 min, t_R(minor) = 16.64 min. Minor diasteroisomer (27 mg, colorless oil): ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52 – 7.25 (m, 9H), 6.19 (br s, 1H), 5.40 (dd, *J* = 12.2, 5.2 Hz, 1H), 5.34 (d, *J* = 12.1 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 4.53 (d, *J* = 8.8 Hz, 1H), 3.80 (dq, *J* = 8.8, 1.5 Hz, 1H), 3.17 (t, *J* = 3.2 Hz, 1H), 2.69 (s, 3H), 2.58 (ddd, *J* = 14.3, 12.2, 3.2 Hz, 1H), 2.00 (ddd, *J* = 14.3, 5.2, 3.2 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 157.8 (C=O), 135.8, 134.5, 133.5, 129.5, 128.8, 128.6, 128.4, 128.4, 128.3, 126.9 (CF_3, q, *J* = 274.4 Hz), 125.9, 74.8, 68.6, 67.3, 57.8 (C-CF_3, q, *J* = 24.1 Hz), 53.9, 42.8, 24.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -69.87 (s, 3F). HPLC (Chiralcel IC, 90:10 hexane/ iPrOH, 1 mL/min) t_R(major) = 9.87 min, t_R(minor) = 6.68 min.

General procedure for the synthesis of fluorinated diamino alcohols

To a solution of the corresponding isoxazolidine **5** or **7** (0.2 mmol) in dry ethanol (0.05 M), Raney ® Nickel (0.5 mL as a slurry in water) was added and the resulting mixture was stirred at room temperature under a hydrogen atmosphere (balloon) for 16 h. The reaction mixture was then filtered through Celite, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the corresponding diaminoalcohol without further purification.

(5*S*,6*S*,8*S*)-8-(aminomethyl)-6-(methylamino)-5-(trifluoromethyl)-5,6,7,8-tetrahydronaphtho[2,3-d][1,3]dioxol-5-yl)methanol (8c): Starting from **5c** and following the general procedure indicated above, **8c** was obtained in quantitative yield (66 mg, pale yellow oil). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.92 (s, 1H), 6.74 (s, 1H), 5.92 (s, 2H), 4.19-4.09 (s, 2H), 3.30 (dd, *J* = 6.2, 3.8 Hz, 1H), 3.10 – 2.92 (m, 2H), 2.88 – 2.73 (m, 1H), 2.50 (s, 3H), 2.17-1.97 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 147.8, 146.8, 133.1, 127.2 (CF_3,q, *J* = 285.5 Hz), 123.5, 109.2, 107.9, 101.4, 65.3, 57.6, 51.1 (C-CF_3, q, *J* = 21.3 Hz), 47.5, 37.7, 34.5, 26.1. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -68.65 (s, 3F). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{20}F_3N_2O_4S$ 333.1421; found 333.1423.

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FULL PAPER

Organocatalytic Enantioselective Synthesis of CF_3-Containing Tetralin Derivatives by Sequential (Hetero)Michael Reaction-Intramolecular Nitrone Cycloaddition

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