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Asymmetric Remote Aldol Cyclization Reaction to Synthesize Trifluoromethylated Heterospirocyclic Frameworks

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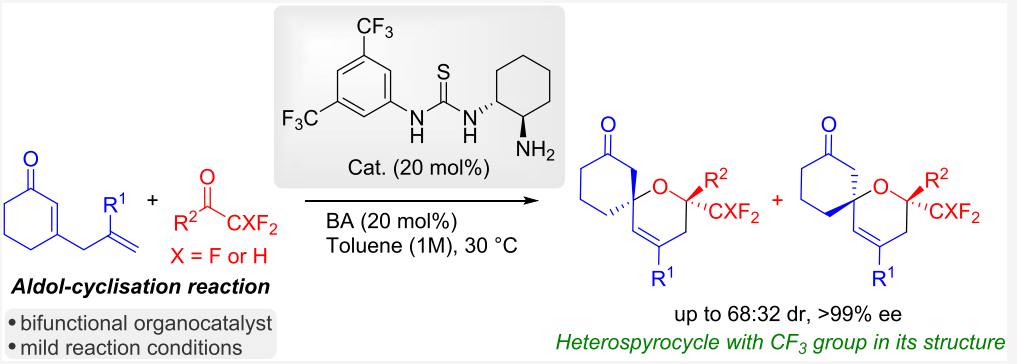

ABSTRACT: The highly enantioselective organocatalytic synthesis of dihydropyran spirocyclic compounds bearing di- and trifluoromethyl groups by aldol cyclization reaction via trienamine using cyclic 2,5-dienones and different di- and trifluoromethylketones is described. Using a bifunctional aminothiourea catalyst, trifluoromethyl-functionalized dihydropyran spirocyclic products were obtained with good yields and enantioselectivities. Subsequent transformation with H_2 and Pd/C has allowed the synthesis of the tetrahydropyran structure with three stereocenters. The plausible reaction mechanism was investigated by computational methods.

INTRODUCTION

Substituted tetra- and dihydropyrans are important structures found in bioactive natural and pharmaceutical products.[1] Chiral heterocycles containing trifluoromethyls in their structure have attracted great interest in the agrochemical and pharmaceutical industry due to the ability of the CF_3 group to enhance the ability to modulate physical and biological properties.[2] The structures shown in Figure 1, including reverse transcriptase inhibitors such as approved Efavirenz **A**[3] and antimalarial Fluoroartemisinin **B**,[4] are selected examples. On the other hand, spirocyclic structures are present in numerous natural and unnatural products[5] and are considered important in medicinal chemistry due to their occurrence in a wide variety of biologically active molecules.[6] For instance, Figure 1 includes heterospirocyclic compounds as Oliceridine **C**, which acts as a safer analgesic drug,[7] whereas Griseofluvin **D** possesses antifungal properties and anticancer effects in mammalian systems.[8] Furthermore, oscillatoxins (OTXs) and aplysiatoxins (ATXs), which are cytotoxins produced by some marine cyanobacteria, show potent inflammatory and tumor-promoting activity through activation of protein kinase C (PKC) and some of their derivatives show cytotoxicity against cancer and leukemia cell lines.[9]

Combining the three features mentioned above, the synthesis of heterospirocyclic compounds with a trifluoromethyl group in their structures is highly desirable. Among all of the methods developed to synthesize pyran derivatives, the hetero-Diels–Alder reaction (HDA) of a diene or its analogous with a carbonyl compound is one of the most widely used tools.[10] On the other hand, cyclic 2,5-dienones have been employed as bisvinylogous precursors to synthesize spirocyclic compounds efficiently, while Chen's group carried out the functionalization of the ε-site by conjugated addition and vinylogous iminium-iminium catalysis to obtain the spirocyclic adducts.[11] Our research group has more recently developed an enantioselective synthesis by Diels–Alder reactions *via* trienamine employing δ-substituted 2,5-dienones[12] (Scheme 1). In this context, continuing with the elaboration of sophisticated and complex chiral organic entities and considering that

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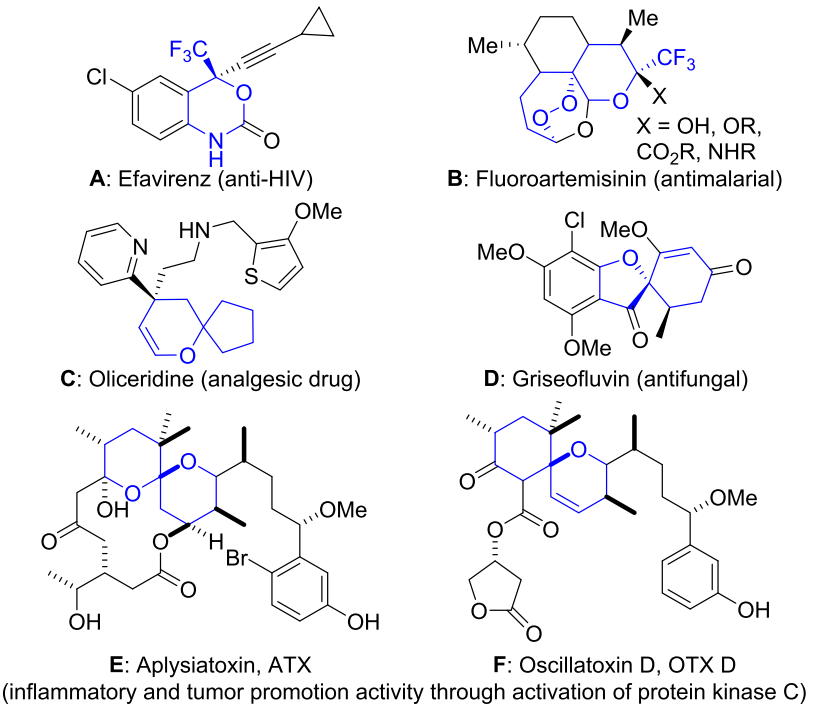
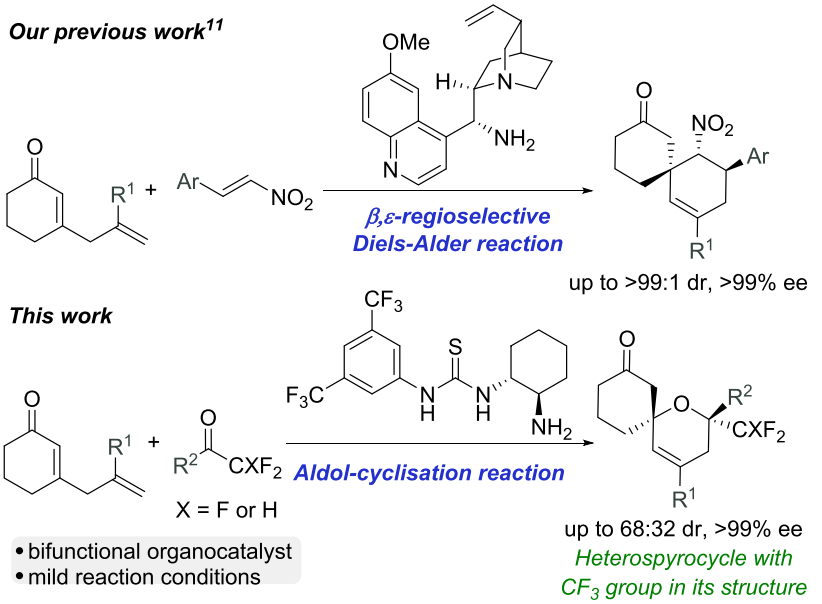


Figure 1. Selected bioactive compounds.

Scheme 1. Synthesis of Spiro- and Heterospirocycle Adducts from 2,5-Dienones



fluorine plays a key role in affecting metabolic stability and alters binding affinities between target proteins and drugs, we envisioned that the use of δ-substituted 2,5-dienones and trifluoromethylketones as reagents with a suitable organocatalyst would allow the formation of sterically hindered heterospirocyclic adducts containing a CF_3 group and a dihydropyran scaffold in their structures *via* a hetero-Diels–Alder reaction or an aldol cyclization reaction (Scheme 1).

RESULTS AND DISCUSSION

Based on the above considerations, the reaction of 2,5-dienone **1a** and trifluoromethylacetophenone **2a** was evaluated. The reaction was assessed by employing different organocatalysts in toluene at room temperature (Table 1). The quinine derivative **I** and the bifunctional amine-sulfonamide **II** did not promote any reactivity (Table 1, entries 1–2). Fortunately, the bifunctional amine-thiourea and amine-urea derivatives **III**–**VI** were able to afford the desired heterospirocycle **3aa** as a major product with different conversions (Table 1, entries 3–6). Although bifunctional cyclohexanediamine-thiourea derivatives **III** and **V** provided the heterospirocycle adducts in good to excellent conversions, the 1,2-diphenylethane-1,2-diamine **IV** led to the corresponding adducts in low conversion (Table 1, entries 3 and 5 vs. 4), with the best results in terms of diastereo- and enantioselectivity obtained by using catalyst **V** (Table 1, entry 5). Cyclohexanediamine-urea **VI** yielded the

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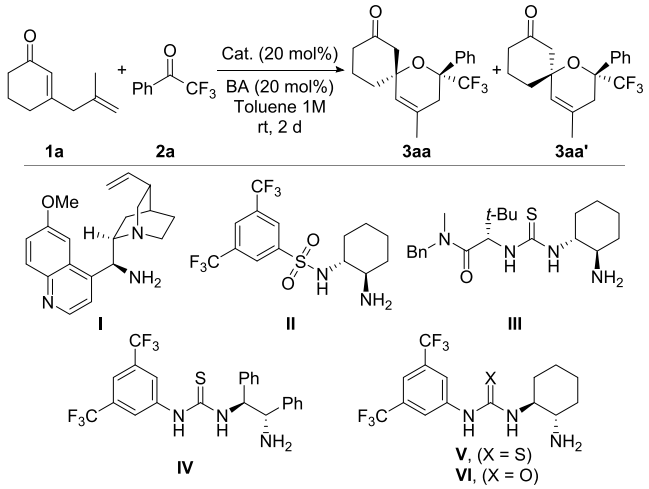
Table 1. Catalyst Screening for the Aldol Cyclization Reaction[a]



entry	cat.	conv. [%][b]	3aa:3aa′[c]	ee 3aa [%][d]	ee 3aa′ [%][d]
1[e]	I	>5			
2[e]	II	>5			
3	III	75[f]	57:43	−34	−30
4	IV	20[g]	65:35	46	38
5	V	90[h]	66:34	98	87
6	VI	70[h]	64:36	41	65
7[i]	V	>95[h]	66:34	99	>99

[a]The reactions were performed with ketone **1a** (0.2 mmol), 2,2,2-trifluoroacetophenone **2a** (0.1 mmol), catalyst (20 mol %), and BA (20 mol %) in toluene (100 μL, 1 M) at room temperature. [b]Conversions were measured by ^{1}H NMR and ^{19}F NMR of crude reaction mixtures considering the 2,2,2-trifluoroacetophenone **2a** limiting reagent. [c]Diastereomeric ratios were measured by ^{1}H NMR and ^{19}F NMR of crude reaction. [d]Enantiomeric excesses measured by high-performance liquid chromatography (HPLC) correspond to the major enantiomer (2*R*,6*R*)-**3aa** and (2*R*,6*S*)-**3aa**′. Negative values indicate that the opposite enantiomer is formed. [e]40% of BA was employed. [f]45% of conversion for **3aa** and **3aa**′ and 30% for a mixture of different adducts. [g]15% of conversion for **3aa** and **3aa**′ and 5% for a mixture of different adducts. [h]15−10% of aldol adducts were observed. [i]The reaction was performed with ketone **1a** (2 mmol), 2,2,2-trifluoroacetophenone **2a** (0.5 mmol), catalyst (20 mol %), and benzoic acid (20 mol %) in toluene (500 μL, 1 M) at 30 °C. BA = Benzoic acid.

desired adducts in a similar diastereomeric ratio, but with lower conversion and enantioselectivity than its analogous thiourea derivative **V** (Table 1, entry 6). It should be mentioned that in all cases, a mixture of aldol adducts was observed as minor products (<15% in most cases). Further optimization was performed with the best organocatalyst **V** using different amounts of reagents and catalyst and a variety of solvents and acidic additives (see the SI for details). None of these modifications had a significant impact, although 30 °C and the use of 4 equiv of 2,5-dienone **1a** were required to achieve better and reproducible results (Table 1, entry 7).

Having determined the best reaction conditions, we investigated the general nature of this process was investigated. The results of a series of experiments are shown in Table 2. First, a selection of aryl-substituted trifluoromethylketones **2a−h** bearing electron-donating and electron-withdrawing groups was successfully tested affording spirocyclic adducts **3aa−ah** and **3aa−ah**′ with moderate diastereoselectivities, moderate to good yields and moderate to excellent enantioselectivities for both diastereoisomers (Table 2, entries 1−8). Interestingly, 2-thyenyl-substituted **2i** was also a suitable reagent, achieving the corresponding cycloadducts in 72% yield, 58:42 diastereomeric ratio, 99% ee for **3ai**, and 90% ee for **3ai**′ (Table 2, entry 9). The alkenyl-substituted trifluoromethyl ketone **2j** gave rise to the corresponding spirocycles in moderate yield (47%) and 66:34 diastereomeric ratio and slightly lower enantioselectivity for both diastereoisomers (80% for **3aj** and 90% ee for **3aj**′) (Table 2, entry 10). Then, a set of aromatic difluoromethylketones **2k−m** were also evaluated affording the desired adducts **3ak−am** and **3ak−am**′ in moderate to excellent yields, 60:40 diastereomeric ratio, and excellent enantioselectivities for both diastereoisomers (Table 2, entries 11−13). Unfortunately, monofluorinated α-fluoroacetophenone **2n** did not provide the desired cycloadduct (Table 2, entry 14). Finally, a good result was obtained for the 5-phenyl-substituted 2,5-dienone **1b** yielding the corresponding spirocycles **3ba** and **3ba**′ in a moderate diastereomeric ratio. Moreover, only one diastereoisomer **3ba** could be isolated in moderate yield and high enantiomeric excess (Table 2, entry 15). To demonstrate the synthetic value of this methodology, the model reaction was performed at 1 mmol scale affording the desired cycloadducts in slightly lower yield and enantioselectivity (Table 2, entry 1, in parentheses) and allowing organocatalyst **V** to be recovered (see the SI). Adducts **3aa** and **3aa**′ were crystallized and its absolute (2*R*,6*R*)-configuration for **3aa** and absolute (2*R*,6*S*)-configuration for **3aa**′ were unequivocally confirmed by monocrystal X-ray diffraction (XRD) analysis, assuming the same absolute configuration for the series of products **3** and **3**′.

In order to get a better understanding of the reaction, DFT calculations were carried out. We computationally studied (m062x/cc-pvtz/smd = toluene//m062x/cc-pvdz) the reaction between **1a** and **2a**. Any attempt of locating transition structures corresponding to a concerted pathway, i.e., a hetero-Diels−Alder reaction, failed, and the structures located corresponding to a stepwise process. So, we propose the catalytic cycle outlined in Scheme 2. We did not detect nonlinear effects (NLE) in the reaction supporting the proposed mechanism (see the SI). Thus, after the formation of the enamine **EN** from the catalyst **TH** and compound **1a** (which could be detected by positive mode electrospray ionization mass spectrometry (ESI-MS) spectrum of the reaction mixture, see the SI), the addition on each face of the ketone **2a** results in two diastereomers of **IN**, as a consequence of the presence in the molecule of the thiourea moiety. Subsequently, intramolecular cyclization can take place on two diastereotopic faces in each isomer, resulting in four possible isomers in **PR** and two pairs of enantiomers in the final product after hydrolysis and catalyst regeneration.

We studied the transformation of enamine **EN** into **PR**. After an exhaustive exploration of the potential energy surface (for details, see the SI), we located two transition structures corresponding to the nucleophilic attack of the enamine by *Re* and *Si* faces of the trifluoromethyl ketone, [**TS1-(R)** and **TS1-(S)**]. Interestingly, these transition structures showed only a H-bond between the carbonyl oxygen and the thiourea moiety (Figure 2). In fact, other transition structures showing the classical chelate thiourea-carbonyl group presented higher barriers due to the strain derived from the intramolecular disposition of the involved groups. For instance, a classical coordination between the carbonyl oxygen and both thiourea

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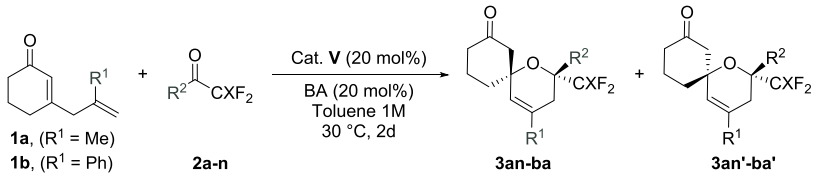
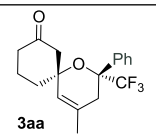
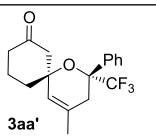
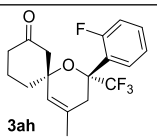
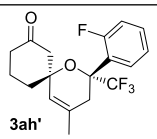
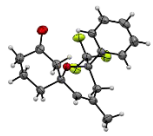
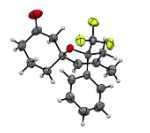
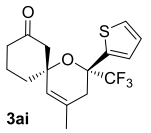
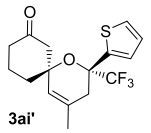
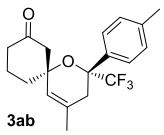
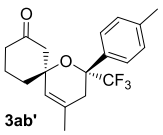
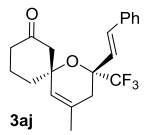
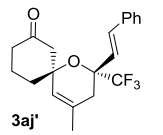
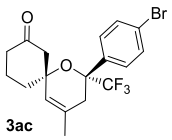
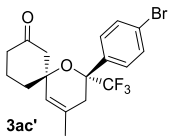
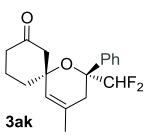
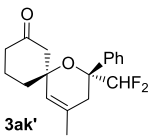
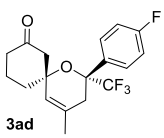
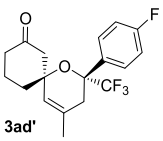
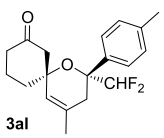
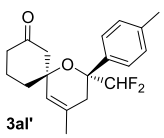
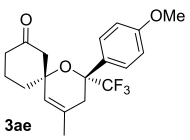
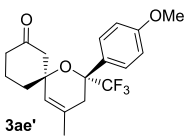
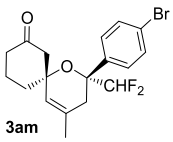
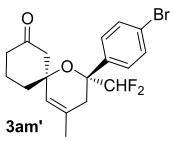
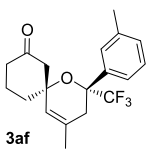
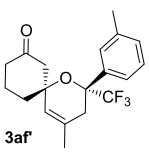
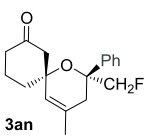
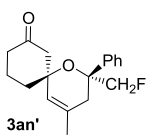
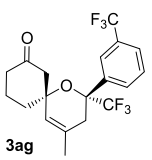
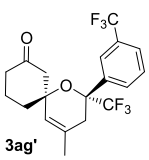
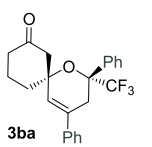
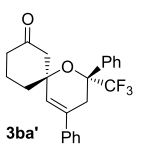
Table 2. Scope of the Reaction[a]



Entry	3	3'	Yield [%][b]	dr 3:3'[c]	ee 3 [%][d]	ee 3' [%][d]	Entry	3	3'	Yield [%][b]	dr 3:3'[c]	ee 3 [%][d]	ee 3' [%][d]
1	 3aa	 3aa'	83 (65)	66:34 (67:33)	99 (88)	>99 (88)	8	 3ah	 3ah'	66	65:35	76	76
							9	 3ai	 3ai'	72	58:42	>99	90
2	 3ab	 3ab'	70	62:38	88	88	10	 3aj	 3aj'	47	66:34	83	80
3	 3ac	 3ac'	65	66:34	80	59	11	 3ak	 3ak'	52	60:40	>99	99
4	 3ad	 3ad'	54	67:33	88	88	12	 3al	 3al'	75	60:40	94	94
5	 3ae	 3ae'	51	65:35	90	95	13	 3am	 3am'	91	60:40	94	94
6	 3af	 3af'	55	68:32	98	88	14	 3an	 3an'	nr	-	-	-
7	 3ag	 3ag'	57	63:37	73	84	15	 3ba	 3ba'	37[e]	63:37	94	nd

[a]The reactions were performed with ketone **1** (2 mmol), 2,2,2-trifluoroacetophenone **2a** (0.5 mmol), catalyst (20 mol %), and benzoic acid (20 mol %) in toluene (500 μL, 1 M) at 30 °C. [b]Yields refers to a 3:3′ diastereoisomeric mixture. [c]Diastereomeric ratios were measured by ^{1}H NMR and ^{19}F NMR of crude reaction mixtures. [d]Enantiomeric excesses measured by HPLC correspond to the major enantiomer (2*R*,6*R*)-**3aa** and (2*R*,6*S*)-**3aa**′. [e]Yield for isolated **3ba**. BA = Benzoic acid. nd = not determined

amino groups or a cyclohexane ring conformation different from a chair resulted in a penalty of 7−8 kcal/mol (see the SI). The corresponding diastereomeric zwitterionic intermediates **IN-(R)** and **IN-(S)** showed an (*E*)-configuration for the newly formed double bond. In the second step, the nucleophilic attack of the oxygen atom to form the spiro compound takes place by the two diastereomeric faces of the corresponding intermediate, leading to the four possible products having (*R*,*R*)- and (*R*,*S*)-configurations coming from **IN-(R)**, and (*S*,*S*)- and (*S*,*R*)-configurations coming from the disfavored intermediate **IN-(S)**. We located the four transition structures, although only those leading to (*R*,*R*)- and (*R*,*S*)-isomers, both

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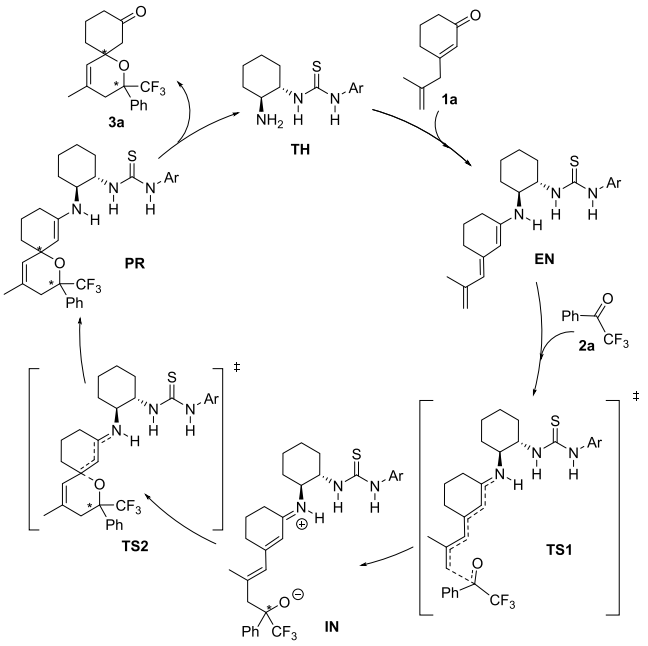
Scheme 2. Proposed Catalytic Cycle



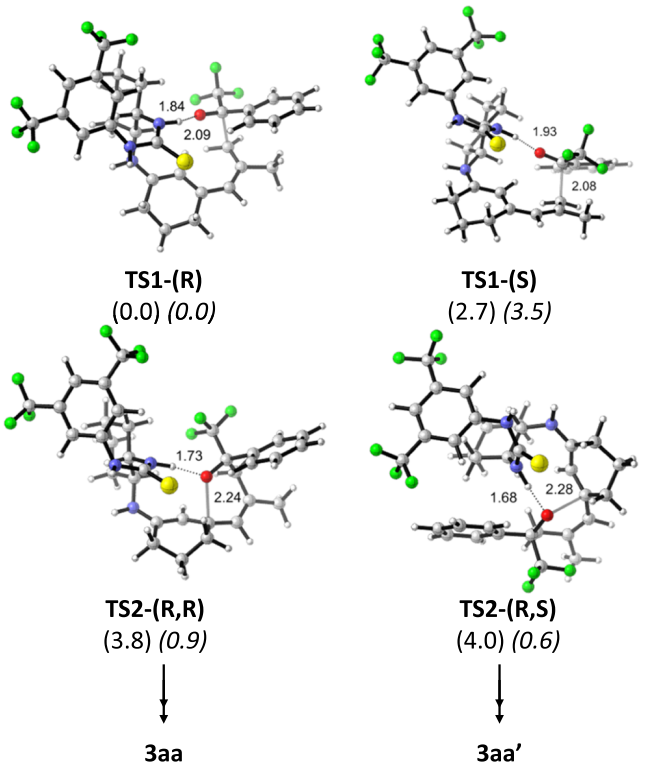


Figure 2. Transition structures corresponding to the formation of **3aa** and **3aa'**. Plain (m062x/cc-pvtz/smd = toluene//m062x/cc-pvdz) and italic (wb97xd/def2tzvp//wb97xd/def2svp/smd = toluene) correspond to relative values (given in kcal/mol) between transition structures of the same row.

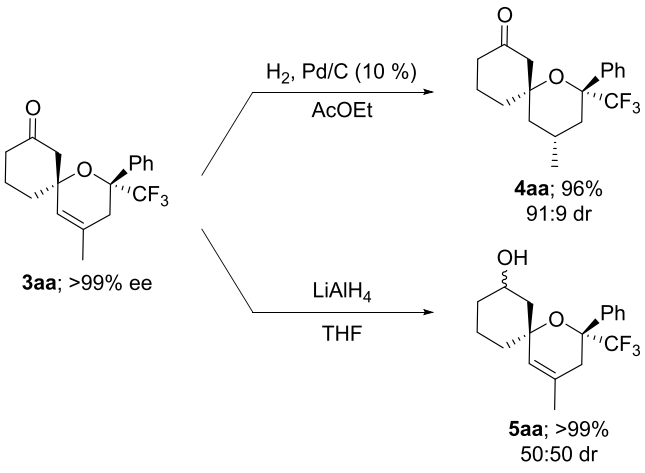
coming from the favored intermediate **IN-(R)**, were considered. The energy differences between transition structures correctly predict the preferential formation of the first stereogenic center with an (*R*)-configuration (difference of 2.7 and 3.5 kcal/mol) and the formation of (*R,R*)- and (*R,S*)-isomers in a similar amount (difference of 0.2 and 0.3 kcal/mol). Both levels of theory used were shown to be sufficiently accurate to correctly predict the results observed experimentally, even though by considering also the transition structures coming from disfavored **IN-(S)**, the level of theory m062x/cc-pvtz/smd = toluene provided better results.

The corresponding energy profile (SI) clearly points out the second step, dealing with **TS-(R,R)** and **TS-(R,S)**, as the rate-determining one. Accordingly, it should be possible to detect some compounds derived from iminium intermediate **IN** such as the corresponding aldol product.

The reaction is a stepwise process resulting from the induced polarity caused by the coordination of the ketone carbonyl group with the thiourea moiety. This coordination has the additional effect of stabilizing the zwitterionic intermediate. It needs to be broken to allow the nucleophilic attack of the oxygen, thereby requiring more energy and becoming the rate-determining step.

To demonstrate the applicability of the developed methodology, the dihydropyran spirocyclic **3aa** adduct was easily transformed in the tetrahydropyran derivative **4aa** with an almost quantitative yield and high diastereomeric ratio by hydrogenation using Pd/C (Scheme 3). On the other hand,

Scheme 3. Synthetic Transformations of Adduct 3aa



the reduction of the carbonyl group by $LiAlH_4$ to the corresponding alcohol was performed affording the spirocycle **5aa** in quantitative yield and 50:50 diastereomeric ratio. The adduct **4aa** was crystallized, and its absolute (2*R*,4*R*,6*S*)-configuration was unequivocally elucidated by XRD analysis (see the SI).

CONCLUSIONS

In summary, a new aldol cyclization reaction using cyclic 2,5-dienones and fluoromethylketones has been exploited in the synthesis of di- and trifluoromethylated dihydropyran spirocycles. It should be noted that the use of a bifunctional aminothiourea catalyst is necessary to obtain the desired heterospirocycles with good to high yields and enantioselectivities. Subsequent one-step, operationally simple transformations provide direct entry to other enantioenriched fluoromethylated di- and tetrahydropyrans. Computational evidence supports the key role of the bifunctional organocatalyst in promoting the reaction as a stepwise process through the aldol reaction followed by cyclization.

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■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01839.

Experimental details, characterization data, DFT calculations, and NMR spectra (PDF)

Accession Codes

CCDC 2335200−2335202 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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