Informe de actividades
Dr. Marcos Hernández Rodríguez

1. Título proyecto:

Uso de métodos computacionales para estudiar agregados supramoleculares para reconocimiento de enantiómeros y catálisis

2. Resumen

Los recursos de supercómputo se usaron en entender procesos catalíticos y reconocimiento de enantiómeros. En los procesos catalíticos se llevaron a cabo dos proyectos: (1) entender el mecanismo como los silanodioles activan electrófilos y (2) modelado de estados de transición de catalizadores bifuncionales en la reacción de 2,4-pentanodiona con β-nitroestireno. En reconocimiento de enantiómeros se modelaron escuaramidas quirales con sustituyentes ariletilo y su aducto con *R* y *S* mandelato.

3. Breve descripción de avances

En la tesis de Hugo García Hernández se estudiaron silanodioles como catalizadores de enlace de hidrógeno (EH) en la reacción de Friedel-Crafts entre el indol y el β-nitroestireno. Experimentalmente se encontró que únicamente a concentraciones muy elevadas procedía la reacción. Esto nos sugirió que existía un agregado responsable de la catálisis y no la unidad monomérica. Por cálculos se encontró que la estructura dimérica es mas estable por 12.6 kcal/mol sobre el monómero y además ese dímero forma aductos mas estables con el electrófilo (De ΔE =-10 kcal/mol para el dímero y ΔE =-8.6 kcal/mol para el monómero).

Se continúo con el análisis de los agregados supramoleculares escuaramida quiral con *R* y *S*-mandelato. Las estabilidades relativas de los agregados diastereoméricos concuerdan con los resultados experimentales por lo que ayudan a fundamentar el proceso de enantiodiscriminación que llevan a cabo los receptores. En los casos de sustituyentes arilo pequeños y electrodonadores forman interacciones CH⋯π entre el grupo arilo de la escuaramida y el fenilo del mandelato los cuales se encuentran ”isolado” en el aducto (Figura 1a y 1b) lo cual los hace mas estables que el aducto diastereomérico (Figura 1c). Este mismo razonamiento sirve para explicar otros sustituyentes los cuales no generan interacciones atractivas sino repulsivas como los grupos: 3,5-bistrifluorometilfenil, *ter*-butilo o naftilo donde la interacción isolado es repulsiva por su cercanía y se reconoce al enantiómero opuesto.

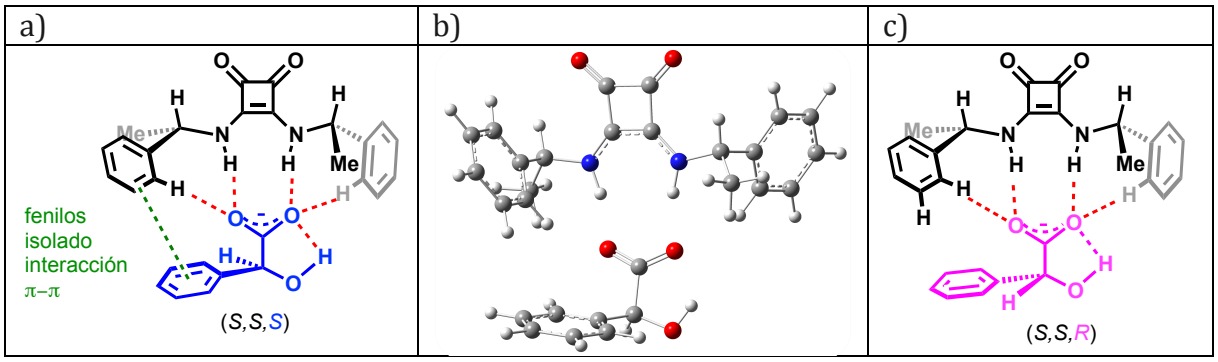

Figura 1. Reconocimiento de mandelatos quirales por la escuaramida C_2 con 1-feniletilo.

Se realizó modelado del estado de transición para la formación del enlace carbono-carbono para la reacción entre el β-nitroestireno y la acetilacetona promovida por catalizadores bifuncionales tiourea/amina terciaria. Se comparó el desempeño de pares de catalizadores diastereoméricos que contienen 1-feniletilo o 2,2,2-trifluoro-1-feniletilo. En todos los casos se modeló la ruta para el enantiómero mayoritario y el minoritario. Se comparó con datos experimentales de velocidad de reacción experimental con energía de activación teórica Ea (diferencia de energía entre el TS y el intermediario previo para el enantiómero mayoritario) y enantioselectividad experimental con la enantioselectividad teórica como la diferencia de energías de activación entre los enantiómeros (ΔEa). Los resultados explican las tendencias observadas entre pares de catalizadores diastereoméricos y mas importan te nos dio indicios de las interacciones atractivas responsables en la selectividad en cada caso.

4. Cálculos realizados

Para los cálculos teóricos de reconocimiento de enantiómeros y catálisis por silanodioles se empleó funcionales de la densidad (M06-2X/6-31+G(d,p) con optimización de geometría y cálculo de frecuencias. En el modelado de los estados de transición con catalizadores bifuncionales se optimizaron en M06-2X/6-31+G(d,p) y cada punto estacionario fue caracterizado como un mínimo o estado de transición por sus frecuencias armónicas. Se llevaron a cabo cálculos de coordenada de reacción en todos los casos para verificar la conectividad entre el estado de transición y los dos mínimos asociados al complejo reactivo y producto. Adicionalmente se hicieron cálculos de punto sencillo en SMD-(tolueno)-M06-2X/6-311++G(d,p) para tener un valor mas exacto en energía.

5. Software utilizado.

Gaussian 09

6. Recursos utilizados.

Recursos consumidos: 98,681

7. Lista de colaboradores.

-M. en C. Eddy Ivanhoe Jiménez Gutiérrez
-M. en C. Margarita Cantú Reyes
-M. en C. Josue Vazquez Chavez
-M. en C. Karen Monserrat Ruiz Díaz
-Q. Howard Díaz Salazar
-M. en C. Wilmer E. Vallejo Narvaéz
-Dr. Tomás Rocha-Rinza

8. Lista de artículos publicados.

-Bifunctional thioureas with α-trifluoromethyl or methyl groups: comparison of catalytic performance on Michael additions
E. Jiménez, W. Vallejo Narváez, C. A. Román-Chavarria, J. Vazquez-Chavez, T. Rocha-Rinza, M. Hernández-Rodríguez,* *J. Org. Chem*. **2016**, *81*, 7419-7431.

9. Lista de alumnos graduados.

Hugo García Hernández
Maestría en Ciencias Químicas, Posgrado en Ciencias Químicas, Universidad Nacional Autónoma de México (2 diciembre 2016)
Título de tesis: Catálisis por puente de hidrógeno con silanoles aplicada a la reacción de Friedel-Crafts entre indol y β-nitroestireno

Howard Yoav Díaz Salazar
Maestría en Ciencias Químicas, Posgrado en Ciencias Químicas, Universidad Nacional Autónoma de México (19 enero 2017)
Título de tesis: Aplicación de escuaramidas quirales en el reconocimiento de moléculas quirales y organocatálisis.

Eddy Ivanhoe Jiménez Gutiérrez
Doctorado en Ciencias Químicas, Posgrado en Ciencias Químicas, Universidad Nacional Autónoma de México (3 diciembre 2016)
Título de tesis: Síntesis y aplicación de organocatalizadores bifuncionales que contienen aminas quirales con el grupo trifluorometilo.

10. Lista de congresos nacionales e internacionales y participantes.

- Bifunctional thioureas with alpha-trifluoromethyl group: synthesis and applications. Eddy Ivanhoe Jiménez Gutiérrez, Wilmer E. Vallejo Narvaez,Tomás Rocha Rinza Marcos Hernández Rodríguez Gordon Research Conference on Stereochemistry, Newport, RI, United States, Julio 2016.
- Reconocimiento molecular de carboxilatos quirales por escuaramidas. Trabajo profesional en modalidad oral, 51º Congreso Mexicano de Química, (30 septiembre 2016).
- Combined experimental and theoretical study of bifunctional organocatalyst with CF_3 or CH_3. The acidity is not all. Eddy Ivanhoe Jiménez, Wilmer Vallejo-Narváez, Tomás Rocha-Rinza, Marcos Hernández-Rodríguez. Simposio por 75º aniversario del Instituto de Química, Cd. Mx., (8 abril 2016).
- Recognition of Chiral Carboxylates with Squaramides. Howard Díaz Salazar, Marcos Hernández-Rodríguez. Simposio por 75º aniversario del Instituto de Química, Cd. Mx., (8 abril 2016).
- Theoretical Prediction and Experimental Realization of Amides and Imides Dimerization. Wilmer Vallejo Narváez, Marcos Hernández Rodríguez, Tomás Rocha Rinza, Simposio por 75º aniversario del Instituto de Química, Cd. Mx., (8 abril 2016).
- Stereoselective Mannich reaction between bis(trimethylsilyl)ketenes and N-terbutanesulfinyl imines. Margarita Cantú Reyes, Isabel Alvarado Beltran, Cecilio Alvarez Toledano, Marcos Hernández Rodríguez. Simposio por 75º aniversario del Instituto de Química, Cd. Mx., (8 abril 2016).

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Bifunctional Thioureas with α-Trifluoromethyl or Methyl Groups: Comparison of Catalytic Performance in Michael Additions

Eddy I. Jiménez, Wilmer E. Vallejo Narváez, Carlos A. Román-Chavarría, Josue Vazquez-Chavez, Tomás Rocha-Rinza, and Marcos Hernández-Rodríguez*

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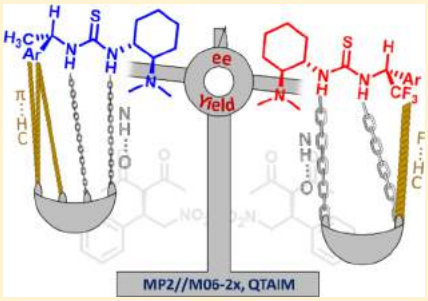
Supporting Information

ABSTRACT: Thioureas are an important scaffold in organocatalysis because of their ability to form hydrogen bonds that activate substrates and fix them in a defined position, which allows a given reaction to occur. Structures that enhance the acidity of the thiourea are usually used to increase the hydrogen-bonding properties, such as 3,5-bis(trifluoromethyl)phenyl and boronate ureas. Herein, we report the synthesis of bifunctional thioureas with a chiral moiety that include either a trifluoromethyl or methyl group. Their catalytic performance in representative Michael addition reactions was used in an effort to compare the electronic effects of the fluorination at the methyl group. The observed differences concerning yields and ee values cannot be attributed solely to the different steric environments; theoretical results indicate distinct interactions within the corresponding transition states. The calculated transition states show that the fluorinated catalysts have stronger N−H···O and C−H···F hydrogen bonds, while the nonfluorinated systems have C−H···π contacts. These results have shown that a variety of hydrogen-bonding interactions are important in determining the yield and selectivity of thiourea organocatalysis. These details can be further exploited in catalyst design.



INTRODUCTION

Hydrogen-bonding catalysis and a chiral counterion strategy have risen recently as a reliable synthetic methodology.[1] Takemoto[2] introduced chiral bifunctional catalysts[3] to activate an electrophile through hydrogen bonds (HB). These systems also contain a tertiary amine that deprotonates a nucleophile which is subsequently added. The Takemoto catalyst (Figure 1a) features a

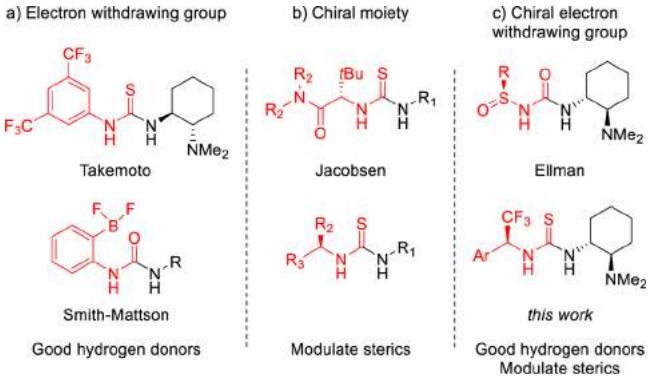


Figure 1. Moieties used to enhance hydrogen bond donor properties or to modulate steric effects in H-bond catalysis and counterion strategies.

3,5-bis(trifluoromethyl)phenyl group[4] that enhances the acidity of the thiourea and thereby increases its hydrogen-bonding properties. Boronate ureas have a similarly enhanced HB donor capacity of the HNC(O) moiety, in this case by means of an internal Lewis acid.[5,6] Stereocontrol of the addition products[7] can be achieved by addition of chiral substituents to the thiourea moiety (Figure 1b); however, this is done at the expense of the HB activation ability. Nonetheless, if a chiral group with electron-withdrawing properties is bound to the thiourea (Figure 1c), a good compromise between the modulation of the steric demands and activation by the catalyst can be accomplished. On this subject, Ellman,[8] Jacobsen, and others[9] have used *N*-sulfinyl ureas that are able to catalyze a variety of reactions. Herein we report the synthesis and application of bifunctional thioureas with a chiral group that incorporates a trifluoromethyl group in its structure.[10] Thioureas featuring trifluoromethyl groups have shown exceptional properties in the recognition of chiral carboxylates with binding constants that are 10 times higher than those for the analogous nonfluorinated compounds.[11] The chiral moiety with $-CF_3$ confers to the thioureas reported in this work (1) good HB properties[12] without the deactivation of the catalyst by intramolecular interactions[13] and (2) the possibility of modulating the steric environment. In addition, the catalysts put forward in this are easily synthesized and allow the incorporation of a variety of functional groups in their structure. This study also considers the corresponding nonfluorinated catalysts[14] to provide insights into the effect of the NH acidity on the yield and enantiomeric excess of the reactions considered in this investigation.

Received: May 6, 2016
Published: July 11, 2016

DOI: 10.1021/acs.joc.6b01063
J. Org. Chem. 2016, 81, 7419−7431

RESULTS AND DISCUSSION

The synthesis of the chiral scaffold with trifluoromethyl groups was performed by the nucleophilic addition of the Ruppert–Prakash reagent to (*S*)-*N*-*tert*-butylsulfinylimines **1a–d**, affording compounds **2a–d** with excellent diastereoselectivity.[15] After removal of the chiral auxiliary, amines **3a–d** were transformed to isothiocyanates **4a–d** and added to both enantiomers of *trans*-*N*,*N*-dimethyl-1,2-diaminocyclohexane[16] to produce the diastereomeric catalysts (*R*,*S*,*S*)-**5a–d** and (*R*,*R*,*R*)-**6a–d** (Scheme 1). This same protocol led to catalysts with a methyl instead of a trifluoromethyl group (thioureas **7a–d** and **8a–d**).[17,18]

The Michael addition of 1,3-dicarbonyl compounds to β-nitrostyrene has become an archetypical reaction to assess the performance of bifunctional catalysts.[19] We employed 2,4-pentanedione as the source of the nucleophile for this reaction. In particular, we focused on the performance of the fluorinated and nonfluorinated systems to compare thioureas with different HB donor properties.

We found that systems with an α-trifluoromethyl group have a strong match–mismatch relationship (Table 1, entries 1–8) as opposed to their nonfluorinated analogs (Table 1, entries 9–16). Additionally, we further studied the effect of the trifluoromethyl group on the yield and enantioselectivity by comparison of the diastereomeric catalysts **5b** and **6b** along with **7b** and **8b**.[20]

Similar trends concerning match–mismatch relationships were found with different nitroalkenes, as reported in Table 2: i.e., fluorinated catalysts **5b** and **6b** have a strong match–mismatch relationship, in contrast with catalysts **7b** and **8b**. Interestingly, **6b** gives yields comparable with those of Takemoto but its performance is less susceptible to structural differences in the Michael acceptor. Because catalysts **6b** and **8b** only differ by three fluorine atoms, we expected that both systems with the

Scheme 1. Synthesis of the Bifunctional Organocatalysts Considered in This Work

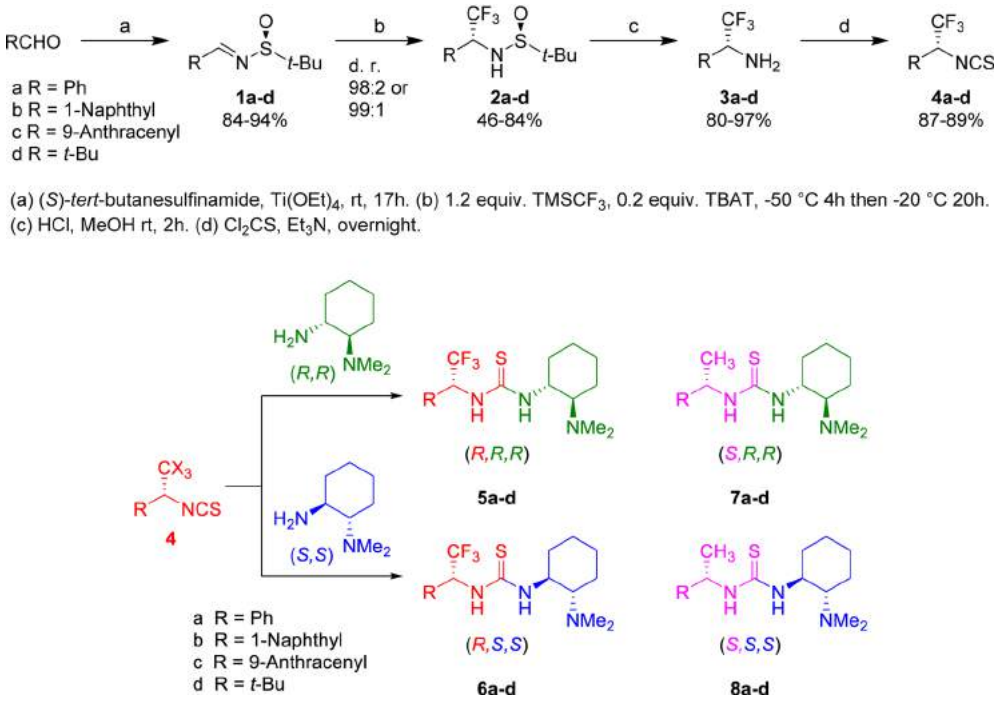
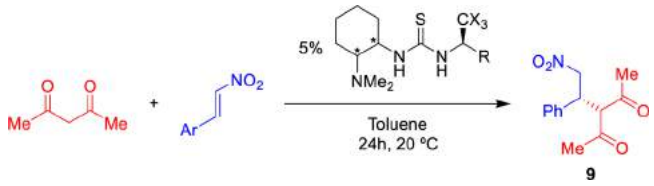


Table 1. Michael Addition of 2,4-Pentanedione to β-Nitrostyrene with the Catalysts Developed in This Work

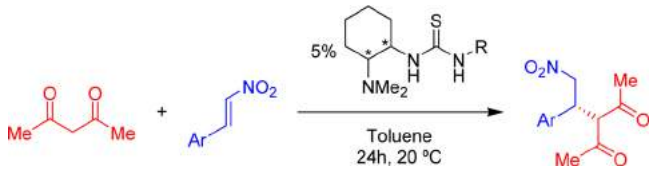


entry	R, X	cat.	yield (%)	ee[a]	entry	R, X	cat.	yield (%)	ee[a]
1	Ph, F	**5a**	82	68	**9**	Ph, H	**7a**	87	86
2		**6a**	96	−89	**10**		**8a**	68	−81
3	1-Naphth, F	**5b**	87	67	**11**	1-Naphth, H	**7b**	94	87
4		**6b**	94	−92	**12**		**8b**	84	−76
5	9-Anthr, F	**5c**	76	46	**13**	9-Anthr, H	**7c**	86	74
6		**6c**	87	−82	**14**		**8c**	75	−60
7	*t*-Bu, F	**5d**	88	69	**15**	*t*-Bu, H	**7d**	87	84
8		**6d**	90	−94	**16**		**8d**	95	−62

[a]Analyzed by CSP-HPLC. Catalysts **5** and **7** afford compound (*R*)-**9**, while the *S* enantiomer is produced with catalysts **6** and **8**.

DOI: 10.1021/acs.joc.6b01063
J. Org. Chem. 2016, 81, 7419–7431

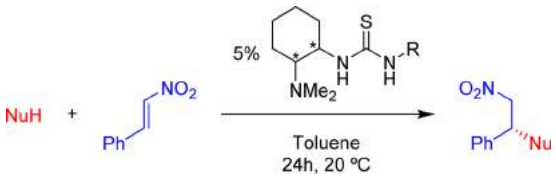
Table 2. Yield and ee Values[a] of the Michael Additions of 2,4-Pentanedione to Different Nitroalkenes Using Catalysts T and 5b−8b

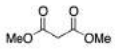
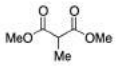
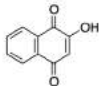


entry	Ar	Prod.	T 3,5-$(CF_3)_2C_6H_3$	5b CH(1-Naphth)CF_3	6b	7b CH(1-Naphth)CH_3	8b
1	4-Me-C_6H_4	10	90 (74)	74 (56)	87 (-87)	93 (76)	90 (-69)
2	4-OMe-C_6H_4	11	92 (75)	86 (51)	90 (-89)	85 (79)	63 (-62)
3	4-Cl-C_6H_4	12	90 (69)	75 (56)	94 (-84)	94 (76)	80 (-68)
4	4-NO_2-C_6H_4	13	86 (80)	58 (64)	86 (-81)	83 (83)	81 (-70)
5	2-Br-C_6H_4	14	86 (86)	88 (49)	92 (-84)	93 (76)	92 (-68)
6	1-Naphth	15	82 (83)	81 (50)	82 (-87)	79 (81)	72 (-72)
7	2-thiophene	16	80 (64)	87 (71)	69 (-89)	80 (78)	72 (-60)

[a]ee values are given in parentheses. Catalysts **T**, **5**, and **7** afford compounds (*R*)-**10**−**15**, while the *S* enantiomer is produced with catalysts **6** and **8**. Compound **16** presents the opposite configuration by CIP rules.

Table 3. Yields and ee Values[a] of the Michael Addition Product of a Variety of Nucleophiles with *trans*-β-Nitrostyrene using Catalysts T and 5b−8b



entry	NuH	Prod.	T 3,5-$(CF_3)_2C_6H_3$	5b CH(1-Naphth)CF_3	6b	7b CH(1-Naphth)CH_3	8b
1		17	83 (88)	66 (68)	69 (-87)	78 (88)	34 (-76)
2		18[b]	88 (92)	61 (72)	57 (-91)	64 (90)	18 (-83)
3		19[c]	73 (64)	77 (25)	96 (-76)	79 (50)	59 (-80)
4		20	96 (88)	98 (87)	84 (-96)	94 (90)	86 (-85)

[a]ee values are given in parentheses. Each diastereomeric catalyst generated a different enantiomer. [b]72 h reaction time. [c]dr. = 7:1 in all experiments.

S,S configuration in the diamine to be the match combination. This, however, was not the case; catalyst **7b** with the diamine having the *R,R* configuration gave better results in this regard.

We found similar yields, selectivities, and match−mismatch relationships for other pronucleophiles addressed in this work: i.e., those leading to products **17**−**20** (Table 3). We noted that the enantioselectivity of **6b** was comparable to that obtained from **7b** with malonate nucleophiles.

Finally, we studied the performance of catalysts **6b** and **7b** in different solvents. We observed with catalyst **6b** much lower yields in ether solvents, but in all cases the reaction was stereoselective (around 90% of the major enantiomer). On the other hand, the nonfluorinated catalyst **7b** presented the opposite trend; the yield was little affected and the stereoselectivity highly depended on the solvent used (Table 4).

The different behavior shown by the presented catalysts could also be attributed to the steric difference between the

Table 4. Solvent Effects in the Michael Addition with Catalysts 6b and 7b

(*R,S,S*) **6b** (*S,R,R*) **7b**

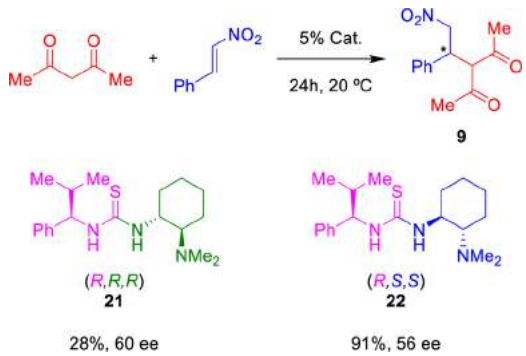
entry	solvent	6b yield (%)	6b ee[a]	7b yield (%)	7b ee[a]
1	Toluene	94	-92	94	87
2	CCl_4	87	-89	93	62
3	DCM	87	-76	93	53
4	MTBE	55	-83	82	57
5	THF	36	-82	87	5

[a]Analyzed by CSP-HPLC. Catalysts **7b** afford compound (*R*)-**9**, while the *S* enantiomer is produced with catalyst **6b**.

DOI: 10.1021/acs.joc.6b01063
J. Org. Chem. 2016, 81, 7419−7431

methyl and trifluoromethyl groups. The van der Waals radii of $-CH_3$ and $-CF_3$ are 2.0 and 2.7 Å, respectively.[21] In addition, the *A* value of trifluoromethyl is higher than that of isopropyl[22] and hence it has been proposed that the $-CF_3$ group is of similar size to[23a] or somewhat smaller than[23b] $-CH(CH_3)_2$. We studied diastereomeric catalysts **21** and **22** with isopropyl substituents to find out if the steric demand is the factor responsible for the difference in the obtained results. We found that the catalysts featuring isopropyl groups have similar selectivity, but their corresponding enantiomeric excesses (60 and 56% as shown in Scheme 2) are considerably lower than those obtained with systems **6a** and **7a** (89 and 87%, respectively). We conclude that there should be other explanations for the observed enantioselectivity. The search for a suitable interpretation of the results considered up to this point motivated the theoretical studies presented below.

Scheme 2. Yields and ee Values of the Michael Addition with Diastereomeric Catalysts 20 and 21



Computational Analysis. We now consider the reaction mechanism of the Michael addition. Takemoto proposed the first mechanism for this reaction, which involves the sequential activation of the electrophile and the nucleophile.[2a] Afterward, Pápai[24] suggested a different mechanism with a lower activation energy than that of Takemoto. Our results with catalyst **6a**, shown in Figure S2 of the Supporting Information, are also consistent with Pápai's mechanism. In this reaction pathway (Figure 2), the nucleophile is first deprotonated by the tertiary amine **A**, and then migrates to the cavity of the thiourea **B**. Subsequently, the electrophile is attacked by the nucleophile−thiourea adduct, forming the trimolecular complex **C**, which is responsible for the orientation of the new carbon−carbon bond $\mathbf{TS_P}$ and the stereochemistry of the product **D**.

A model catalyst with a phenyl rather than a naphthyl group was used to reduce the number of atoms in the system and hence the computation time of the calculations. This is particularly reasonable inasmuch as the results obtained with catalysts including either $-C_6H_5$ or $-C_{10}H_7$ within their structure are similar (Table 1). In this way, we explored the energy profile with diastereomeric catalysts **5a** and **6a** along with their nonfluorinated counterparts **7a** and **8a**.

The energy profiles in Figure 3 show that the activation barrier for the trifluoromethyl systems **6a** is less than the corresponding value for **5a** (4.6 and 6.7 kcal/mol, respectively) in accordance with the observed rate (k_{obs} = 0.0092 and 0.0066, respectively; see Figure S1 and Table S1 in the Supporting Information). In the nonfluorinated catalyst, the opposite configuration of the diamine has a smaller activation barrier (4.7 kcal/mol for **7a** and

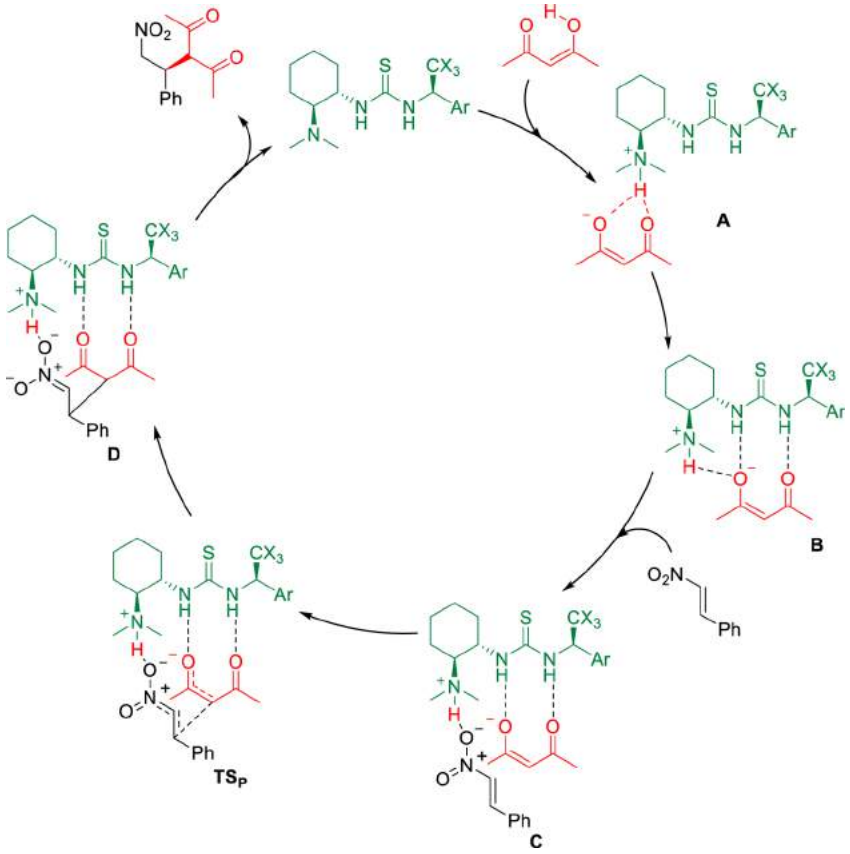


Figure 2. Bifunctional catalyst mechanism proposed by Pápai.

DOI: 10.1021/acs.joc.6b01063
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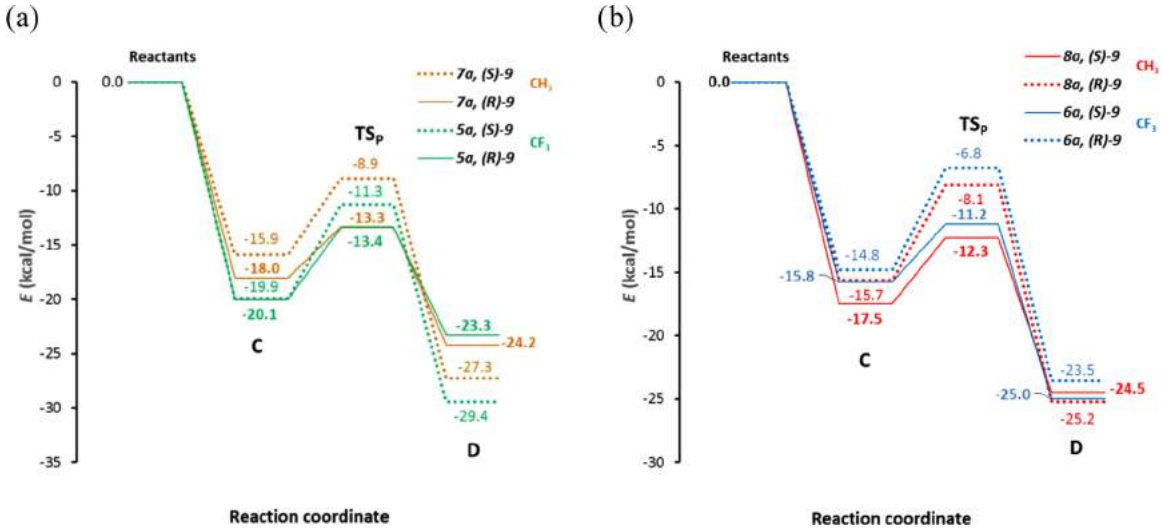

Figure 3. Gibbs energy profile of the rate-limiting step in Pápai's mechanism for the Michael addition of 2,4-pentanedione and β-nitrostyrene with trifluoromethyl catalysts **5a** and **6a** and their nonfluorinated analogues **7a** and **8a**. The calculations were performed with the COSMO-(toluene)-RIJCOSX-MP2/aug-cc-pVDZ//M06-2x/6-31+g(d) level of theory. The structures of **C**, **TS**$_P$, and **D** are shown in Figure 2. (a) Catalysts with the *R,R* configuration in the diamine **5a** and **7a** generate the (*R*)-**9** product (b) Catalysts with the *S,S* configuration **6a** and **8a** yield the (*S*)-**9** compound.

5.2 kcal/mol for **8a**) also in agreement with the observed rates (k_{obs} = 0.0331 and 0.0042, respectively). Although the theoretical calculations predict correctly the relative reaction rate for the diastereomeric pairs **5a** vs **6a** and **7a** vs **8a**, the computations are not fully consistent when the relative rates of all four systems are compared. This discrepancy may be attributable to factors such as product inhibition and the reversibility of the reaction,[25,26] which are not taken into account in the computational analysis.

Figure 3 also shows that the fluorinated catalysts lead to different activation energies for the formation of each enantiomer, thereby favoring the observed enantioselectivity of the reaction. The calculated differences in activation energies are 2.0 and 3.5 kcal/mol for **5a** and **6a**, respectively, predicting correctly that **6a** is more enantioselective. With the nonfluorinated systems, these differences are 2.3 and 2.4 kcal/mol for **7a** and **8a**, respectively, which explains the lack of a strong match−mismatch relationship in these catalysts (Tables 1−3).

Further structural analysis of the transition states revealed the following.

(1) Thioureas attached with a trifluoromethyl group generate a shorter HB with the nucleophile,[26] as expected (Table S2 in the Supporting Information). These shorter and stronger hydrogen bonds in the fluorinated systems can be responsible for the lack of significant solvent effects on the enantioselectivity obtained with catalyst **6b**. This is buttressed by the fact that solvent effects are more pronounced in the ee achieved using **7b**, as reported in Table 4.

(2) There are other interactions that involve the arylethyl groups which are particular to each catalyst. The structures of the systems with an *R,R* configuration of the diamine (**5a** and **7a**) present the phenyl ring on the same side of the approaching β-nitrostyrene in a way that a T-shaped $\pi-\pi$ contact is formed between the phenylethyl group of the thiourea and the $-C_6H_5$ part of PhCH=CHNO$_2$ (Figure 4). The observed distances between the centroids of the phenyl rings are 4.72 and 4.62 Å for **5a** and **7a**, respectively. These values are close to the optimal distance for this interaction (5.0 Å) computed with high-level ab initio calculations.[27]

On the other hand, fluorinated and nonfluorinated catalysts with the *S,S* configuration in the diamine (**8a** and **6a**) lead to transition states with the $-CH_3$ and $-CF_3$ groups on the same side as the approaching nitrostyrene. Therefore, the phenylethyl group in catalyst **8a** is rotated to form the aforementioned $\pi-\pi$ interaction, whereas the structure produced with catalyst **6a** presents interactions between two fluorine atoms and an ortho C−H of the nitrostyrene molecule,[28] as shown in Figure 5 and confirmed with the topological analysis of the electron density (vide infra).

After having considered the energetic and structural aspects of the transition states of the Michael addition, we analyzed the interactions between the catalysts, the enolate, and the nitrostyrene by means of quantum chemical topology.[29] Figure 4 shows the molecular graph of the transition states for Pápai's mechanism formed with catalysts **5a** and **7a**. Both systems present bond paths between sulfur and the hydrogen atoms of the stereogenic carbon bonded to the thiourea. These trajectories of $\nabla\rho(\mathbf{r})$ suggest a moderate rigidity of the bifunctional catalysts, which facilitates the formation of the supramolecular complex. The interactions between both the fluorinated and nonfluorinated thioureas with the two reactants include five hydrogen bonds. Tables S3 and S5 in the Supporting Information report some selected topological properties of the charge distribution at the corresponding bond critical points. As expected, these hydrogen bonds are described as closed shell interactions, reflected in the sign of the Laplacian of the charge density, $\nabla^2\rho(\mathbf{r}) > 0$, in the intermolecular region. The $-CF_3$ catalyst **5a** has stronger NH···O hydrogen bonds (E_H in Table S3) and two CH···π interactions, while the nonfluorinated compound **7a** presents three CH···π interactions. We also noted that the phenyl group in the catalyst responsible for these CH···π interactions has a less negative charge in compound **5a** due to the inductive effect of the trifluoromethyl group (Table S5). These weak interactions might explain the better performance of **7a** in comparison with that of **5a**. Considering the size of the aromatic ring in the catalyst, we can assume that the 9-anthracenyl group is too bulky for an optimal performance of the catalyst and the phenyl does not have a large enough molecular area for effective $\pi-\pi$ interactions. The naphthyl group provides a better compromise between the establishment of efficient $\pi\cdots\pi$ interactions and the avoidance of steric hindrance.

DOI: 10.1021/acs.joc.6b01063
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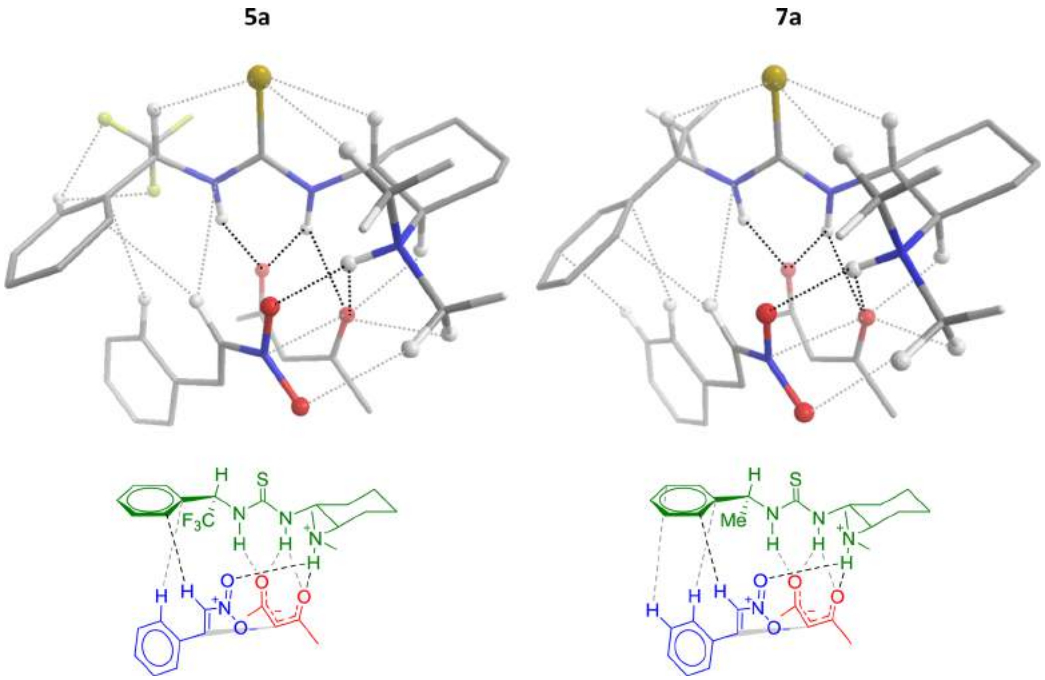

Figure 4. Noncovalent interactions within the transition states for the Pápai's mechanism with catalysts **5a** and **7a**. The complete molecular graphs of these systems can be observed in Tables S4 and S6 of the Supporting Information.

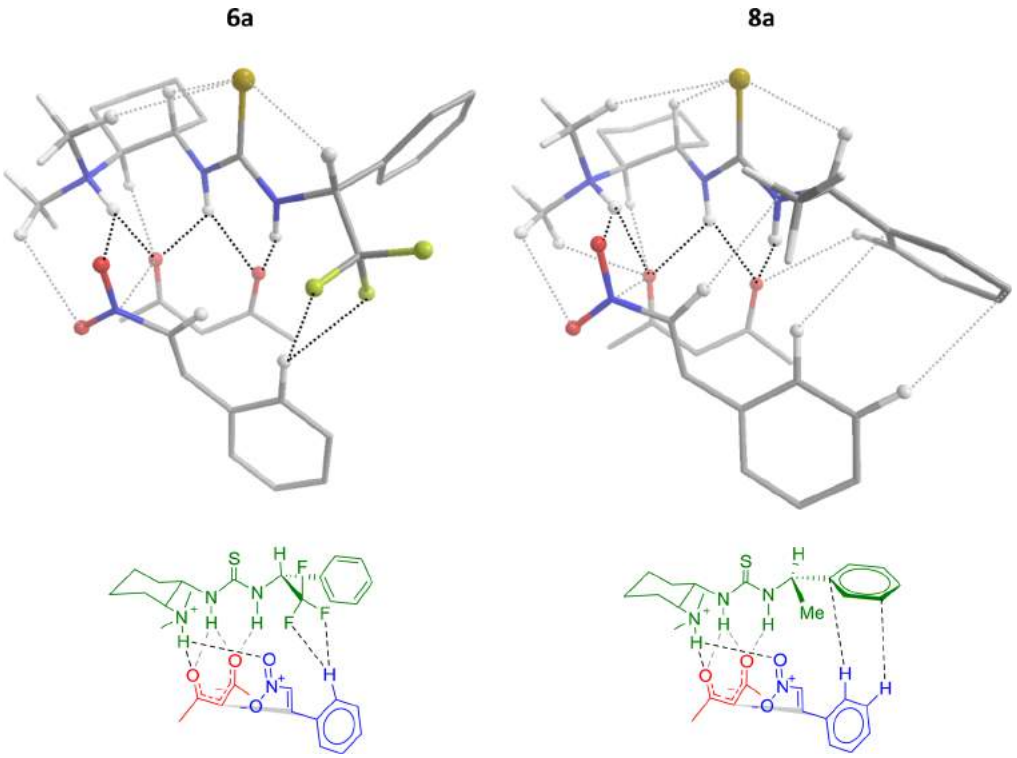

Figure 5. Noncovalent interactions within the transition states for Pápai's mechanism with catalysts **6a** and **8a**. The complete molecular graphs of these systems can be found in Tables S5 and S7 in the Supporting Information.

Figure 5 shows a similar topological analysis of the electron density for the transition states with systems **6a** and **8a**. Once more, the fluorinated catalyst has stronger NH···O hydrogen bonds than the nonfluorinated analogue. In particular, compound **6a** forms the strongest $NH_1 \cdots O_4$ interaction (see Table S4 in the Supporting Information). Apart from these interactions, there are other hydrogen bonds between catalyst **6a** or **8a** and the reactants that depend on the conformation of the $-CHPhCX_3$ group (X = F, H). The fluorinated catalyst presents HBs between two F atoms and an ortho hydrogen of the phenyl group of nitrostyrene, whereas the nonfluorinated system exhibits $-CH \cdots \pi$ bonds linking the two $-C_6H_5$ rings in the corresponding transition state. Again, the interactions between the reactants and catalyst **6a** are stronger than those found for **8a**. Overall, the topological analysis of the charge distribution indicates that the $-CF_3$ group leads to a stronger association of a

DOI: 10.1021/acs.joc.6b01063
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bifunctional thiourea with the reactants and thereby promotes the catalytic process more efficiently, in good agreement with the larger yield and enantiomeric excess of **6a** in comparison with **8a**. In addition, these CF···HC interactions could explain the ineffectiveness of systems with isopropyl (**21** and **22**). The *i*-Pr group produces no significant attractive forces and only provides steric hindrance. In the mismatch combination **21**, the isopropyl is on the same side of the approaching nitrostyrene, interfering in this way with the docking of this electrophile.

The computational analysis indicates that the fluorinated and nonfluorinated catalysts behave differently on account of their distinct secondary noncovalent interactions. The trifluoromethyl group in the catalyst **6a** is on the same side of the approaching β-nitrostyrene, and hence, the fluorine atoms form CF···H−C interactions. However, the nonfluorinated catalyst **7a** has the aromatic fragment on the same side of the approaching electrophile, which allows $\pi-\pi$ interactions to be maximized. Therefore, although fluorinated catalyst **6a** presents the strongest NH···O HBs, nonfluorinated system **7a** exhibits a greater number of secondary noncovalent interactions (CH···π and CH···O), which results in the similar performances of both catalysts.

■ CONCLUSION

We found that the incorporation of chiral groups with an α-trifluoromethyl moiety in bifunctional thioureas has a modest positive effect on the yield and selectivity of the Michael additions considered in this work. Nevertheless, the new catalysts **6** present stronger NH···O hydrogen bonds and CF···HC interactions with the reactants in comparison to their methylated counterparts. The methylated systems **7**, on the other hand, exhibit more CH···π and CH···O secondary interactions, which explains the comparable yield and selectivity. However, the chiral group presented in this work shows a good compromise between enhanced HB donor properties and controlled steric demands, which could be of interest to hydrogen-bonding organocatalysis.

■ EXPERIMENTAL SECTION

Computational Studies. The geometries of all intermediates and transition states were completely optimized with the M06-2x/6-31+G(d)[30] approximation as implemented in the Gaussian 09 package.[31] Each stationary structure was characterized as a local minimum or a saddle point of first order by means of the computation of the corresponding harmonic frequencies. Intrinsic reaction coordinate calculations were carried out in all cases to verify that the localized transition state structures connect the two minima on the potential energy hypersurface associated with reactants and products. Solvent (toluene) effects were considered through the COSMO model and single-point energy calculations of all the stationary points with COSMO-(Toluene)-RIJCOSX-MP2/aug-cc-pVDZ.[32]

The topological analysis of the electron density was done in accordance with the quantum theory of atoms in molecules (QTAIM)[29] and using the AIMAll program.[33] In particular, we considered the critical points of the charge distribution related to different elements of molecular structure defined in QTAIM, especially those associated with bonding between two atoms. The characterization of the different interactions between the bifunctional catalysts addressed in this study and the reactants of the Michael addition was done in terms of the properties of $\rho(\mathbf{r})$, including $\nabla^2\rho(\mathbf{r})$ and the density of the potential energy, $V(\mathbf{r})$, from which hydrogen bond formation energies can be estimated as in ref 34.

General Considerations. All starting materials were used directly as obtained commercially. THF was distilled from sodium benzophenone ketyl. Flash column chromatography was carried out with silica gel 60 (0.4/0.63 mm, 230−400 mesh); TLC was performed with silica gel F254 plates. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm downfield from TMS, and coupling constants are in hertz. Mass spectra were obtained by EI. HRMS (FAB and DART) were measured with quadrupole and TOF mass spectrometers; CSP-HPLC analysis was performed using the indicated chiral column and UV detector.

2,2,2-Trifluoro-1-arylamines and precursors have been reported previously (see ref 15).

General Procedure for the Synthesis of Sulfinylimines 1a−d. One equivalent (15 mmol) of the corresponding aldehyde was dissolved in 40 mL of anhydrous THF under a nitrogen atmosphere. Then, we added 6.2 mL (30 mmol, 2 equiv) of titanium tetraethoxide and 1.8 g (15 mmol, 1 equiv) of (*S*)-*tert*-butylsulfinamide and stirred the mixture at room temperature for 17 h. The reaction mixture was poured into 40 mL of brine with vigorous stirring, and the resulting suspension was filtered over Celite. The cake was washed with EtOAc (20 mL × 3). The organic layer was separated, and the aqueous phase was extracted with EtOAc (15 mL × 3). The combined organic phases were dried with Na_2SO_4 and concentrated afterward. The final product was purified by FC with hexane/EtOAc 10/0 to 8/2. The acquired NMR spectra of target compounds matched those previously reported.

*(S)-N-Benzylidene-tert-butanesulfinamide (**1a**).*[35a] Colorless liquid, 91% yield (2.86 g). R_f = 0.23 (hexane/ethyl acetate, 9/1). $[\alpha]_D^{25}$ = +97.5 (*c* 1.15, $CHCl_3$) (lit.[35a] $[\alpha]_D^{25}$ = +99.7 (*c* 1.15, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H), 7.68 (m, 2H), 7.42−7.19 (m, 3H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.4, 133.8, 132.1, 129.0, 128.6, 57.3, 22.3. IR (film): $\tilde{\nu}$ (cm^{-1}) 3355, 3065, 2961, 2926, 2870, 1606, 1573, 1479, 1451, 1363, 1314, 1216, 1173, 1118, 1085, 877, 855, 758, 735, 693. MS-EI (70 eV): *m*/*z* (%) 209 (2) $[M]^+$, 153 (100), 136 (34), 126 (11), 105 (92), 77 (66), 71 (19), 57 (100), 51 (35), 4 (68), 29 (36), 18 (6).

*(S)-N-[(1-Naphthyl)methylidene]-tert-butanesulfinamide (**1b**).*[35b,c] White solid, 84% yield (3.27 g). R_f = 0.51 (hexane/ethyl acetate, 8/2). Mp: 48−50 °C (lit.[35b] *R* enantiomer mp 52−54 °C). $[\alpha]_D^{25}$ = +4.4 (*c* 1.13, $CHCl_3$) (lit.[35c] *R* enantiomer $[\alpha]_D^{25}$ −4.5 (*c* 1, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.16 (s, 1H), 9.02 (d, *J* = 8.6 Hz, 1H), 8.08−7.96 (m, 2H), 7.95−7.86 (m, 1H), 7.71−7.60 (m, 1H), 7.60−7.48 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.6, 134.0, 133.4, 132.0, 131.4, 129.6, 129.0, 128.1, 126.6, 125.3, 124.5, 57.8, 22.8. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3061, 2995, 2966, 2917, 2862, 1596, 1562, 1510, 1473, 1458, 1440, 1386, 1359, 1333, 1234, 1208, 1174, 1158, 1076, 1033, 1012, 977, 798, 772, 698, 581, 549.519, 465, 440, 409. MS-EI (70 eV): *m*/*z* (%) 260 (5) $[M + H]^+$, 203 (100), 186 (12), 155 (50), 127 (23), 101 (3), 77 (4), 57 (13), 41 (2).

*(S)-N-[(9-Anthracenyl)methylidene]-tert-butanesulfinamide (**1c**).*[15b] Yellow solid, 90% yield (4.18 g). R_f = 0.33 (hexane/ethyl acetate, 8/2). Mp: 134−136 °C (lit.[15b] *R* enantiomer mp 137−138 °C). $[\alpha]_D^{25}$ = +76.0 (*c* 1, $CHCl_3$) (lit.[15b] *R* enantiomer $[\alpha]_D^{25}$ −80.8 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.92 (s, 1H), 8.88 (d, *J* = 9.0 Hz, 2H), 8.58 (s, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.47−7.67 (m, 4H), 1.38 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 139.1, 132.7, 131.4, 131.3, 129.3, 128.1, 125.7, 124.6, 57.7, 22.8. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3048, 2960, 2922, 2862, 1621, 1579, 1553, 1517, 1443, 1360, 1250, 1173, 1076, 1022, 982, 958, 914, 788, 732, 690, 603, 575, 539, 505, 450, 405. MS-EI (70 eV): *m*/*z* (%) 309 (2) $[M]^+$, 253 (33), 203 (100), 178 (16), 176 (15), 151 (5).

*(S)-N-[2,2-Dimethylpropylilidene]-tert-butanesulfinamide (**1d**).*[35d] Yellow oil, 94% yield (2.67 g). R_f = 0.42 (hexane/ethyl acetate, 9/1). $[\alpha]_D^{25}$ = +117.8 (*c* 1.16, $CHCl_3$) (lit.[35d] $[\alpha]_D^{25}$ = +99.7 (*c* 1.15, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 1H), 1.01 (s, 9H), 0.98 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.4, 56.2, 37.7, 26.5, 22.1. IR (film): $\tilde{\nu}$ cm-1 = 3349, 3069, 2964, 2930, 2904, 2870, 1738, 1620, 1474, 1459, 1429, 1364, 1262, 1186, 1162, 1118, 1086, 879, 845, 741, 709. MS-DART (positive): *m*/*z* (%) 190 (100) $[M + H]^+$.

General Procedure for Trifluoromethyl Addition (2a−d). A 20 mmol amount (1 equiv) of sulfinylimine **1** and 2.15 g (4 mmol, 0.2 equiv) of TBAT (tetrabutylammonium difluorotriphenylsilicate) were suspended in 60 mL of anhydrous THF under a nitrogen atmosphere. The reaction mixture was cooled to −50 °C, and then 3.6 mL (24 mmol, 1.2 equiv) of $TMSCF_3$ was added. The reaction mixture was stirred for 4 h at −50 °C and 20 h at −20 °C. The reaction was

DOI: 10.1021/acs.joc.6b01063
J. Org. Chem. 2016, 81, 7419−7431

quenched with 60 mL of aqueous ammonium chloride solution and extracted with EtOAc (50 mL × 3). The combined organic phases were dried with Na_2SO_4 and then concentrated. The product was purified by FC with hexane/EtOAc as eluent (proportions indicated in each compound). The acquired NMR spectra of the compounds matched with previously reported data.[15a]

*(S)-N-[(R)-1-Phenyl-2,2,2-trifluoroethyl]-tert-butanesulfinamide (**2a**).*[15a] Purified by FC hexane/EtOAc, 7/3. White solid, 59% yield (3.30 g). R_f = 0.52 (hexane/ethyl acetate, 1/1), Mp: 95−97 °C. $[\alpha]_D^{25}$ = +75.2 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (m, 5H), 5.00−4.70 (m, 1H), 3.68 (br, 1H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 129.7, 129.3, 128.1, 124.7 (q, *J* = 281.6 Hz), 61.5 (q, *J* = 30.6 Hz), 57.1, 22.5. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3117, 2994, 2964, 2928, 2904, 2867, 1712, 1667, 1498, 1455, 1425, 1365, 1259, 1149, 1118, 1097, 1051, 1011, 930, 909, 849, 760, 699, 590, 555, 512, 452. MS-EI (70 eV): *m/z* (%) 279 (1) $[M]^+$, 223 (69), 216 (5), 176 (12), 159 (91), 145 (22), 140 (46), 126 (5), 109 (55), 104 (28), 91 (9), 77 (24), 57 (100), 51 (12), 41 (68), 29 (34).

*(S)-N-[(R)-1-(1-Naphthyl)-2,2,2-trifluoroethyl]-tert-butanesulfinamide (**2b**).*[15a] Purified by FC hexane/EtOAc, 6/4. White solid, 84% yield (5.53 g). R_f = 0.48 (hexane/ethyl acetate, 6/4). Mp: 127−131 °C. $[\alpha]_D^{25}$ = +203.0 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.6 Hz, 1H), 7.98−7.85 (m, 2H), 7.71−7.58 (m, 2H), 7.58−7.45 (m, 2H), 5.83−5.61 (m, 1H), 3.78 (d, *J* = 5.1 Hz, 1H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.1, 131.0, 130.6, 129.9, 129.3, 127.5, 126.5, 125.6, 125.3, 125.2 (q, *J* = 282.0 Hz), 122.7, 57.2, 56.2 (q, *J* = 31.1 Hz), 22.5. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3216, 3051, 2965, 2904, 1596, 1510, 1458, 1395, 1366, 1328, 1301, 1244, 1176, 1112, 1053, 888, 858, 797, 775, 737, 698, 623, 562, 525, 442. MS-EI (70 eV): *m/z* (%) 330 (23) $[M + H]^+$, 273 (11), 256 (41), 225 (4), 209 (100), 189 (18), 176 (15), 159 (29), 154 (26), 128 (27), 87 (11), 77 (3), 57 (39), 41 (4).

*(S)-N-[(R)-1-(9-Anthracenyl)-2,2,2-trifluoroethyl]-tert-butanesulfinamide (**2c**).*[15a,35e] Purified by FC hexane/EtOAc, 9/1 to 7/3. Yellowish solid, 69% yield (5.24 g). R_f = 0.32 (hexane/ethyl acetate, 7/3). Mp: 153−156 °C. $[\alpha]_D^{25}$ = +182.7 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.46 (d, *J* = 9.1 Hz, 1H), 8.30 (d, *J* = 9.1 Hz, 1H), 8.04 (t, *J* = 8.4 Hz, 2H), 7.68−7.44 (m, 4H), 6.47 (qd, *J* = 8.5, 3.7 Hz, 1H), 4.23 (d, *J* = 3.4 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.0, 131.5, 131.4, 131.2, 130.4, 129.8, 129.7, 128.1, 127.8, 127.1, 125.9 (q, *J* = 283.8 Hz), 125.4, 125.0, 124.9, 124.4, 123.0, 57.2, 56.5 (q, *J* = 32.4 Hz). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3374, 2961, 2930, 2870, 1624, 1466, 1331, 1253, 1157, 1109, 1072, 930, 888, 864, 786, 729, 701, 597, 534, 458. MS-EI (70 eV): *m/z* (%) 379 (5) $[M]^+$, 323 (15), 259 (100), 238 (5), 204 (14), 189 (4), 178 (43), 151 (3), 88 (2), 57 (13), 42 (2).

*(S)-N-[(R)-1-(tert-Butyl)-2,2,2-trifluoroethyl]-tert-butanesulfinamide (**2d**).*[15a] Purified by FC hexane/EtOAc, 7/3. White solid, 46% yield (2.39 g). R_f = 0.34 (hexane/ethyl acetate, 7/3. TLC stain PMA). Mp: 97−100 °C. $[\alpha]_D^{25}$ = +79.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.44 (m, 2H), 1.25 (s, 9H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 125.9 (q, *J* = 283.7 Hz), 66.3 (q, *J* = 26.9 Hz), 57.1, 33.6, 27.5, 22.6. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3223, 2989, 2965, 2915, 2876, 1733, 1477, 1370, 1346, 1263, 1222, 1202, 1150, 1104, 1050, 941, 921, 878, 839, 704, 606, 576, 510, 465, 431. EM (IE, 70 eV): *m/z* (%) 259 (3) $[M]^+$, 203 (65), 196 (4), 188 (6), 170 (4), 156 (4), 119 (3), 105 (5), 98 (3), 87 (7), 77 (3), 61 (10), 57 (100), 41 (94), 29 (51), 18 (5).

General Procedure for Amine Synthesis (3a−d). Sulfinamide **2** (15 mmol) was suspended in 10 mL of methanol. Then, 7.5 mL (30 mmol, 2 equiv) of 4 M HCl in dioxane was added. After 2 min the suspension became a clear solution and was stirred at room temperature for 1 h. It was concentrated and the residue dissolved in 60 mL of dichloromethane. The organic layer was washed with 60 mL of NaOH (10% aqueous), and the aqueous phase was re-extracted with DCM (40 mL × 2). The combined organic layers were dried with Na_2SO_4 (anhydrous) and concentrated. The recorded NMR spectra are similar to those of the amine hydrochlorides.[15a]

*(R)-1-Phenyl-2,2,2-trifluoroethylamine (**3a**).* Purified by FC hexane/EtOAc, 6/4. Colorless liquid, 97% yield (2.55 g). R_f = 0.56 (hexane/ethyl acetate, 6/4). $[\alpha]_D^{25}$ −12.2 (*c* 1, $CHCl_3$) (lit.[35f] $[\alpha]_D^{25}$ −17.4 (*c* 3.4, EtOH)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51−7.22 (m, 5H), 4.37 (q, *J* = 7.5 Hz, 1H), 1.80 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 129.0, 128.7, 127.9, 125.8 (q, *J* = 281.2 Hz), 58.0 (q, *J* = 29.6 Hz). IR (film): $\tilde{\nu}$ (cm^{-1}) 3394, 3324, 3066, 3036, 2982, 2940, 2871, 1734, 1622, 1495, 1476, 1456, 1391, 1365, 1259, 1155, 1118, 987, 890, 758, 702, 625, 585. MS-EI (70 eV): *m/z* (%) 176 (100) $[M + H]^+$, 137 (39). HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_8H_9F_3N$ 176.0687; found 176.0690.

*(R)-1-(1-Naphthyl)-2,2,2-trifluoroethylamine (**3b**).* Purified by FC hexane/EtOAc, 6/4. White solid, 97% yield (3.28 g). R_f = 0.41 (hexane/ethyl acetate, 7/3). Mp: 50−51 °C. $[\alpha]_D^{25}$ −4.8 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.3 Hz, 1H), 7.95−7.81 (m, 2H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.63−7.42 (m, 3H), 5.32 (q, *J* = 7.2 Hz, 1H), 1.85 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.0, 131.9, 131.7, 129.7, 129.2, 126.9, 126.3 (q, *J* = 282.3 Hz), 126.0, 125.4, 125.2, 122.9, 52.9 (q, *J* = 30.0 Hz). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3374, 3281, 3191, 3057, 2910, 1599, 1513, 1399, 1369, 1339, 1258, 1184, 1152, 1115, 1030, 1003, 953, 913, 863, 799, 775, 759, 736, 689, 533, 456. MS-EI (70 eV): *m/z* (%) 225 (22) $[M]^+$, 209 (6), 189 (4), 186 (3), 156 (100), 129 (45), 101 (4), 78 (12), 63 (4), 51 (3). HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{12}H_{11}F_3N$ 226.0844; found 226.0852.

*(R)-1-(9-Anthracenyl)-2,2,2-trifluoroethylamine (**3c**).* Purified by FC hexane/EtOAc, 9/1 to 7/3. Yellow solid, 80% yield (3.30 g). R_f = 0.32 (hexane/ethyl acetate, 7/3). Mp: 110−113 °C. $[\alpha]_D^{25}$ −45.1 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (d, *J* = 8.7 Hz, 1H), 8.48 (s, 1H), 8.21 (d, *J* = 9.1 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 2H), 7.68−7.32 (m, 4H), 6.09 (q, *J* = 9.1 Hz, 1H), 2.05 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.6, 132.2, 131.4, 131.3, 130.6, 130.3, 129.8, 129.5, 128.9, 127.3, 126.5, 126.0, 125.1, 124.9, 123.1, 121.34, 53.7 (q, *J* = 31.4 Hz). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3392, 3302, 3051, 1624, 1523, 1362, 1255, 1146, 1119, 1099, 1008, 930, 911, 888, 860, 838, 810, 727, 625, 530, 452, 375. MS-EI (70 eV): *m/z* (%) 275 (30) $[M]^+$, 259 (4), 139 (4), 206 (100), 178 (24), 103 (20). HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{16}H_{13}F_3N$ 276.1000; found 276.1012.

*(R)-1-(tert-Butyl)-2,2,2-trifluoroethylamine Hydrochloride (**3d**).* The amine has a low boiling point; therefore, at the end of the reaction, ether was added and then the hydrochloride of **3d** precipitated. It was filtered to give a white solid in 93% yield (2.67 g). $[\alpha]_D^{25}$ −1.4 (*c* 0.94, CH_3OH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.17 (s, 3H), 4.00 (q, *J* = 8.8 Hz, 1H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 124.65 (q, *J* = 284.0 Hz), 58.42 (q, *J* = 27.7 Hz), 32.43, 26.43. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 2938, 2853, 2029, 1593, 1527, 1275, 1220, 1187, 1122, 1077, 1046, 900, 694, 583, 553, 519, 470. MS-DART (positive): *m/z* (%) 156 (100) $[M + H]^+$

General Procedure for the Isothiocyanate Synthesis (4a−d). Amine **3** (5 mmol, 1 equiv) was dissolved in 20 mL of DCM and cooled to 0 °C. We added 0.42 mL of thiophosgene (5.5 mmol, 1.1 equiv) followed by 0.83 mL of triethylamine (6 mmol, 1.2 equiv). The reaction mixture was stirred for 30 min at 0 °C and 17 h at room temperature. The reaction mixture was washed with 10 mL of $NaHCO_3$ (saturated aqueous) and then was dried and concentrated. The product was purified by flash chromatography with a 95/5 hexane/EtOAc mixture, giving the different isothiocyanates as slightly yellow liquids. Note that (1) a better yield of **3a** was obtained when the order of addition was reversed (DCM, thiophosgene, amine, and triethylamine) and (2) the isothiocyanate **4d** has a low boiling point and, therefore, a one-pot procedure was performed to obtain catalysts **5d** and **6d**.

*(R)-1-Phenyl-2,2,2-trifluoroethylisothiocyanate (**4a**).* Purified by FC hexane/EtOAc, 95/5. Yellow liquid, 88% yield (956 mg). R_f = 0.60 (hexane/ethyl acetate, 9/1). $[\alpha]_D^{25}$ −7.2 (*c* 2.11, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 5H), 5.19 (q, J = 6.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 130.5, 130.3, 129.2, 127.9, 122.7 (q, J = 282.5 Hz), 62.4 (q, J = 33.4 Hz). IR (film): $\tilde{\nu}$ (cm^{-1}) 3070, 3039, 2925, 2044, 1496, 1456, 1339, 1259, 1188, 1136, 871, 832, 757, 698, 632. MS-DART (positive): *m/z* (%) 218 (5) $[M + H]^+$, 150 (100). HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_9H_7F_3NS$ 218.0251; found 218.0246.

*(R)-1-(1-Naphthyl)-2,2,2-trifluoroethylisothiocyanate (**4b**).* Purified by FC hexane/EtOAc, 95/5. Slightly yellow solid, 87% yield (1.16 g). R_f = 0.56 (hexane/ethyl acetate, 9/1). Mp: 50−52 °C. $[\alpha]_D^{25}$ +15.4 (*c* 1.43, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96−7.85 (m, 3H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.69−7.44 (m, 3H), 6.07 (q, *J* =

DOI: 10.1021/acs.joc.6b01063
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6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1, 133.9, 131.0, 130.6, 129.3, 127.5, 127.0, 126.4, 126.3, 125.3, 123.2 (q, J = 283.4 Hz), 122.1, 58.5 (q, J = 33.8 Hz). IR (film): $\tilde{\nu}$ (cm^{-1}) 3055, 2932, 2253, 2041, 1864, 1719, 1599, 1514, 1379, 1338, 1301, 1256, 1188, 1133, 1032, 951, 916, 895, 863, 837, 797, 775, 753, 732, 694, 633. MS-DART (positive): m/z (%) 268 (41) [M + H]$^+$, 209 (100), 136 (15), 117 (30). HRMS (DART/TOF): m/z [M + H]$^+$ calcd for $C_{13}H_9F_3NS$ 268.0408; found 268.0409.

*(R)-1-(9-Anthracenyl)-2,2,2-trifluoroethylisothiocyanate (**4c**).* Purified by FC hexane/EtOAc, 95/5. Yellow solid, 89% yield (1.41 g). R_f = 0.48 (hexane/ethyl acetate, 9/1). Mp: 113−115 °C. $[\alpha]_D^{25}$ −151.6 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (d, J = 9.0 Hz, 1H), 8.58 (s, 1H), 8.10 (s, 1H), 8.04 (d, J = 8.9 Hz, 2H), 7.72−7.56 (m, 2H), 7.56−7.41 (m, 2H), 6.97 (q, J = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 131.9, 131.2, 130.9, 130.3, 130.0, 129.6, 128.2, 127.4, 125.8, 125.5, 125.2, 122.0, 120.0, 57.7 (q, J = 35.2 Hz). IR (film): $\tilde{\nu}$ (cm^{-1}) 3057, 2963, 2923, 2238, 2111, 2024, 1721, 1675, 1623, 1523, 1449, 1344, 1268, 1176, 1154, 1115, 1039, 1018, 961, 896, 878, 847, 827, 788, 726, 689, 599, 531, 492, 404. MS-EI (70 eV): m/z (%) 317 (67) [M]$^+$, 259 (100), 239 (30), 209 (15), 204 (13), 189 (25), 176 (8), 163 (5), 150 (4), 124 (10), 119 (5), 105 (5), 88 (11), 69 (4), 62 (3). HRMS (DART/TOF): m/z [M + H]$^+$ calcd for $C_{17}H_{11}F_3NS$ 318.0564; found 318.0556.

General Procedure for the Preparation of Bifuncional Catalysts 5−8 and T. The corresponding isothiocyanate (2 mmol, 1 equiv) was dissolved in 7 mL of DCM. *N,N*-Dimethyl-2-aminocyclohexanamine (2.4 mmol, 1.2 equiv) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated and the catalyst purified by flash chromatography with EtOAc as eluent followed by a 90/10/1 $CH_2Cl_2/CH_3OH/NH_4OH$ mixture.

For catalysts **5d**−**8d** the isothiocyanate needed for the thiourea has a low boiling point. We applied a one-pot protocol to circumvent this issue. After the reaction with thiophosgene occurred, it was washed with a solution of aqueous sodium bicarbonate and dried with anhydrous Na_2SO_4 prior to the addition of the diamine. Thus, the yield was calculated from the starting amine **3d** or the nonfluorinated analogue.

*1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(1R,2R)-2-(dimethylamino)-cyclohexyl]thiourea (**T**).*[2a] White solid, 82% yield (678 mg). R_f = 0.38 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 57−60 °C. $[\alpha]_D^{25}$ −34.6 (c 1, $CHCl_3$) (lit.[2a] $[\alpha]_D^{16}$ −32.7 (c 0.99, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 2H), 7.45 (s, 1H), 4.04 (br s, 1H), 2.59−2.36 (m, 2H), 2.28 (s, 6H), 1.96−1.71 (m, 2H), 1.71−1.57 (m, 1H), 1.37−1.00 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.4 (br), 141.3, 131.6 (q, J = 33.3 Hz), 123.2 (q, J = 272.5 Hz), 122.3 (br), 116.8 (hept, J = 4.1 Hz), 66.8, 55.3, 40.0 (br), 32.5, 24.8, 24.5, 21.8. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3239, 3043, 2936, 2862, 2792, 1620, 1540, 1466, 1379, 1273, 1170, 1125, 1062, 1037, 969, 939, 881, 849, 756, 701, 678, 652, 594, 561, 481. MS-EI (70 eV): m/z (%) 414 (3) [M + H]$^+$, 394 (4), 368 (8), 340 (3), 335 (5), 296 (3), 271 (100), 252 (28), 221 (6), 213 (35), 202 (14), 194 (6), 163 (14), 142 (11), 125 (32), 84 (38), 71 (16), 58 (14), 46 (3). HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{17}H_{22}F_6N_3S$ 414.1439; found 414.1444.

*1-[1-(R)-Phenyl-2,2,2-trifluoroethyl]-3-[(1R,2R)-2-(dimethylamino)cyclohexyl]thiourea (**5a**).* White solid, 90% yield (647 mg). R_f = 0.33 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 55−57 °C. $[\alpha]_D^{25}$ +45.6 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74−7.09 (m, 6H), 6.56−6.29 (m, 1H), 4.57 (br, 0.5H), 3.64 (br, 1H), 2.37 (s, 7H), 2.18−2.01 (m, 1H), 1.96−1.63 (m, 3H), 1.31−1.11 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.5, 133.9, 128.9, 128.7, 128.4, 125.0 (q, J = 281.8 Hz), 67.7 (br), 60.3 (q, J = 32.1 Hz), 56.9 (br), 40.6, 33.2, 24.6, 24.5, 23.3 (br). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3259, 3036, 2932, 2861, 2788, 1739, 1542, 1452, 1372, 1322, 1254, 1233, 1169, 1116, 1030, 951, 873, 758, 703, 639, 558, 515, 424. MS-EI (IE, 70 eV): m/z (%) 359 (2) [M]$^+$, 314 (18), 217 (21), 211 (18), 159 (100), 148 (24), 125 (76), 109 (49), 97 (15), 84 (68), 71 (28), 58 (22). HRMS (DART/TOF): m/z [M + H]$^+$ calcd for $C_{17}H_{25}F_3N_3S$ 360.1721; found 360.1715.

*1-[1-(R)-(1-Naphthyl)-2,2,2-trifluoroethyl]-3-[(1R,2R)-2-(dimethylamino)cyclohexyl]thiourea (**5b**).* White solid, 87% yield (712 mg). R_f = 0.38 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 85−89 °C. $[\alpha]_D^{25}$ +210.8 (c 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ δ 8.43 (d, J = 8.6 Hz, 1H), 7.91−7.71 (m, 2H), 7.66−7.28 (m, 5H), 7.14 (br, 2H), 3.34 (br, 1H), 2.49−2.34 (m, 1H), 2.27 (s, 6H), 1.90−1.42 (m, 4H), 1.26−0.91 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.3, 133.9, 131.8, 130.6, 129.6, 128.8, 127.2, 126.2, 125.4 (q, J = 282.7 Hz), 125.4, 125.0, 123.8, 67.7 (br), 57.1, 55.2 (m), 40.8, 33.1, 24.6, 24.3, 23.1 (br). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3247, 3044, 2933, 2860, 2791, 1538, 1446, 1374, 1347, 1253, 1232, 1166, 1117, 1030, 949, 874, 849, 796, 775, 750, 700, 633, 593, 534, 481, 432. MS-EI (70 eV): m/z (%) 409 (3) [M]$^+$, 364 (22), 267 (46), 209 (75), 189 (21), 159 (27), 125 (100), 97 (18), 84(53), 58 (24). HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{21}H_{27}F_3N_3S$ 410.1878; found 410.1873.

*1-[1-(R)-(9-Anthracenyl)-2,2,2-trifluoroethyl]-3-[(1R,2R)-2-(dimethylamino)cyclohexyl]thiourea (**5c**).* Yellow solid, 71% yield (652 mg). R_f = 0.32 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 119−122 °C. $[\alpha]_D^{25}$ + 191.1 (c 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.06−9.64 (br, 0.6H), 8.67 (s, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 8.17 (q, J = 9.9 Hz, 1H), 8.00 (d, J = 9.1 Hz, 2H), 7.74−7.21 (m, 4H), 6.56 (br, 1H), 3.39 (br, 1H), 2.42 (s, 7H), 1.99−1.46 (m, 4H), 1.31−0.95 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.1, 132.3 (br), 131.8 (br), 130.5, 130.0 (br), 129.4 (br), 127.8, 127.5 (br), 126.0 (br), 125.1 (br), 124.8, 124.3 (br), 124.0 (br), 68.4 (br), 58.9 (br), 56.8 (q, J = 30.6 Hz), 42.1 (br), 33.0, 24.9, 24.5. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3200, 3034, 2937, 2861, 2835, 2791, 1624, 1582, 1537, 1449, 1397, 1376, 1354, 1298, 1252, 1234, 1164, 1117, 1092, 1043, 1018, 951, 877, 847, 787, 732, 702, 634, 618, 602. MS-EI (70 eV): m/z (%) 459 (6) [M]$^+$, 317 (56), 259 (100), 248 (27), 239 (18), 209 (15), 189 (11), 142 (20), 125 (38), 84 (50), 71 (14), 58 (16), 49 (11). HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{25}H_{29}F_3N_3S$ 460.2034; found 460.2029.

*1-[1-(R)-(tert-Butyl)-2,2,2-trifluoroethyl]-3-[(1R,2R)-2 (dimethylamino)cyclohexyl]thiourea (**5d**).* Yellow solid, 45% yield (305 mg). R_f = 0.55 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 160−162 °C. $[\alpha]_D^{25}$ +61.2 (c 0.57, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.59 (br, 1H), 5.16 (m, 1H), 3.85 (s, 1H), 3.65 (s, 1H), 2.54−2.42 (m, 1H), 2.35 (s, 6H), 2.29−2.18 (m, 1H), 1.98−1.69 (m, 3H), 1.34−1.20 (m, 4H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.8, 126.2 (q, J = 283.3 Hz), 68.2, 63.5 (q, J = 27.4 Hz), 57.7, 41.1, 34.6, 33.4, 27.4, 24.8, 24.6, 23.8. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3257, 3219, 3061, 2935, 2859, 2775, 1544, 1372, 1317, 1261, 1203, 1161, 1107, 1035, 947, 874, 751, 705, 565, 435. MS-DART (positive): m/z (%) 340 (100) [M + H]$^+$. HRMS (DART/TOF): m/z [M + H]$^+$ calcd for $C_{15}H_{29}F_3N_3S$ 340.2034; found 340.2028.

*1-[1-(R)-Phenyl-2,2,2-trifluoroethyl]-3-[(1S,2S)-2-(dimethylamino)cyclohexyl]thiourea (**6a**).* White solid, 97% yield (697 mg). R_f = 0.35 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 136−137 °C. $[\alpha]_D^{25}$ −52.5 (c 0.55, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62−7.17 (m, 6H), 6.60−6.31 (m, 1H), 6.13 (br, 0.3H), 3.69 (br, 1H), 2.44 (br, 1H), 2.21 (s, 7H), 1.90−1.64 (m, 3H), 1.29−1.14 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.7, 133.7, 128.9, 128.8, 128.1, 124.9 (q, J = 281.8 Hz), 67.9 (br), 59.9 (q, J = 32.5 Hz), 56.8 (br), 40.6, 33.2, 29.7, 24.6, 24.5, 23.0 (br). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3274, 3068, 2936, 2860, 2827, 2787, 1537, 1452, 1380, 1318, 1234, 1211, 1170, 1114, 1068, 1034, 946, 876, 847, 754, 705, 670, 619, 558, 508, 422. MS-DART (positive): m/z (%) 360 (100) [M + H]$^+$. HRMS (DART/TOF): m/z [M + H]$^+$ calcd for $C_{17}H_{25}F_3N_3S$ 360.1721; found 360.1717.

*1-[1-(R)-(1-Naphthyl)-2,2,2-trifluoroethyl]-3-[(1S,2S)-2-(dimethylamino)cyclohexyl]thiourea (**6b**).* White solid, 90% yield (737 mg). R_f = 0.36 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1), Mp: 103−104 °C. $[\alpha]_D^{25}$ −8.3 (c 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71−8.29 (m, 1H), 7.87 (d, J = 7.5 Hz, 2H), 7.73−7.44 (m, 4H), 7.10 (s, 1H), 6.90−5.53 (br, 1H), 3.75 (br, 2H), 2.32−1.62 (m, 10H), 1.31−1.11 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.5, 133.8, 131.8, 130.0, 129.7, 128.7, 127.1, 126.1, 125.5 (q, J = 282.8 Hz), 125.1, 124.9, 123.9, 67.7 (br), 56.6, 55.5 (m), 40.1, 33.1, 24.5, 24.4, 22.8. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3274, 3068, 2936, 2860, 2827, 2786, 1536, 1452, 1380, 1318, 1303, 1233, 1170, 1114, 1068, 1034, 946, 875, 847, 754, 705, 670, 619, 558, 508, 422. MS-DART (positive): m/z (%) 410 (100) [M + H]$^+$, 372 (6). HRMS (FAB) m/z [M + H]$^+$ calcd for $C_{21}H_{27}F_3N_3S$ 410.1878; found 410.1879.

*1-[1-(R)-(9-Anthracenyl)-2,2,2-trifluoroethyl]-3-[(1S,2S)-2-(dimethylamino)cyclohexyl]thiourea (**6c**).* Yellow solid, 80% yield

DOI: 10.1021/acs.joc.6b01063
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(735 mg). R_f = 0.40 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 118−121 °C. $[\alpha]_D^{25}$ +72.9 (*c* 1.02, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.85−8.33 (m, 3H), 8.04 (d, *J* = 8.3 Hz, 2H), 8.00−7.83 (m, 1H), 7.76−7.36 (m, 4H), 6.97 (s, 1H), 3.64 (m, 1.26H), 2.55−2.30 (m, 2H), 2.32−2.09 (m, 7H), 1.36−0.92 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.4, 131.8 (br), 130.7, 129.8 (br), 127.6 (br), 127.5 (br), 125.1, 123.9 (br), 67.0, 57.2 (br), 56.0 (q, *J* = 32.3 Hz), 40.3, 32.7, 25.0, 24.6, 22.8 (br). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3250, 3050, 2932, 2859, 2788, 1624, 1528, 1448, 1319, 1232, 1160, 1110, 1029, 951, 874, 785, 728, 699, 631, 588, 534, 474, 425. MS-DART (positive): *m/z* (%) 460 (100) $[M + H]^+$. HRMS (FAB) *m/z* $[M + H]^+$ calcd for $C_{25}H_{29}F_3N_3S$ 460.2034; found 460.2028.

*1-[1-(R)-(tert-Butyl)-2,2,2-trifluoroethyl]-3-[(1S,2S)-2-(dimethylamino)cyclohexyl]thiourea (**6d**).* Yellow solid, 36% yield (244 mg). R_f = 0.48 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 121−125 °C. $[\alpha]_D^{25}$ −16.7 (*c* 0.54, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 6.29 (s, 1H), 5.21 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 2.78 (m, 1H), 2.50 (s, 6H), 2.32−2.17 (m, 1H), 2.04−1.66 (m, 3H), 1.37−1.22 (m, 4H), 1.11 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.5, 126.2 (q, *J* = 284.9 Hz), 67.3, 62.8 (q, *J* = 24.9 Hz), 55.8, 40.3, 34.5, 33.2, 27.3, 24.6, 24.5, 22.7. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3259, 2930, 2860, 1546, 1367, 1319, 1258, 1239, 1204, 1156, 1029, 949, 919, 854, 731, 707, 570, 433. MS-DART (positive): *m/z* (%) 340 (100) $[M + H]^+$. HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{15}H_{29}F_3N_3S$ 340.20343; found 340.20347.

*1-[(S)-1-Phenylethyl]-3-[(1R,2R)-2-(dimethylamino)cyclohexyl]thiourea (**7a**).*[17b] Hygroscopic white solid, 85% yield (519 mg). R_f = 0.32 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). $[\alpha]_D^{25}$ +14.7 (*c* 1, $CHCl_3$) (lit.[17b] $[\alpha]_D^{25}$ + 16.0 (*c* 1.18, $CHCl_3$)). ^1H NMR (300 MHz, $CDCl_3$): δ 8.24−7.36 (br, 0.5H), 7.39−7.06 (m, 5H), 6.24 (s, 1H), 5.04 (s, 1H), 3.55 (m, 1H), 3.12 (s, 1H), 2.37−2.24 (m, 1H), 2.16 (s, 6H), 1.83−1.48 (m, 3H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.29−0.69 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.4, 143.0, 128.7, 127.4, 126.1, 67.3, 56.2, 53.7, 40.2, 32.9, 24.9, 24.5, 22.7, 22.2. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3259, 3058, 3030, 2967, 2932, 2859, 2828, 2786, 1649, 1538, 1495, 1450, 1400, 1356, 1267, 1237, 1209, 1187, 1152, 1088, 1062, 1039, 953, 873, 758, 734, 699. MS-EI (70 eV): *m/z* (%) 306 (11) $[M + H]^+$, 306 (9), 260 (7), 155 (7), 125 (100), 105 (40), 84 (25), 71 (9), 58 (9). HRMS (FAB) *m/z* $[M + H]^+$ calcd for $C_{17}H_{28}N_3S$ 306.2004; found 306.2000.

*1-[(S)-1-(1-Naphthyl)ethyl]-3-[(1R,2R)-2-(dimethylamino)-cyclohexyl]thiourea (**7b**).* White solid, 64% yield (455 mg). R_f = 0.40 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 49−52 °C. $[\alpha]_D^{25}$ +71.7 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.58−7.45 (m, 3H), 7.39 (t, *J* = 7.7 Hz, 1H), 6.28 (s, 1H), 5.96 (s, 1H), 4.98−4.43 (br, 0.2H), 3.45 (s, 1H), 2.41−2.09 (m, 2H), 2.02 (s, 6H), 1.68 (d, *J* = 6.6 Hz, 5H), 1.59−1.48 (m, 1H), 1.18−0.89 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.3, 138.4 (br), 133.8, 130.9 (br), 128.7, 128.1, 126.4, 125.7, 125.3, 123.4 (br), 122.6, 67.2, 56.0, 50.0, 39.8, 32.9, 24.6, 24.3, 22.0 (br), 21.0 (br). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3249, 3044, 2928, 2856, 2827, 2781, 1529, 1448, 1397, 1352, 1324, 1261, 1234, 1261, 1234, 1206, 1186, 1095, 1036, 951, 870, 799, 777, 725, 647, 593, 555, 479, 430. MS-DART (positive): *m/z* (%) 356 (100) $[M + H]^+$. HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{30}N_3S$ 356.2160; found 356.2160.

*1-[(S)-1-(9-Anthracenyl)ethyl]-3-[(1R,2R)-2-(dimethylamino)-cyclohexyl]thiourea (**7c**).* Chiral amine and isothiocyanate was obtained according to the literature procedure.[15b] White solid, 87% yield (705 mg). R_f = 0.48 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 135−136 °C. $[\alpha]_D^{25}$ +52.6 (*c* 1.02, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.53 (d, *J* = 8.9 Hz, 2H), 8.37 (s, 1H), 7.97 (d, *J* = 9.7 Hz, 2H), 7.88−7.58 (br, 0.47H), 7.59−7.36 (m, 4H), 6.56 (s, 2H), 3.69 (m, 1H), 2.13 (s, 7H), 1.89 (d, *J* = 7.2 Hz, 3H), 1.65 (br, 2H), 1.49−1.35 (m, 1H), 1.26−1.17 (m, 2H), 1.15−0.96 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.0, 131.7, 129.6, 129.0, 128.2, 126.2, 124.9, 124.2, 66.9, 55.5, 49.9, 40.0, 32.4, 24.7, 24.2, 22.3, 21.8. MS-DART (positive): *m/z* (%) 406 (62) $[M + H]^+$, 372 (14), 205 (100), 143 (50). HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}N_3S$ 406.2317; found 406.2314.

*1-[(S)-1,2,2-Trimethylpropyl]-3-[(1R,2R)-2-(dimethylamino)-cyclohexyl]thiourea (**7d**).* White solid, 57% yield (325 mg). R_f = 0.32 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 149−152 °C, $[\alpha]_D^{25}$ +20.2 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.73−7.33 (br, 0.5H), 6.91 (s, 1H), 5.70−5.22 (br, 0.5H), 4.15 (br, 1H), 3.95 (s, 1H), 2.82−2.61 (m, 1H), 2.42 (s, 7H), 2.00−1.65 (m, 3H), 1.43−1.16 (m, 4H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 67.3, 58.3, 56.0, 40.3, 34.8, 33.2, 26.5, 24.9, 24.5, 23.0, 15.6. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3233, 3064, 2934, 2857, 2824, 2776, 1740, 1539, 1471, 1450, 1359, 1330, 1273, 1246, 1205, 1118, 1088, 1064, 1041, 956, 874, 725, 670, 602, 569, 517, 473, 433. MS-EI (70 eV): *m/z* (%) 286 (4) $[M + H]^+$, 240 (8), 194 (2), 185 (9), 166 (2), 143 (3), 125 (100), 97 (14), 84 (33), 71 (10), 58 (10), 44 (5). HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{15}H_{32}N_3S$ 286.2317; found 286.2312.

*1-[(S)-1-Phenylethyl]-3-[(1S,2S)-2-(dimethylamino)cyclohexyl]-thiourea (**8a**).*[17b] Hygroscopic white solid, 83% yield (507 mg). R_f = 0.25 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). $[\alpha]_D^{25}$ +7.6 (*c* 1.15, $CHCl_3$) (lit.[17b] $[\alpha]_D^{25}$ −6 (*c* 0.2, $CHCl_3$) for the enantiomer). ^1H NMR (300 MHz, $CDCl_3$): δ 8.02−7.01 (m, 6H), 6.57 (br, 1H), 4.93 (br, 1H), 3.59 (m, 1H), 2.68 (br, 1H), 2.29 (br, 1H), 2.07−1.58 (m, 9H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.29−0.98 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.4, 142.9, 128.6, 127.3, 125.8, 66.6, 55.8, 53.5, 39.3, 32.6, 24.9, 24.3, 23.4 (br), 21.5 (br). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3349, 3282, 3064, 3035, 2971, 2932, 2849, 2825, 2782, 1532, 1491, 1441, 1399, 1356, 1335, 1285, 1250, 1228, 1201, 1146, 1087, 1041, 1008, 952, 905, 879, 836, 759, 697, 609, 557, 445, 418. MS-DART (positive): *m/z* (%) 306 (100) $[M + H]^+$. HRMS (FAB) *m/z* $[M + H]^+$ calcd for $C_{17}H_{28}N_3S$ 306.2004; found 306.1998.

*1-[(S)-1-(1-Naphthyl)ethyl]-3-[(1S,2S)-2-(dimethylamino)cyclohexyl]-thiourea (**8b**).* White solid. 56% yield (398 mg). R_f = 0.25 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 70−73 °C. $[\alpha]_D^{25}$ +36.1 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.29−8.04 (m, 1H), 8.04−7.71 (m, 2H), 7.71−7.29 (m, 4H), 6.36 (s, 1H), 5.74 (br, 1H), 4.12 (q, *J* = 7.1 Hz, 0.3H), 3.40 (s, 1H), 2.68 (br, 0.4H), 2.04 (m, 1H), 1.79−1.54 (m, 5H), 1.53−1.13 (m, 7H), 1.12−0.82 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 138.3, 134.0, 130.8 (br), 128.9 (br), 128.3, 126.6, 125.8, 125.7 (br), 122.7, 67.0 (br), 55.9, 50.0, 38.9, 32.8 (br), 25.0 (br), 24.4, 23.2 (br), 22.3 (br), 21.8 (br). IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3349, 3276, 3037, 2970, 2929, 2857, 2826, 2781, 1526, 1449, 1354, 1334, 1232, 1203, 1041, 951, 873, 798, 776, 724, 697, 558, 490, 447. MS-DART (positive): *m/z* (%) 356 (100) $[M + H]^+$, 155 (8), 143 (11). HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{30}N_3S$ 356.2146; found 356.2150.

*1-[(S)-1-(9-Anthracenyl)ethyl]-3-[(1S,2S)-2-(dimethylamino)-cyclohexyl]thiourea (**8c**).* Chiral amine and isothiocyanate were obtained according to the literature procedure.[15b] Yellow solid, 78% yield (632 mg). R_f = 0.47 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 120−124 °C. $[\alpha]_D^{25}$ +124.0 (*c* 0.24, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.57 (br, 2H), 8.44 (s, 1H), 8.02 (d, *J* = 7.8 Hz, 2H), 7.77−7.33 (m, 5H), 6.25 (br, 1H), 6.02 (s, 1H), 3.29 (m, 1H), 2.72 (br, 1H), 1.91 (d, *J* = 6.4 Hz, 3H), 1.68−1.47 (m, 3H), 1.45−1.09 (m, 3H), 1.00 (s, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 131.9, 129.7, 129.1, 128.8, 126.6, 125.0, 123.7, 66.0, 56.5, 50.0, 38.6, 32.5, 25.1, 24.4, 22.0, 21.1. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3209, 2927, 2856, 2779, 1662, 1526, 1448, 1319, 1233, 1203, 1157, 1041, 883, 837, 788, 730, 633, 491. MS-DART (positive): *m/z* (%) 406 (32) $[M + H]^+$, 247 (54), 205 (48), 201 (100), 157 (17), 143 (44). HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}N_3S$ 406.2317; found 406.2297.

*1-[(S)-1,2,2-Trimethylpropyl]-3-[(1S,2S)-2-(dimethylamino)-cyclohexyl]thiourea (**8d**).*[35g] White solid, 55% yield (314 mg). R_f = 0.29 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp: 106−109 °C. $[\alpha]_D^{25}$ +37.6 (*c* 1.09, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.28 (s, 1H), 6.97 (br, 1H), 3.89 (s, 2H), 2.75−2.54 (m, 1H), 2.34 (s, 7H), 1.93−1.53 (m, 3H), 1.33−1.06 (m, 4H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.83 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 66.9, 58.1, 55.2, 39.8, 34.6, 33.0, 26.3, 24.7, 24.3, 22.3, 15.8. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3277, 3066, 2932, 2860, 2777, 1536, 1473, 1446, 1344, 1270, 1242, 1201, 1119, 1090, 993, 953, 873, 852, 729, 672, 569, 429. MS-DART (positive): *m/z* (%) 286 (100) $[M + H]^+$. HRMS (DART/TOF): *m/z* $[M + H]^+$ calcd for $C_{15}H_{32}N_3S$ 286.2317; found 286.2329.

*1-((1R,2R)-2-(Dimethylamino)cyclohexyl)-3-((R)-2-methyl-1-phenylpropyl)thiourea (**21**).* (*R*)-2-Methyl-1-phenylpropylamine-amine was obtained according to the literature procedure.[37] Yellow solid, 79% yield (526 mg). R_f = 0.56 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1), mp 186−189 °C. $[\alpha]_D^{25}$ −7.2 (*c* 2.04, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (m, 2H), 7.26 (m, 5H), 5.30 (s, 1H), 4.56

DOI: 10.1021/acs.joc.6b01063
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(s, 1H), 3.29 (m, 1H), 2.76 (s, 6H), 2.37−2.21 (m, 1H), 2.18−2.02 (m, 2H), 2.00−1.89 (m, 1H), 1.79−1.69 (m, 1H), 1.43−1.22 (m, 4H), 1.02 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.1, 141.3, 128.3, 127.4, 127.1, 67.2, 63.9, 54.5 (br), 39.4, 34.1, 32.8, 24.6, 24.2, 22.9 (br), 19.6, 18.9. IR (KBr): $\tilde{\nu}$ (cm^{-1}) 3255, 3058, 2922, 2854, 1552, 1449, 1366, 1314, 1214, 1169, 1031, 990, 874, 755, 702, 617, 568, 526. MS-DART (positive): m/z (%) 334 (100) [M + H]$^+$. HRMS (DART/TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{32}N_3S$ 334.2317; found 334.2306.

*1-((1S,2S)-2-(Dimethylamino)cyclohexyl)-3-((R)-2-methyl-1-phenylpropyl)thiourea (**22**).* (R)-2-Methyl-1-phenylpropylamine-amine was obtained according to the literature procedure.[37] Yellow solid, 90% yield (600 mg). R_f = 0.51 ($CH_2Cl_2/CH_3OH/NH_4OH$, 90/10/1). Mp 92−96 °C. $[\alpha]_D^{25}$ −12.8 (c 0.94, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44−7.17 (m, 5H), 6.81 (br, 1H), 5.40 (br, 1H), 4.92 (br, 1H), 4.01 (br, 1H), 2.75−2.57 (m, 1H), 2.44 (s, 6H), 2.33−2.18 (m, 1H), 2.08−1.78 (m, 3H), 1.66 (m, 1H), 1.38−1.15 (m, 4H), 1.00 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.5 (br), 141.0 (br), 128.3, 127.4, 127.2, 67.1, 64.2, 55.3, 40.0, 34.0, 32.7, 24.6, 24.3, 22.4, 19.4, 19.0. IR (KBr): $\tilde{\nu}$ cm^{-1} = 3272, 3056, 2926, 2854, 1533, 1449, 1364, 1308, 1269, 1210, 1095, 1029, 952, 873, 744, 698, 665, 569, 532, 486. MS-DART (positive): m/z (%) 334 (100) [M + H]$^+$. HRMS (DART/TOF): m/z [M + H]$^+$ calcd for $C_{19}H_{32}N_3S$ 334.2317; found 334.2324.

General Procedure for Michael Addition to Nitrostyrenes. We dissolved 29.8 mg (1 equiv, 0.2 mmol) of β-nitrostyrene and 0.05 equiv (0.01 mmol) of the bifunctional thiourea in 0.66 mL of dry toluene in a 4 mL screw cap dram vial with a magnetic stirrer. The reaction mixture was stirred for 10 min, and then the nucleophile was added (1.5 equiv. 0.30 mmol). The mixture was agitated for 24 h at 20 °C. The solvent was removed and purified in FC with a 7/3 hexane/EtOAc mixture. The reported yields and weights were obtained with catalyst **6b**.

*(S)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (**9**).*[2b] White solid, 94% yield (46.8 mg). Mp: 101−104 °C. $[\alpha]_D^{25}$ +179.3 (c 1, $CHCl_3$) (91% ee) (lit.[2b] R enantiomer mp 112−114, $[\alpha]_D^{25}$ −175.4 (c 1.08, $CHCl_3$), 89% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50−6.95 (m, 5H), 4.68−4.54 (m, 2H), 4.40−4.29 (m, 1H), 4.27−4.12 (m, 1H), 2.23 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.8, 201.1, 136.1, 129.3, 128.5, 128.0, 78.2, 70.6, 42.9, 30.5, 29.8. HPLC: Chiralpak IA, hexane/ethanol 85/15, 0.8 mL/min, λ 220 nm, retention times 14.5 min (S), 22.9 min (R).

*(S)-3-(2-Nitro-1-(4-methylphenyl)ethyl)pentane-2,4-dione (**10**).*[36a] White solid, 87% yield (45.8 mg). Mp: 93−95 °C. $[\alpha]_D^{25}$ +170.2 (c 1, $CHCl_3$) (87% ee) (lit.[36a] R enantiomer $[\alpha]_D^{25}$ −194.1 (c 1, $CHCl_3$), 97% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 4.61 (d, J = 1.4 Hz, 1H), 4.60−4.58 (m, 1H), 4.35 (d, J = 10.9 Hz, 1H), 4.28−4.12 (m, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0, 201.2, 138.5, 133.0, 130.2, 128.0, 78.5, 71.0, 42.6, 30.5, 29.6, 21.2. HPLC: Chiralpak IC3, hexane/ethanol 85/15, 0.6 mL/min, λ 220 nm, retention times 15.6 min (S), 20.1 (R).

*(S)-3-(1-(4-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (**11**).*[36a] White solid, 90% yield (50.2 mg). Mp: 100−103 °C. $[\alpha]_D^{25}$ +153.4 (c 1.0, $CHCl_3$) (89% ee) (lit.[36a] R enantiomer $[\alpha]_D^{25}$ −191.6 (c 1, $CHCl_3$), 98% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 4.60 (d, J = 1.4 Hz, 1H), 4.58 (s, 1H), 4.33 (d, J = 10.9 Hz, 1H), 4.25−4.14 (m, 1H), 3.77 (s, 3H), 2.28 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.8, 201.1, 159.6, 129.1, 127.66, 114.7, 78.4, 71.0, 55.2, 42.1, 30.3, 29.4. HPLC: Chiralpak IC3, hexane/ethanol 85/15, 0.6 mL/min, λ 254 nm, retention times 12.0 min (S), 16.5 min (R).

*(S)-3-(1-(4-Chlorophenyl)-2-nitroethyl)pentane-2,4-dione (**12**).*[36b] White solid, 94% yield (53.3 mg). Mp: 112−115 °C, $[\alpha]_D^{25}$ +131.7 (c 1.0, $CHCl_3$) (84% ee) (lit.[36b] (R) enantiomer mp 119−121 °C $[\alpha]_D^{25}$ −132.5 (c 1.04, $CHCl_3$), 88% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 4.74−4.57 (m, 2H), 4.36 (d, J = 10.7 Hz, 1H), 4.32−4.17 (m, 1H), 2.33 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5, 200.7, 134.8 (2C), 129.7, 129.5, 78.1, 70.8, 42.3, 30.6, 29.8. HPLC: Chiralpak IC3, hexane/ethanol 85/15, 0.6 mL/min, λ 220 nm, retention times 7.0 min (S), 9.8 min (R).

*(S)-3-(2-Nitro-1-(4-nitrophenyl)ethyl)pentane-2,4-dione (**13**).*[36c] Beige solid, 86% yield (50.6 mg). Mp: 110−113 °C. $[\alpha]_D^{25}$ +99.9 (c 1.03, $CHCl_3$) (84% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.77−4.55 (m, 2H), 4.38 (s, 2H), 2.33 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9, 143.8, 129.3, 124.6, 77.5, 70.3, 42.5, 30.7, 30.1. HPLC: Chiralpak IC3, hexane/ethanol 85/15, 0.6 mL/min, λ 250 nm, retention times 11.6 min (S), 16.1 (R).

*(S)-3-(1-(2-Bromophenyl)-2-nitroethyl)pentane-2,4-dione (**14**).*[36a] White solid, 92% yield (60.3 mg). Mp: 77−79 °C, $[\alpha]_D^{25}$ +185.0 (c 1, $CHCl_3$) (84% ee) (lit.[36a] R enantiomer $[\alpha]_D^{25}$ −218.5 (c 1, $CHCl_3$), 98% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 1H), 7.30 (m, 1H), 7.22−7.09 (m, 2H), 4.93−4.80 (m, 1H), 4.80−4.52 (m, 3H), 2.29 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.1, 201.0, 135.3, 134.2, 130.1, 129.1, 128.4, 124.7, 76.4, 69.3, 41.3, 31.1, 28.5. HPLC: Chiralpak IA, hexane/ethanol 85/15, 0.8 mL/min, λ 220 nm, retention times 11.1 min (S), 13.8 (R).

*(S)-3-(1-(Naphthalen-1-yl)-2-nitroethyl)pentane-2,4-dione (**15**).*[36b] Yellow liquid, 82% yield (49.1 mg). $[\alpha]_D^{25}$ +171.4 (c 1.50, $CHCl_3$) (87% ee) (lit.[36b] R enantiomer $[\alpha]_D^{25}$ −182.0 (c 1.0, $CHCl_3$), 95% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 8.3 Hz, 1H), 7.85 (dd, J = 24.8, 8.0 Hz, 2H), 7.74−7.48 (m, 2H), 7.48−7.12 (m, 2H), 5.46−5.11 (m, 1H), 5.07−4.48 (m, 3H), 2.32 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.4, 200.9, 134.4, 132.1, 130.9, 129.6, 129.3, 127.5, 126.5, 125.4, 124.99 (br), 122.0, 77.9, 70.6, 36.6, 31.1, 28.8. HPLC: Chiralpak IA, hexane/ethanol 85/15, 0.8 mL/min, λ 220 nm, retention times 11.7 min (S), 14.5 min (R).

*(R)-3-(2-Nitro-1-(thiophen-2-yl)ethyl)pentane-2,4-dione (**16**).*[17c] Beige solid, 69% yield (35.2 mg). $[\alpha]_D^{25}$ +126.5 (c 1.10, $CHCl_3$) (89% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−7.19 (m, 1H), 7.01−6.83 (m, 2H), 4.66 (d, J = 5.3 Hz, 2H), 4.61−4.49 (m, 1H), 4.41 (d, J = 10.1 Hz, 1H), 2.30 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.6, 200.8, 138.6, 127.5, 127.1, 125.9, 78.6, 71.2, 38.3, 30.7, 29.8. HPLC: Chiralcel OJ, hexane/ethanol 70/30, 1.0 mL/min, λ 220 nm, retention times 33.4 min (S), 41.9 min (R).

*Dimethyl (S)-2-(1-Phenyl-2-nitroethyl)malonate (**17**).*[2b] White solid, 69% yield (38.8 mg). Mp: 50−55 °C. $[\alpha]_D^{25}$ +6.0 (c 1.10, $CHCl_3$) (87% ee) (lit.[2b] R enantiomer mp 63−64 °C, $[\alpha]_D^{25}$ −6.15 (c 1.10, $CHCl_3$), 89% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.13 (m, 5H), 5.03−4.77 (m, 2H), 4.25 (td, J = 8.8, 5.6 Hz, 1H), 3.87 (d, J = 9.1 Hz, 1H), 3.76 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 167.4, 136.2, 129.2, 128.6, 128.0, 54.9, 53.2, 53.0, 43.1. HPLC: Chiralpak IC3, hexane/ethanol 85/15, 0.6 mL/min, λ 220 nm, retention times: 9.1 min (R), 10.6 (S).

*Dimethyl (R)-2-Methyl-2-(1-phenyl-2-nitroethyl)malonate (**18**).*[2b] White solid, 57% yield (33.6 mg). Mp: 124−127 °C. $[\alpha]_D^{25}$ −28.5 (c 1.00, $CHCl_3$) (93% ee) (lit.[2b] S enantiomer mp 130−132 °C, $[\alpha]_D^{25}$ +32.3 (c 1.06, $CHCl_3$), 93% ee). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.27 (m, 3H), 7.19−7.12 (m, 2H), 5.11−4.99 (m, 2H), 4.21−4.14 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 170.9, 135.1, 129.1, 129.0, 128.7, 56.9, 53.2, 53.0, 48.5, 20.5. HPLC: Chiralpak IC3, hexane/ethanol 85/15, 0.6 mL/min, λ 220 nm, retention times 7.1 min (R), 9.2 (S).

*Ethyl ξ-1-((R)-2-Nitro-1-phenylethyl)-2-oxocyclopentane-1-carboxylate (**19**).*[36d] Colorless liquid, 96% yield (58.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46−7.12 (m, 5H), 5.18 (dd, J = 13.6, 3.9 Hz, 1H), 5.02 (dd, J = 13.5, 10.9 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.08 (dd, J = 10.9, 3.9 Hz, 1H), 2.58−2.22 (m, 3H), 2.05−1.79 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.5, 169.4, 135.4, 129.4, 128.9, 128.4, 76.6, 62.5, 62.3, 46.3, 38.0, 31.3, 19.5, 14.1. HPLC: Chiralpak IC3, hexane/ethanol 85/15, 0.6 mL/min, λ 220 nm, retention times 9.1 min (R), 11.3 (S).

*(R)-2-Hydroxy-3-(2-nitro-1-phenylethyl)naphthoquinone (**20**).*[36e] Yellow solid, 84% yield (54.3 mg). Mp: 148−150 °C. $[\alpha]_D^{25}$ −15.6 (c 0.33, $CHCl_3$) (96% ee) (lit.[31e] S enantiomer mp 147−149 °C, $[\alpha]_D^{25}$ +37 (c 1.0, acetone)). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20−7.99 (m, 2H), 7.89−7.62 (m, 3H), 7.55−7.41 (m, 2H), 7.38−7.19 (m, 3H), 5.56−5.41 (m, 1H), 5.38−5.25 (m, 1H), 5.22−5.08 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.6, 181.1, 153.2, 137.5, 135.4, 133.2, 132.6, 129.0, 128.3, 127.8, 127.2, 126.3, 120.8, 76.4, 39.7.

DOI: 10.1021/acs.joc.6b01063
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HPLC: Chiralcel OJ, hexane/ethanol 70/30, 0.8 mL/min, λ 220 nm, retention times 22.2 min (*S*), 41.4 (*R*).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01063.

Kinetics of the addition of 2,4-pentanodione to β-nitrostyrene and QTAIM analysis of the transition states with catalysts **5a**−**8a**, Takemoto's and Pápai's calculated mechanisms with catalyst **6a**, ^{1}H and ^{13}C NMR spectra of compounds obtained in this work, HPLC traces, and Cartesian coordinates and energies of computed structures (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the DGAPA-UNAM (project IN209915) and CONACyT (grant 254014) for financial support, and the DGCTIC, UNAM, for supercomputer resources (SC16-1-IR-109 and SC16-1-IG-99). E.I.J., W.E.V.N., and J.V.-C. gratefully acknowledge the CONACyT/México for Ph.D. scholarships. We also thank L. C. Márquez, E. García, and L. M. Ríos for HPLC analysis and J. Pérez, L. Velasco, M. C. García for mass analysis. T R.-R. and M.H.-R. express their gratitude to M. A. Peña, M. I. Chávez, E. Huerta, B. Quiroz, I. M. Aguilar, G. Cortés, and D. Vázquez for technical support.

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J. Org. Chem. 2016, 81, 7419−7431

UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO

PROGRAMA DE MAESTRÍA Y DOCTORADO EN CIENCIAS QUÍMICAS

APLICACIÓN DE ESCUARAMIDAS QUIRALES EN EL RECONOCIMIENTO DE MOLÉCULAS QUIRALES Y ORGANOCATÁLISIS

TESIS

PARA OPTAR POR EL GRADO DE

MAESTRO EN CIENCIAS

PRESENTA

Q. HOWARD YOAV DÍAZ SALAZAR

DR. MARCOS HERNÁNDEZ RODRÍGUEZ
INSTITUTO DE QUÍMICA

CIUDAD UNIVERSITARIA, CD. MX., ENERO 2017

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T E S I S
PARA OPTAR POR EL GRADO DE

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Q. HOWARD YOAV DÍAZ SALAZAR

México, CD. MX. ENERO 2017

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El presente trabajo de investigación se desarrolló en el laboratorio 1-2 del edificio A del Instituto de Química de la UNAM con financiamiento de DGAPA-UNAM (proyecto IN209915) y CONACyT (proyecto 254014). Se emplearon recursos de supercómputo a través de DGTIC-UNAM (SC16-1-IR-109). También se agradece a CONACyT México por la beca de maestría otorgada (Becario No. 576662)

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UNIVERSIDAD NACIONAL AUTÓNOMA DE MEXICO

PROGRAMA DE MAESTRÍA Y DOCTORADO EN CIENCIAS QUÍMICAS

Catálisis por puente de hidrógeno con silanoles aplicada a la reacción de Friedel-Crafts entre indol y β-nitroestireno.

PROYECTO DE INVESTIGACIÓN
PARA OPTAR POR EL GRADO DE
MAESTRO EN CIENCIAS

PRESENTA.

Q. Hugo García Hernández.

Dr. Marcos Hernández Rodríguez.
Instituto de Química. Circuito Exterior s/n, Ciudad Universitaria. Delegación Coyoacán, C.P. 04510, CDMX.

Ciudad de México, Noviembre 2016.

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Agradecimientos

Al Programa de Maestría y Doctorado en Ciencias Químicas y al Instituto de Química de la UNAM, por las facilidades otorgadas para el desarrollo de este trabajo.

Al Dr. Marcos Hernández Rodríguez, por el incontable tiempo y las infinitas enseñanzas que recibí bajo su asesoría.

A la Q. María de los Ángeles Peña González, por los espectros que me ayudo a obtener y la capacitación que recibí para el uso de los equipos de RMN. A la M. en C. Lucía del Carmen Márquez Alonso, a la Q. Eréndira García Ríos y a la M. en C. Lucero Mayra Rios Ruiz por los cromatográmas que me ayudaron a obtener. Al Dr. Francisco Javier Pérez Flores, al I.Q. Luis Velasco Ibarra y a la Dra. María del Carmen García González por los espectros de masas que me ayudaron a obtener.

A CONACyT México, por la beca otorgada con el número 625304 y número de becario 336324.

A DGAPA-UNAM (proyecto IN209915) y CONACyT (proyecto 254014) por los financiamientos otorgados. Se emplearon recursos de supercomputo a través de DGCTIC, UNAM (SC16-1-IR-109).

A los miembros de mi jurado: al Dr. José Luis Arias Téllez, la Dra. Teresa Mancilla Percino, al Dr. Héctor García Ortega, al Dr. Vojtech Jancik y a la Dra. María del Carmen Virginia Ortega Alfaro, por el tiempo que se tomaron para leer el presente informe y por los consejos que recibí de cada uno de ellos.

Este trabajo se desarrolló en el laboratorio 1-2 del Instituto de Química, UNAM.

Programa de Maestría y Doctorado en Ciencias Químicas

Síntesis y aplicación de organocatalizadores bifuncionales que contienen aminas quirales con el grupo trifluorometilo

M. en C. Eddy Ivanhoe Jiménez Gutiérrez

TESIS DE DOCTORADO

Dr. Marcos Hernández Rodríguez

Asesor

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SÍNTESIS Y APLICACIÓN DE ORGANOCATALIZADORES BIFUNCIONALES QUE CONTIENEN AMINAS QUIRALES CON EL GRUPO TRIFLUOROMETILO

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“I Can Change Almost Anything, But I Can’t Change Human Nature”
Dr. Manhattan, Watchmen

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Este trabajo se desarrolló en el laboratorio 1-2 del edificio A del Instituto de Química de la UNAM. Con financiamientos de DGAPA-UNAM (proyecto IN209915) y CONACyT (proyecto 254014). Se emplearon recursos de supercómputo a través de DGCTIC, UNAM (SC16-1-IR-109). También se agradece a CONACyT, México por la beca doctoral (Becario No. 240069).

AGRADECIMIENTOS

- A la máxima casa de estudios: **Universidad Nacional Autónoma de México (UNAM)** por brindarme el conocimiento y las herramientas necesarias en mi formación profesional.

- Al **Programa de Apoyo a Proyectos de Investigación e Innovación Tecnológica (PAPIIT)** por la financiación a través del proyecto IN209915.

- Al **Consejo Nacional de Ciencia y Tecnología (CONACyT)** por el subsidio 254014 y la beca otorgada durante mis estudios de doctorado (Becario No. 240069).

- A la **Dirección General de Cómputo y de Tecnologías de Información y Comunicación (DGCTIC)** por los recursos de computación (SC16-1-IR-109).

- A mi asesor, el Dr. Marcos Hernández Rodríguez que no sólo me indicó la importancia de la organocatálisis en la química sino también me *espoilió* varias series, incluida la muerte de un Stark en Game of Thrones, no lo olvidaré.

- Al Dr. Tomás Rocha Rinza por su característico asesoramiento y colaboración en la parte computacional y a Wilmer Esteban Vallejo por el desarrollo de los cálculos computacionales; además, un gran amigo (*a.k.a. vato loco*) a pesar de no dejar de quejarse de que toda la comida en México "pica" aunque no tenga chile.

- Al alumno Carlos Román por su apoyo y perseverancia en el desarrollo de la síntesis de las azlactonas.

- Al personal técnico del Instituto de Química. A la Q. María de los Ángeles Peña, la M. en C. Elizabeth Huerta, la Dra. María Isabel Chávez y al M. en C. Héctor Ríos por la resonancia magnética nuclear. La M. en C. Lucero Mayra Rios, la Q. Eréndira García y la M. en C. Lucía del Carmen Márquez por los análisis de HPLC. La Dra. María del Carmen García, el Dr. Francisco Javier Pérez y al I.Q. Luis Velasco por los análisis de espectrometría de masas. A la Q.F.B. María del Rocío Patiño por los análisis de infrarrojo y rotación óptica.

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