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Computational Study-Led Organocatalyst Design: A Novel, Highly Active Urea-Based Catalyst for Addition Reactions to Epoxides

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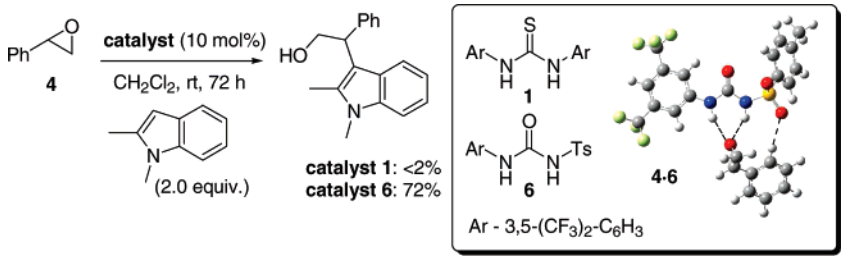

An in silico study examined the stabilities of hydrogen-bonded complexes between simple thiourea catalysts and three different electrophiles and identified a novel, highly active *N*-tosyl urea catalyst for the promotion of addition reactions to epoxide electrophiles. Synthesis and evaluation of **6** revealed it to be a powerful catalyst for the addition of 1,2-dimethylindole to styrene oxide under conditions in which simple *N*,*N*-bis-aryl ureas and thioureas (including **1**) are inactive. Subsequent studies determined **6** to be compatible with a range of indole and epoxide substrates (including (*E*)-stilbene oxide) and found that relatively poor nucleophiles such as sterically and electronically deactivated anilines, thiophenol, and benzyl alcohol could be efficiently and regioselectively added to oxiranes under mild conditions.

Introduction

It has been known for almost a century that small, metal-free organic molecules can act as effective catalysts in a variety of synthetically useful transformations;[1] however, it is only in the past decade that this field of endeavor has caught the interest of a significant proportion of the research community. This renaissance has resulted in spectacular progress in a relatively short period of time and has propelled organocatalysis from obscurity to prominence as a complementary technology to transition metal(ion)-based catalysis in a number of synthetically useful transformations.[2] In the 1980s, Etter and co-workers observed that *N*,*N*-diaryl ureas cocrystallized via the formation of two hydrogen bonds with a variety of guests incorporating Lewis basic functional groups such as −nitroaromatics, ethers, ketones, and sulfoxides.[3,4] Curran and Kuo,[5,6] Jacobsen and Sigman,[7] and Schreiner and Wittkopp[8,9] later pioneered the exploitation of this binding mode in catalysis as a method for the activation of electrophiles incorporating hydrogen-bond accepting functionality.[10,11]

Schreiner and Wittkopp first introduced 3,3′,5,5′-tetratrifluoromethyl thiocarbanilide (**1**) as an active catalyst for the

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promotion of Diels−Alder reactions between cyclopentadiene and α,β-unsaturated dienophiles.[8,9] Catalyst **1** possesses a flat, rotationally restricted structure with two syn-periplanar N−H bonds available for hydrogen-bond (HB) donation.[8,9] The trifluoromethyl groups augment the HB donating ability of the catalyst without being either Lewis basic enough to lead to appreciable catalyst self-association or close enough to the thiourea moiety to hinder substrate binding.[12] This catalyst has proven to be remarkably versatile; subsequently, it has been shown to act as an efficient promoter of a number of reactions[13] including the addition of cyanide and silyl ketene acetals to nitrones,[14] the Baylis−Hillman reaction,[15] Friedel−Crafts-type reactions,[16] acetalizations,[17] Claisen rearrangements,[6,18] ring-opening reactions of oxiranes,[19] acyl Strecker reactions,[20] imine reductions,[21,22] and tetrahydropyranylations.[23]

While **1** has proven to be highly active in certain transformations (particularly those involving condensation[17,23]), in view of the considerable manifest interest in this field and the recent advent of highly active Brønsted acidic[24] phosphoric acid organocatalysts,[25,2b,i,k] it is somewhat surprising that the evaluation of more acidic (thio)urea analogues of **1** as catalysts has not been reported. As part of an ongoing program aimed at both the expansion of the scope of (thio)urea derivative-mediated catalysis and the development of new catalyst systems, we undertook an unusual yet potentially rapid and convenient in silico approach to catalyst design in which the relative compatibility of a given catalyst−substrate pair is determined based on the stability of the catalyst−substrate complex (via DFT methods), the results of which guide the course of subsequent experimental studies. A key feature of this strategy is the concentration on the interaction between the catalyst and the electrophilic reaction component. We reasoned that while such an approach ignores the reaction transition state (the stabilization of which is key in the design of any catalyst system), this is less of a disadvantage in an exergonic process in which one aspires toward the development of catalysts in which proton transfer occurs as early as possible on the reaction coordinate and is compensated for by the general applicability of the data (i.e., a transition state calculation is specific for one reaction, while the current approach could provide useful indicators of compatibility over a range of reactions in which the nucleophilic component is varied) and the relative speed and simplicity of the calculations involved.

Results and Discussion

The geometries and HB patterns exhibited by a series of (thio)urea-based organic catalysts and their complexes with a number of substrates were theoretically studied using DFT. This study allows the prediction of catalyst reactivity and substrate recognition/interaction and, additionally, tests the predictability of the model with subsequent experimental studies.

To determine the existence of HBs and their characteristics, the computed electron charge density for each complex was analyzed using the atoms in molecules (AIM)[26] methodology. According to this formalism, a necessary condition for the establishment of an interaction between two atoms is the formation of a bond critical point (bcp), which corresponds to a point where the electron density function is a minimum along the bond path and maximum in the other directions. Hence, an interaction can be characterized by the properties of the electron density in that point, and thus, an electron density [ρ(bcp)] of approximately 10^{-2} au and a positive Laplacian of the charge density [$\nabla^2\rho$(bcp)] at the bcp correspond to what is defined as closed-shell interaction of the HB type.

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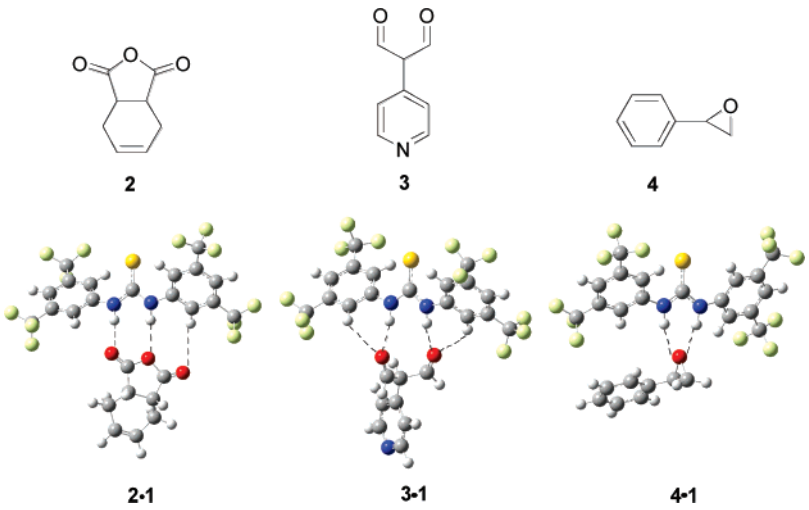

FIGURE 1. Minimum energy structure of the complexes found between **1** and **2**−**4** optimized at the B3LYP/6-31+G* level.

TABLE 1. Interaction Energies, HB Distances, ρ(bcp), and $\nabla^2\rho$(bcp) Found for Complexes 2·1, 3·1, and 4·1 Computed at the B3LYP/6-31+G* Level of Theory

complex	E_I (kcal mol^{-1})	HB distance (Å)	ρ(bcp)	$\nabla^2\rho$(bcp)
2·1	−10.0	NH···O 2.07	0.0201	0.0640
		NH···O 2.23	0.0135	0.0468
		CH···O 2.91	0.0035	0.0140
3·1	−10.7	NH···O 2.05	0.0198	0.0667
		NH···O 2.11	0.0166	0.0595
		CH···O 2.66	0.0056	0.0224
		CH···O 2.81	0.0046	0.0181
4·1	−12.8	NH···O 2.02	0.0219	0.0723
		NH···O 2.08	0.0187	0.0640

Initially, we explored the amenability of different substrates containing anhydride (**2**), aldehyde (**3**), or oxirane (**4**) functionalities to interaction with **1**. These particular substrates were chosen based on their inherent (yet discrete) reactivity and synthetic utility, the fact that they have been little studied (in the context of (thio)urea-mediated catalysis), and the presence of one, two, or three O atoms (i.e., HB acceptors) in both sp^2 and sp^3 hybridization modes. Considering the rigidity of the symmetrical catalyst **1** and the previous computational studies on this material carried out by Schreiner et al.,[8−10,19,23] and Strassner et al.,[18] only that conformer of minimum energy that orients both thiourea NH protons toward the substrate was considered. Regarding the substrates, different approaches for the interaction were taken to cover all conformational possibilities, and the global minimum energy complexes shown in Figure 1 were obtained after optimization at the B3LYP/6-31+G* level.

In terms of interaction energy (calculated as the difference between the total energy of the complex minus the sum of the total energy of the host and guest (Table 1)), the most stable complex was that formed between the thiourea **1** and the oxirane derivative (**4·1**, Figure 1). Considering that it has been postulated that the activity of this type of organocatalyst is driven by the formation of an intramolecular net of HB interactions, this is an extremely interesting outcome. The catalyst model used has two HB donors in the thiourea moiety; therefore, it could be expected (a priori) that the larger the number of HB acceptors (O atoms) in the substrate, the stronger the interaction. However, the most stable complex was that formed with the oxirane-type substrate containing a single O atom. We next proceeded to analyze the nature and pattern of the interactions in each complex.

In the case of complex **2·1**, we began from a configuration where the anhydride group established bifurcated HBs between the central O atom and the two NH atoms and two secondary bifurcated interactions between the C═O groups and the NH of the urea and a CH from each phenyl ring. After optimization, the system evolved to that shown in Figure 1, where parallel multiple HBs were found between one of the C═O moieties and one NH, the central O atom and the other NH, and finally the second C═O bond and one CH from a phenyl ring. In all cases, a bcp was found between the interacting atoms, and the characteristics of the electron density at those bcps correspond to HB interactions (Table 1). In the case of **3·1**, the final optimized complex shows two bifurcated interactions between each of the C═O groups and one NH of the thiourea and a CH from the proximal phenyl ring. All the aforementioned interactions were characterized as HBs according to the electron density properties found in the corresponding four bcp values (Table 1). Finally, in complex **4·1**, a bifurcated HB is detected between the oxirane heteroatom and both thiourea NH protons as seen both from the localization of two bcps and the electronic characteristics indicated by those points (Table 1).

It has been demonstrated that there is a clear correlation between the HB distance and the electron density at the bcp [ρ(bcp)].[27] Thus, the shorter the HB distance, the larger the electron density and, therefore, the stronger the interaction. Accordingly, it seems clear that the interaction between the catalyst and the substrate will be favored not by the number (complexes **2·1** and **3·1** incorporate three and four HBs, respectively, whereas **3·1** is characterized by only two strong HBs) but by the strength of the HBs in the complex (Table 1).

We next explored the interaction of a more acidic catalyst (**5**: an *N*-tosyl analogue of **1**) with **4**. Initially, the conformational space of this new[28] catalyst was explored at molecular

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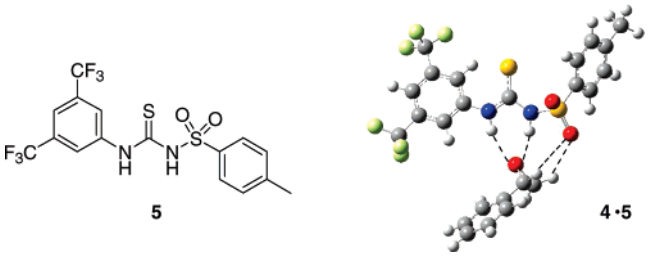


FIGURE 2. Minimum energy structure of the complexes found between **5** and **4** optimized at the B3LYP/6-31+G* level.

TABLE 2. Interaction Energy, HB Distance, ρ(bcp), and $\nabla^2\rho$(bcp) Found for Complex 4·5, Computed at the B3LYP/6-31+G* Level of Theory

complex	E_I (kcalmol^{-}1)	HB distance (Å)	ρ(bcp)	$\nabla^2\rho$(bcp)
4·5	−14.0	NH···O 1.90	0.0303	0.0933
		NH···O 2.18	0.0145	0.0529
		CH···O(S) 2.81	0.0050	0.0195
		CH···O(S) 3.05	0.0030	0.0133

mechanics level. Three discrete minima were found with the appropriate orientation of the NH thiourea groups (vide supra). Considering that both the catalyst and the substrate are not symmetrically substituted, four different approaches for the interaction were possible, all of which were explored. Twelve complexes were found at the B3LYP/6-31G* level, which were minima on the potential energy surface exhibiting, in 75% of the cases, interaction energies were stronger than those associated with complex **4·1**. This is a strong indication that the oxirane better interacts with nonsymmetrically substituted **5** than with the symmetrical thiourea **1**. The most stable complexes (within a range of 2 kcal mol^{-1} over the minima) were optimized with the 6-31+G* basis set—converging to four complexes. The most stable complex **4·5** is shown in Figure 2, and the corresponding interaction energy and analysis of the HB intramolecular interactions found are presented in Table 2. In complex **4·5** (and in all of the optimized complexes investigated), not only is the expected bifurcated interaction between the O atom (from the oxirane) and the two thiourea NH hydrogen atoms formed, but also secondary interactions are observed between one of the sulfonamide O atoms and either the methylene hydrogen atoms of the oxirane ring (as is the case with complex **4·5**) or a CH of the substrate phenyl moiety (Figure 2).

In each of the complexes between **4** and **5** examined, all interactions established between the host and the guest were identified as HBs according to both AIM theory and analysis of the electron density. The data obtained for the most stable complex **4·5** are shown in Table 2.

An examination of this data reveals that the HBs established between the NH of the thiourea and the oxirane O atom are even stronger (i.e., shorter bond length distances and larger values of ρ(bcp)) than the corresponding interactions in complex **4·1**. In addition, even though the secondary interactions with the sulfonamide O atoms are weak, they seem to contribute to the total stability of the complex. At this juncture, we were confident that we had computationally identified a promising novel catalyst−substrate interaction and proceeded to commence experimentation to validate the in silico findings. Unfortunately, while catalyst **5** was readily prepared from the corresponding *N*-tosyl aniline/thiophosgene and exhibited high activity, it was not sufficiently hydrolytically stable to be of use as a general-

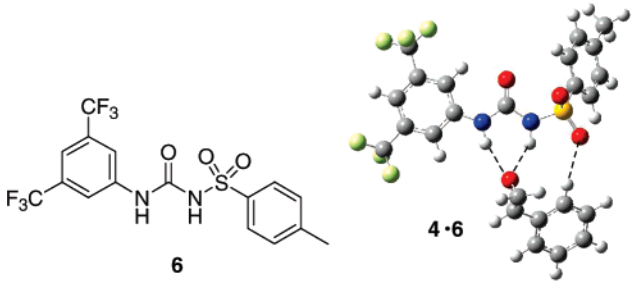


FIGURE 3. Minimum energy structure of the complexes found between **6** and **4** optimized at the B3LYP/6-31+G* level.

TABLE 3. Interaction Energy, HB Distance, ρ(bcp), and $\nabla^2\rho$(bcp) Found for Complex 4·6, Computed at the B3LYP/6-31+G* Level of Theory

complex	E_I (kcal mol^{-}1)	HB distance (Å)	ρ(bcp)	$\nabla^2\rho$(bcp)
4·6	−14.1	NH···O 1.97	0.0240	0.0795
		NH···O 2.09	0.0181	0.0627
		CH···O(S) 2.48	0.0086	0.0307

purpose organocatalyst and often decomposed before complete conversion of the starting materials in a number of test reactions. We were therefore encouraged to evaluate (in silico) the corresponding *N*-tosyl urea **6** in the expectation that this material would offer a greater catalyst stability without requiring a significant compromise on activity. To our delight, treatment of the interaction between **6** and **4** in the same fashion as used previously yielded analogous interaction energies to the corresponding thiourea complexes, and the absolute minimum, complex **4·6** (Figure 3), was calculated to be actually 0.06 kcal mol^{-1} more stable than **4·5** (Table 3). As in the case of **4·5**, the complexes formed with urea **6** show not only HBs with the urea NH protons but also secondary interactions between one of the sulfonamide O atoms and CH groups of the oxirane or phenyl rings of the substrate. In particular, the most stable complex **4·6** possesses two very strong NH···O HBs and a secondary weak HB formed between one of the O atoms of the sulfonamide and an ortho-hydrogen atom of the substrate benzene ring (Figure 3 and Table 3).[29]

With a potential novel catalyst and substrate identified, attention now was turned toward the nucleophilic reaction component and experimental studies. While this work was in progress, Schreiner and Kleiner reported the first (thio)urea catalyzed addition of aliphatic amines, thiophenol, and alcohols to epoxides.[19] Yields were low to moderate in dichloromethane solvent; however, the same reactions (which require ultrasonication before the addition of the nucleophile) under the influence of hydrophobic amplification in water were highly efficient. As a starting point, we selected indole derivatives as the nucleophilic reaction partner as (a) they do not incorporate a basic

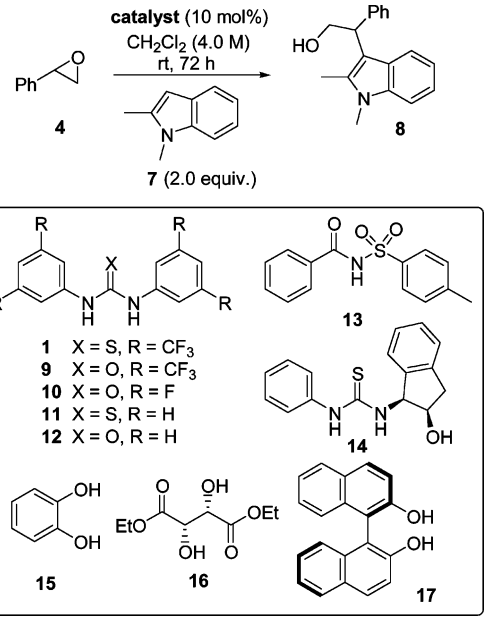
(29) All interactions established between both components in each of the complexes studied were identified as HBs according to AIM theory and analysis of the electron density. Only results obtained for the most stable complex **4·6** are shown in Table 3 for the sake of simplicity.

(30) For examples of metal(ion)-based catalysis of this reaction, see: (a) Kantam, M. L.; Laha, S.; Yadav, J.; Sreedhar, B. *Tetrahedron Lett.* **2006**, *47*, 6213. (b) Azizi, M.; Mehrazama, S.; Saidi, M. R. *Can. J. Chem.* **2006**, *84*, 800. (c) Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2004**, *346*, 573. (d) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386.

(31) Kotsuki, H.; Hayashida, K.; Shimanouchi, T.; Nishizawa, H. *J. Org. Chem.* **1996**, *61*, 984.

(32) Subsequently, an interesting report involving the efficient catalysis of this reaction using HBF_4-SiO_2 has appeared: Bandgar, B. P.; Patil, A. V. *Tetrahedron Lett.* **2007**, *48*, 173.

TABLE 4. Organocatalyzed Addition of 7 to 4



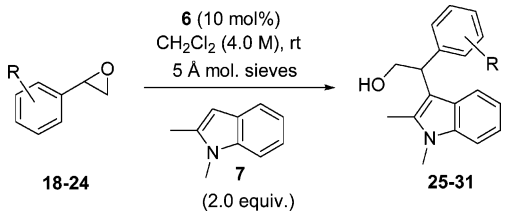
entry	catalyst	time (h)	yield (%)[a]
1	None	72	0
2	**1**	72	<2
3	**9**	72	0
4	**10**	72	0
5	**11**	72	0
6	**12**	72	0
7	**6**	72	71
8	**13**	72	56
9	**14**	72	0
10	**15**	72	39[b]
11	**16**	72	0
12	**17**	245	21[b,c]

[a] Refers to isolated yield after chromatography. [b] Conversion, determined by ^{1}H NMR spectroscopy. [c] (*R*)-BINOL afforded **8** as a racemate: no kinetic resolution was observed.

functionality that could possibly deprotonate the acidic urea **6**, (b) the 3-alkyl indole addition products from such reactions are useful synthetic building blocks for the construction of molecules of biological interest,[30] and (c) at the outset of this study, the previous benchmark for organocatalysis of this reaction involved the use of a silica gel catalyst and elevated temperatures and pressures (10 kbar) to afford moderate to good adduct yields.[31,32]

The results of initial catalyst screening studies are presented in Table 4. The addition of 1,2-dimethylindole (**7**) to **4** in dichloromethane does not proceed at room temperature (entry 1 in Table 4). The same reaction catalyzed by **1** (10 mol %) afforded only traces of adduct **8** (entry 2 in Table 4), and *N*,*N*-diaryl (thio)ureas **9**−**12** were inactive (entries 3−6 in Table 4). Gratifyingly, *N*-tosyl urea **6** identified in the in silico study as potentially suitable for use in conjunction with **4** proved to be an effective catalyst capable of furnishing **8** in good isolated yield after 72 h (entry 7 in Table 4). We did not observe significant decomposition of **6** in this reaction. The contribution of the urea moiety to the activity of **6** is underlined by the catalytic inferiority of acyl sulfonamide **13** (entry 8 in Table 4): although it is noteworthy that this material is superior to **1** and **9**−**12** under these conditions. Thiourea **14**, which possesses an additional HB donating functionality, did not catalyze the reaction, while of the diols **15**−**17**, only catechol **15** exhibited an appreciable catalytic activity.

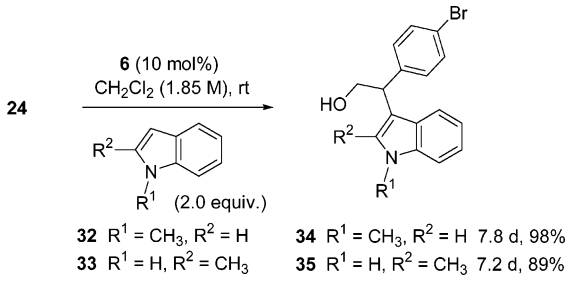
TABLE 5. Addition of 7 to Styrene Oxides 18−24 Catalyzed by 6



entry	substrate	product	time (h)	yield (%)[a]
1	**18** R = 2-OCH$_3$	**25** R = 2-OCH$_3$	26	90[b]
2	**19** R = 4-OCH$_3$	**26** R = 4-OCH$_3$	26	90
3	**20** R = 2-CH$_3$	**27** R = 2-CH$_3$	48	98
4	**21** R = 4-CH$_3$	**28** R = 4-CH$_3$	48	94
5	**22** R = 2-Cl	**29** R = 2-Cl	621	80
6	**23** R = 4-Cl	**30** R = 4-Cl	163	93
7	**24** R = 4-Br	**31** R = 4-Br	77	92

[a] Refers to isolated yield after chromatography. [b] Same reaction without molecular sieves gave 75% isolated yield.

SCHEME 1. Addition of 1- and 2-Methylindoles to 24 Catalyzed by 6



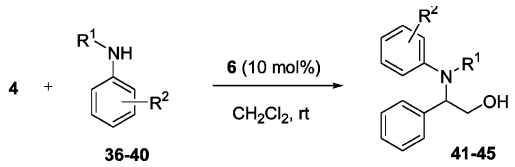
Next, the compatibility of **6** with styrene oxides of variable steric and electronic characteristics was investigated (Table 5). A range of styrene oxides **18**−**24** could be converted to indole derivatives **25**−**31** in good to excellent yields. Both ortho- and para-substitution is well-tolerated by the catalyst, and styrene oxides with electron-rich aromatic rings (entries 1−4 in Table 5) react at considerably faster rates than their more electron deficient counterparts (entries 5−7 in Table 5). Indoles other than **7** can also be employed as the nucleophile: both 1- and 2-methylindole derivatives could be reacted with **24** to give **34** and **35** in good yields (Scheme 1).

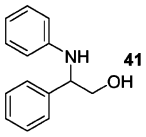
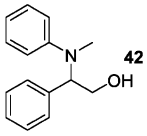
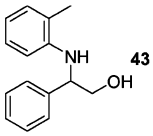
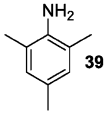
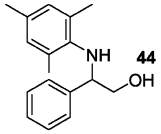
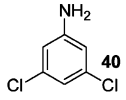
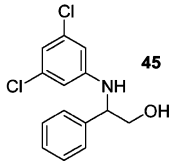
The success of these Friedel−Crafts-type reactions prompted us to investigate the compatibility of **6** with other nucleophiles. Preliminary experiments focused on the use of aliphatic amines;[33] however, these were found to be sufficiently reactive under our reaction conditions to give considerable levels of amino alcohol products in the absence of catalyst; furthermore, Schreiner and Kleiner[19] had recently developed efficient catalytic methodologies for their use in aqueous solvent; therefore, we decided that the addition of less reactive aniline nucleophiles to **4** would provide a more instructive test of the catalyst's activity and utility (Table 6).

Catalyst **6** could promote the efficient and highly regioselective formation of *β*-amino alcohol products derived from aniline (entry 1 in Table 6), *N*-methyl aniline, and (remarkably) either sterically or electronically deactivated derivatives thereof

(33) For the first examples of catalysis of this reaction (using a biphenylenediol catalyst), see: (a) Hine, J.; Linden, S.-M.; Kanagasabapathy, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 1082. (b) Hine, J.; Linden, S.-M.; Kanagasabapathy, V. M. *J. Org. Chem.* **1985**, *50*, 5096.

TABLE 6. Organocatalyzed Addition of Anilines to Styrene Oxide



entry	substrate	product	time (h)	yield (%)[a]
1[b]	 **36**	 **41**	91	86
2[b]	 **37**	 **42**	91	78[b]
3[c]	 **38**	 **43**	90	75[e]
4[d]	 **39**	 **44**	147	92
5	 **40**	 **45**	71	84

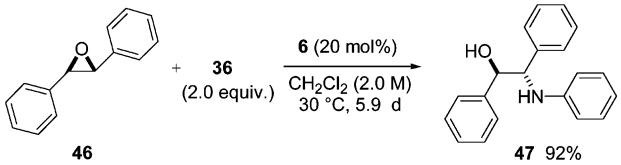
[a] Refers to isolated yield after chromatography. [b] 2.0 M concentration. The crude reaction mixture was determined to be a 94:6 ratio of regioisomers using ^{1}H NMR spectroscopy. The yield cited corresponds to that of the isomer shown. [c] 1.5 M concentration. [d] Using 20 mol % **6**. [e] Crude reaction mixture was determined to be a 92:8 ratio of regioisomers using ^{1}H NMR spectroscopy.

(entries 3−5 in Table 6) at 10 mol % levels. Only the considerably hindered amine **39** required an augmented catalyst loading of 20 mol %. While Schreiner and Kleiner's study[19] did not utilize aniline substrates, Saidi and Azizi[34] recently reported (in a study concerned with the addition of amines to epoxides in water) that aromatic amines gave poor adduct yields with all oxirane electrophiles except terminal epoxide **4**[35] under conditions that resulted in smooth reactions using aliphatic amines. Accordingly, we were pleased to find that **6** could catalyze the addition of aniline to the more hindered (*E*)-stilbene oxide (**46**) in high yield at 30 °C (Scheme 2)

The scope of these catalyzed processes was not restricted to carbon- and nitrogen-based nucleophiles. Thiophenol (**48**) and the weakly nucleophilic benzyl alcohol (**50**) could also be added

(34) Azizi, N.; Saidi, M. R. *Org. Lett.* **2005**, *7*, 3649.
(35) Only one example (using aniline itself) as the nucleophile was given.

SCHEME 2. Addition of Aniline to (*E*)-Stilbene Oxide Catalyzed by 6



SCHEME 3. Addition of Thiophenol and Benzyl Alcohol to 18− and 19 Catalyzed by 6

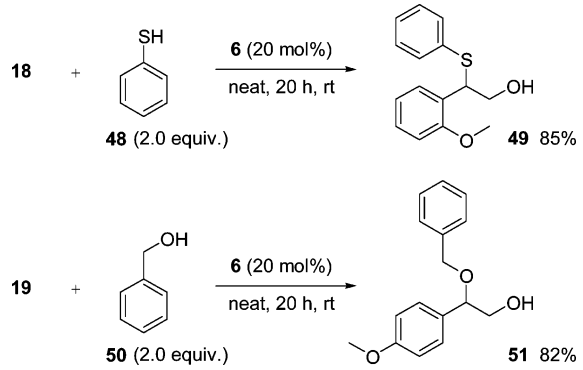


TABLE 7. Interaction Energies (kcal/mol), HB Distances (Å), ρ(bcp), and $\nabla^2\rho$(bcp) Found for Complexes 41a·6 and 41b·6 Computed at the B3LYP/6-31+G* Level of Theory

complex	E_I (kcal mol^{-}1)	HB distance (Å)	ρ(bcp)	$\nabla^2\rho$(bcp)
41a·6	−11.5	NH···N 2.26	0.0176	0.0466
		NH···O 1.94	0.0288	0.0852
		OH···O(S) 1.95	0.0253	0.0855
		NH···O 2.23 (intra)	0.0168	0.0774
41b·6	−13.0	NH···O 2.20	0.0158	0.0524
		NH···O 1.88	0.0310	0.0990
		NH···O(S) 2.23	0.0133	0.0476
		CH···O(S) 2.55	0.0069	0.0269

to methoxy substituted styrene oxides **18**− and **19** in good yield at room temperature with the assistance of **6** (Scheme 3). In the absence of the catalyst, no conversion of **18**− and **19** was observed after the same reaction time in either process.

Finally, we studied, from a theoretical point of view, the relative affinities of the catalyst for the substrate and the product obtained after the addition of aniline to styrene oxide. The possible complexes formed between urea catalyst **6** and **41** were analyzed. Initially, the conformational space of the product was explored, and the conformer of minimum energy was identified and then used for the rest of the calculations. The catalyst conformer utilized was that previously determined (vide supra). Considering the structure of both molecules, all possible approximations were taken into account at the B3LYP/6-31G* level, and 12 complexes of minimum energy were identified. Eight of these involved interactions between the catalyst urea moiety and the O atom of the hydroxyl group of the product. The other four approximations involved dual interactions between the urea and both the O(H) and the N(H) groups of the product. Those conformers of minimum energy for each approximation were further optimized at the 6-31+G* level, resulting in two different complexes of minimum energy (**41a·6** and **41b·6** (Table 7 and Figure 4)).

Complex **41a·6** is formed between the catalyst (acting as a HB donor) and **41** with both the product amino and the hydroxyl groups acting as HB acceptors (Figure 4), and an additional

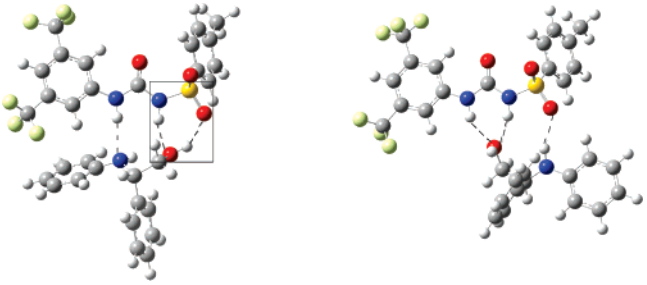


FIGURE 4. Structure of minimum energy found for the complexes formed between **41** and **6**: complexes **41a·6** (left) and **41b·6** (right). The ring of cooperative HBs in complex **41a·6** is framed.

HB is formed between the hydroxylic proton and one of the O atoms of the SO_2 moiety. Complex **41b·6** is characterized by bifurcated HBs between the O atom of the product and the urea protons and two secondary interactions between the product amino and the methine protons as HB donors with one of the catalyst's sulfonamide O atoms.

Analyzing the electron density surface, it was possible to identify four HBs in each complex. In the case of the **41a·6** complex, parallel HBs are formed between the urea NH groups and the N (medium HB) and O (very strong HB) atoms of the product, and a very strong HB is established between the hydroxyl group of the product (which acts now as a HB donor) and one of the sulfonamide O atoms. Additionally, an intramolecular NH···O(H) HB is found in the product molecule (Table 7). The reason behind the strength of the NH···O and OH···O(S) bonds lies in the cooperative effect established between these two HBs formed through the O−H group.[36] Thus, it is possible to identify a ring of HBs connected in a cooperative fashion: (S−)N−H···O−H···O−S(≡N).

In complex **41b·6**, bifurcated HBs are formed between both urea NH protons and hydroxyl O atom. Additionally, two weak HBs are established between the NH and one CH group of the product and one of the sulfonamide O atoms. These two complexes, which are the most stable of all the possible complexes found at lower levels of computation, are less stable than complex **4·6** found between the catalyst and the oxirane derivative (Table 7).

Conclusion

To summarize, we utilized computational DFT methods to evaluate the stabilities of hydrogen-bonded complexes between thio(urea) catalysts and three different electrophiles that incorporate Lewis-basic oxygen-based functionality. These data were then used to select a (thio)urea−electrophile pair predicted to be best suited for use in catalytic reactions in conjunction with a generic nucleophile. While this approach ignores the reaction transition state, it is rapidly executed, and the results can potentially be applied to a range of reactions involving a given electrophile and a number of various nucleophiles if discretion is exercised regarding nucleophile compatibility with the catalyst's acidity. The results of these investigations strongly indicated that the previously unknown acidic urea-based catalyst **6** would potentially be able to serve as a more active promoter of addition reactions to epoxide derivatives than benchmark literature catalyst **1**. Synthesis and evaluation of **6** led to the validation of this computational study-guided design strategy: **6** possessed unprecedented activity for a (thio)urea catalyst and promoted the addition of indole **7** to styrene oxide at room temperature under conditions that other (thio)urea derivatives (including **1**) did not. The catalyst was robust and of high synthetic utility: various styrene oxides (including a nonterminal analogue) and indoles were tolerated, and (demonstrating the general applicability of the methodology) it was found that the catalyst was equally proficient in the promotion of C−N, C−S, and C−O bond formation via the addition of weak nucleophiles to epoxides under conditions that do not give reactions in the absence of **6**. We are currently investigating the use of this strategy in the design of more complex bifunctional catalyst systems.

(36) Rozas, I. *Phys. Chem. Chem. Phys.* **2007**, *9*, 2782.

Experimental Section

Synthesis of Catalyst 6. A 10 mL round-bottomed flask charged with 3,5-trifluoromethylaniline (600 μL, 3.84 mmol) and dichloromethane (5.0 mL) was fitted with a septum and placed under an atmosphere of Ar. Subsequently, *p*-toluenesulfonyl isocyanate (643 μL, 4.22 mmol) was added via a syringe. A white precipitate was observed after 10 min. The solution was left to stir overnight. The reaction was filtered, and the product was purified by recrystallization (CH_2Cl_2-hexane) to give **6** (1.52 g, 93%) as a white solid, mp 185−187 °C. ^{1}H NMR ($CDCl_3$) δ 8.94 (br s, 1H, NH), 7.95 (s, 2H), 7.83−7.86 (d, 2H, J = 5.4 Hz), 7.66 (s, 1H), 7.48 (br s, 1H), 7.39−7.41 (d, 2H, J = 5.4 Hz), 2.48 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 148.4, 145.9, 138.2, 136.0, 132.6 (q, J = 33.9 Hz), 130.4, 126.9, 122.9 (q, J = 273.0 Hz) 119.8, 118.1, 21.6. IR (Nujol) 3157, 1693, 1276, 1162, 1147, 680 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{16}H_{12}N_2O_3SF_6Na$ $(M + Na)^+$ 449.0371, found 449.0389

Procedure A: Synthesis of 8 Catalyzed by 6. A 1 mL reaction vessel equipped with a stir bar and charged with **6** (29.3 mg, 0.069 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **7** (200 mg, 1.37 mmol), CH_2Cl_2 (40.4 μL), and **4** (78.5 μL, 0.688 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 72 h. Column chromatography of the reaction mixture (4:1 hexane/ethyl acetate, R_f 0.3) yielded **8** (129 mg, 71%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.49−7.51 (d, 1H, J = 8.0 Hz), 7.27−7.36 (m, 5H), 7.16−7.22 (m, 2H), 7.02−7.06 (app. t, 1H, J = 7.5 Hz), 4.52−4.56 (app. t, 1H, J = 7.8 Hz), 4.36−4.38 (m, 2H), 3.71 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 141.9, 137.0, 135.3, 128.4, 127.9, 126.7, 126.3, 120.7, 119.3, 119.2, 109.2, 108.9, 65.2, 45.4, 29.7, 10.7. NMR spectral data are consistent with that in the literature.[30c] IR (neat): 3399, 2936, 1600, 1177, 1031, 739 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{18}H_{19}NONa$ $(M + Na)^+$ 288.1364, found 288.1358.

Synthesis of 25. A 1 mL reaction vessel equipped with a stir bar charged with **6** (29.3 mg, 0.0688 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **7** (200 mg, 1.37 mmol), CH_2Cl_2 (40 μL), and **18** (103.3 mg, 0.688 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 26 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.5) yielded **25** (183 mg, 90%) as a pale yellow solid, mp 124−126 °C. ^{1}H NMR (DMSO-d_6) δ 7.48−7.50 (m, 2H), 7.28−7.30 (d, 1H, J = 7.8 Hz), 7.10−7.14 (app. t, 1H, J = 7.8 Hz), 6.95−6.99 (app. t, 1H, J = 7.5 Hz), 6.83−6.90 (m, 3H), 4.58−4.62 (m, 2H), 4.16−4.20 (app. t, 1H, J = 9.5 Hz), 3.94−3.99 (app. t, 1H, J = 8.8 Hz), 3.72 (s, 3H), 3.62 (s, 3H), 2.40 (s, 3H).^{13}C NMR (DMSO-d_6) δ: 157.0, 136.2, 133.9, 130.8, 127.9, 126.7, 126.6, 119.8, 119.5, 118.9, 118.0, 110.6, 110.4, 108.9, 62.7, 55.3, 38.6, 29.3, 10.3. IR (Nujol): 3327, 2917, 1596, 1462, 1117, 1027, 732 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{19}H_{21}NO_2Na$ $(M + Na)^+$ 318.1470, found 318.1464.

Synthesis of 26. A 1 mL reaction vessel equipped with a stir bar charged with **6** (29.3 mg, 0.0688 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **7** (200 mg, 1.37 mmol), CH_2Cl_2 (40.4 μL), and **19** (78.5 μL, 0.688 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 26 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.5) yielded **26** (183 mg, 90%) as a pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.32−7.34 (dd, 2H, J = 8.0 Hz), 7.23−7.26 (d, 2H, J = 8.0 Hz), 6.98−7.02 (app. t, 1H, J = 7.5 Hz), 6.84−6.88 (app t, 1H, J = 7.5 Hz), 6.79−6.81 (d, 2H, J = 8.0 Hz), 4.68−4.70 (app t, 1H, J = 5.5 Hz), 4.26−4.30 (app t, 1H, J = 7.3 Hz), 4.17−4.23 (m, 1H), 3.93−3.98 (m, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 2.36 (s, 3H) ^{13}C NMR (DMSO-d_6) δ: 157.1, 136.3, 135.4, 133.6, 128.9, 126.5, 119.7, 118.8, 118.2, 113.3, 111.6, 109.0, 64.0, 55.0, 44.1, 29.3, 10.4. IR (neat): 3399, 3048, 2933, 1610, 1511, 1034 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{19}H_{21}NO_2Na$ (M + Na)$^+$ 318.1470, found 318.1461.

Synthesis of 27. A 1 mL reaction vessel equipped with a stir bar charged with **6** (29.3 mg, 0.0688 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **7** (200 mg, 1.37 mmol), CH_2Cl_2 (78 μL), and **20** (92.3 mg, 0.688 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 48 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.45) yielded **27** (188 mg, 98%) as a pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.57−7.59 (d, 1H, J = 7.8 Hz), 7.28−7.32 (app t, 2H, J = 7.8 Hz), 7.18−7.21 (m, 1H), 7.06 (m, 2H), 6.96−7.00 (app t, 1H, J = 7.8 Hz), 6.80−6.83 (app t, 1H, J = 7.3 Hz), 4.68−4.70 (app t, 1H, J = 5.4 Hz), 4.37−4.40 (app t, 1H, J = 7.3 Hz), 4.12−4.18 (m, 1H), 3.91−3.97 (m, 1H), 3.62 (s, 3H), 2.33 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 140.8, 136.6, 136.3, 134.0, 130.1, 127.3, 126.7, 125.6, 125.3, 119.6, 118.4, 118.1, 109.6, 108.9, 63.5, 41.7, 29.3, 19.3, 10.4. IR (neat): 3410, 3049, 2251, 1657, 1470, 1008 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{19}H_{21}NONa$ (M + Na)$^+$ 302.1521, found 302.1511.

Synthesis of 28. A 1 mL reaction vessel equipped with a stir bar charged with **6** (29.3 mg, 0.0688 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **7** (200 mg, 1.37 mmol), CH_2Cl_2 (78 μL), and **21** (92.3 mg, 0.688 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 48 h. Column chromatography of the reaction mixture (4:1 hexane/ethyl acetate, R_f 0.3) yielded **28** (181 mg, 94%) as a pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.31−7.35 (app t, 2H, J = 6.8 Hz), 7.20−7.22 (d, 2H, J = 8.0 Hz), 6.98−7.04 (m, 3H), 6.84−6.87 (app t, 1H, J = 7.3 Hz), 4.67−4.69 (app t, 1H, J = 5.0 Hz), 4.26−4.30 (app t, 1H, J = 7.3 Hz), 4.18−4.24 (m, 1H), 3.93−3.98 (m, 1H), 3.63 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 140.5, 136.3, 134.3, 133.6, 128.5, 127.9, 126.5, 119.7, 118.8, 118.2, 111.5, 108.9, 63.8, 44.6, 29.3, 20.6, 10.4. IR (neat): 3392, 3047, 2923, 1470, 1036, 739 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{19}H_{21}NONa$ (M + Na)$^+$ 302.1521, found 302.1516.

Synthesis of 29. A 1 mL reaction vessel equipped with a stir bar charged with **6** (29.3 mg, 0.0688 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **7** (200 mg, 1.37 mmol), CH_2Cl_2 (64 μL), and **22** (106.4 mg, 0.688 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 621 h. Column chromatography of the reaction mixture (4:1 hexane/ethyl acetate, R_f 0.3) yielded **29** (165 mg, 80%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.62−7.65 (d, 1H, J = 8.0 Hz), 7.57−7.59 (d, 1H, J = 7.5 Hz), 7.35−7.37 (d, 1H, J = 8.0 Hz), 7.29−7.32 (d, 1H, J = 8.5 Hz), 7.14−7.24 (m, 3H), 7.04−7.08 (app t, 1H, J = 7.5 Hz), 4.86−4.89 (dd, 1H, J = 6.5, 9.0 Hz), 4.37−4.42 (m, 1H), 4.27−4.31 (m, 1H), 3.70 (s, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 139.3, 136.8, 135.5, 134.1, 129.7, 129.1, 127.5, 126.7, 126.6, 120.5, 119.2, 118.8, 108.9, 107.8, 64.2, 43.0, 29.5, 10.6. IR (neat): 3400, 2935, 1611, 1468, 1040, 741 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{18}H_{18}NONaCl$ (M + Na)$^+$ 322.0975, found 322.0984.

Synthesis of 30. A 1 mL reaction vessel equipped with a stir bar charged with **6** (29.3 mg, 0.0688 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **7** (200 mg, 1.37 mmol), CH_2Cl_2 (66 μL), and **23** (137 mg, 0.688 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 163 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.3) yielded **30** (191 mg, 93%) as a clear oil. ^{1}H NMR (DMSO-d_6) δ 7.28−7.37 (m, 6H), 6.99−7.03 (app t, 1H, J = 7.8 Hz), 6.85−6.89 (app t, 1H, J = 7.5 Hz), 4.80−4.83 (app t, 1H, J = 5.0 Hz), 4.32−4.35 (app t, 1H, J = 7.0 Hz), 4.21−4.27 (m, 1H), 3.92−3.97 (m, 1H), 3.64 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 142.6, 136.3, 133.8, 130.0, 129.9, 127.8, 126.3, 119.9, 118.6, 118.4, 110.9, 109.1, 63.6, 44.3, 29.4, 10.4. IR (neat): 3434, 2250, 1661, 1056, 822, 759, cm^{-1}. HRMS (ESI, m/z) calcd for $C_{18}H_{19}NOCl$ (M + H)$^+$ 300.1155, found 300.1147.

Synthesis of 31. A 1 mL reaction vessel equipped with a stir bar charged with **6** (29.3 mg, 0.0688 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **7** (200 mg, 1.37 mmol), CH_2Cl_2 (66 μL), and **24** (137 mgs, 0.688 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 77 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.3) yielded **31** (218 mg, 92%) as a pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.42−7.44 (d, 2H, J = 8.0 Hz), 7.30−7.35 (m, 4H), 6.99−7.03 (app t, 1H, J = 7.5 Hz), 6.86−6.89 (app t, 1H, J = 7.5 Hz), 4.80−4.83 (m, 1H), 4.30−4.34 (m, 1H), 4.21−4.27 (m, 1H), 3.92−3.97 (m, 1H), 3.64 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 143.0, 136.3, 133.9, 130.7, 130.4, 126.3, 119.9, 118.6, 118.5, 118.4, 110.8, 109.1, 63.6, 44.3, 29.4, 10.4. IR (neat): 3435, 2251, 2125, 1661, 1055, 822, 760 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{18}H_{18}NONaBr$ (M + Na)$^+$ 366.0469, found 366.0461.

Synthesis of 34. A 1 mL reaction vessel equipped with a stir bar charged with **6** (33.3 mg, 0.0782 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **32** (200 μL, 1.56 mmol), CH_2Cl_2 (424 μL), and **24** (155.7 mg, 0.782 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 7.8 days. Column chromatography of the reaction mixture (3:1 hexane/ethyl acetate, R_f 0.5) yielded **34** (235 mg, 91%) as a white solid, mp 141−143 °C. ^{1}H NMR ($CDCl_3$) δ 7.43−7.45 (m, 3H), 7.32−7.34 (d, 1H, J = 8.3 Hz), 7.23−7.26 (m, 3H), 7.06−7.09 (app. t, 1H, J = 6.8 Hz), 6.97 (s, 1H), 4.45−4.47 (app. t, 1H, J = 6.8 Hz), 4.23−4.26 (dd, 1H, J = 6.7, 10.9 Hz), 4.15−4.18 (dd, 1H, J = 6.8, 10.9 Hz), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 141.0, 137.3, 131.6, 130.0, 127.2, 126.7, 122.0, 120.5, 119.3, 119.2, 113.9, 109.4, 66.2, 45.0, 32.8. IR (Nujol): 3302, 2923, 1377, 1053, 1007, 731 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{17}H_{17}NOBr$ (M + H)$^+$ 330.0494, found 330.0495.

Synthesis of 35. A 1 mL reaction vessel equipped with a stir bar charged with **6** (32.5 mg, 0.0762 mmol) and 5 Å molecular sieves (40 mg) was fitted with a septum and placed under an atmosphere of Ar (balloon). Compound **33** (200 mg, 1.52 mmol), CH_2Cl_2 (261 μL), and **24** (151.7 mg, 0.762 mmol) were then added, the septum was replaced with a cap, and the resulting solution was stirred at ambient temperature for 7.2 days. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.5) yielded **35** (221 mg, 89%) as a yellow wax. ^{1}H NMR (DMSO-d_6) δ 10.80 (br s, 1H), 7.42−7.44 (d, 2H, J = 8.5 Hz), 7.28−7.31 (m, 3H), 7.20−7.22 (d, 1H, J = 8.0 Hz), 6.91−6.95 (app t, 1H, J = 7.5 Hz), 6.80−6.84 (app t, 1H, J = 7.5 Hz), 4.78−4.81 (app t, 1H, J = 5.0 Hz), 4.17−4.28 (m, 2H), 3.91−3.96 (m, 1H), 2.34 (s, 3H). ^{13}C NMR (DMSO-d_6) δ: 143.2, 135.2, 132.2, 130.7, 130.4, 127.3, 119.8, 118.5, 118.4, 118.2, 110.7, 110.5, 63.6, 44.2, 12.0. IR (neat): 3399, 3325, 2926,

1618, 1487, 1010, 740 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{17}NOBr$ $(M + H)^+$ 330.0494, found 330.0498.

Synthesis of 41. Prepared as per procedure A using **6** (37.4 mg, 0.087 mmol), **36** (80 μL, 0.877 mmol), CH_2Cl_2 (240 μL), and **4** (100 μL, 0.877 mmol). The reaction was stirred for 91 h. Column chromatography of the reaction mixture (1:1 CH_2Cl_2/hexane, R_f 0.5) yielded **41** (161 mg, 86%) as a pale brown wax. ^{1}H NMR ($CDCl_3$) δ 7.35−7.41 (m, 4H), 7.29−7.31 (m, 1H), 7.11−7.15 (app t, 2H, J = 7.8 Hz), 6.70−6.73 (app t, 1H, J = 7.5 Hz), 6.60−6.61 (d, 2H, J = 9.0 Hz), 4.53−4.56 (dd, 1H, J = 4.5, 7.0 Hz), 3.97−4.00 (dd, 1H, J = 4.0, 11.0 Hz), 3.78−3.82 (dd, 1H, J = 7.0, 11.0 Hz), 3.52 (s, 1H), 1.55 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 146.7, 139.6, 128.7, 128.4, 127.2, 126.3, 117.5, 113.4, 67.0, 59.4. NMR spectral data are consistent with that in the literature.[37] IR (neat): 3399, 3025, 2874, 1599, 1501, 1316, 1066, 697 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{16}NO$ $(M + H)^+$ 214.1232, found 214.1227.

Synthesis of 42: Major Isomer (Table 6). Prepared as per procedure A using **6** (37.4 mg, 0.087 mmol), **37** (95 μL, 0.877 mmol), CH_2Cl_2 (225 μL), and **4** (100 μL, 0.877 mmol). The reaction was stirred for 91 h. Column chromatography of the reaction mixture (1:1 CH_2Cl_2/hexane, R_f 0.4) yielded **42** (177 mg, 78%) as a pale yellow viscous oil. ^{1}H NMR ($CDCl_3$) δ 7.28−7.31 (m, 5H), 7.15−7.17 (d, 2H, J = 8.8 Hz), 6.96−6.98 (d, 2H, J = 8.0 Hz), 6.83−6.87 (app t, 1H, J = 7.3 Hz), 5.10−5.14 (dd, 1H, J = 6.0, 9.0 Hz), 4.12−4.20 (m, 2H), 2.73 (s, 3H), 2.13 (br s, 1H). NMR spectral data are consistent with that in the literature.[38] ^{13}C NMR ($CDCl_3$) δ: 151.0, 137.3, 129.1, 128.4, 127.5, 127.0, 118.3, 114.7, 64.5, 61.5, 31.9. IR (neat): 3383, 2884, 1597, 1503, 1030, 746, 695 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{18}NO$ $(M + H)^+$ 228.1388, found 228.1387.

Synthesis of 42: Minor Isomer. Prepared as per procedure A using **6** (37.4 mg, 0.087 mmol), **37** (95 μL, 0.877 mmol), CH_2Cl_2 (225 μL), and **4** (100 μL, 0.877 mmol). The reaction was stirred for 91 h. Column chromatography of the reaction mixture (1:1 CH_2Cl_2/hexane, R_f 0.3) yielded **42** (8 mg, 3%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.39−7.47 (m, 4H), 7.28−7.36 (m, 3H), 6.87−6.90 (d, 2H, J = 8.5 Hz), 6.79−6.83 (app t, 1H, J = 7.3 Hz), 5.02−5.05 (dd, 1H, J = 4.5, 9.0 Hz), 3.44−3.57 (m, 2H), 2.97 (s, 3H), 2.55 (br s, 1H). NMR spectral data are consistent with that in the literature.[42] ^{13}C NMR ($CDCl_3$) δ: 149.5, 141.5, 128.8, 128.1, 127.4, 125.5, 117.1, 112.8, 71.3, 61.6, 38.9. HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{18}NO$ $(M + H)^+$ 228.1388, found 228.1379.

Synthesis of 43. Prepared as per procedure A using **6** (37.4 mg, 0.0877 mmol), **38** (93 μL, 0.877 mmol), CH_2Cl_2 (386 μL), and **4** (100 μL, 0.877 mmol). The reaction was stirred for 90 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.5) yielded **43** (183 mg, 99%) as a pale gray−green solid, mp 81−83 °C. ^{1}H NMR ($CDCl_3$) δ 7.35−7.7.42 (m, 4H), 7.28−7.32 (m, 1H), 7.10−7.12 (d, 1H, J = 7.0 Hz), 6.97−7.01 (app t, 1H, J = 8.7 Hz), 6.66−6.70 (app t, 1H, J = 7.6 Hz), 6.41−6.42 (d, 1H, J = 7.6 Hz), 4.57−4.59 (dd, 1H, J = 4.0, 7.0 Hz), 4.4 (br s, 1H), 3.99−4.03 (dd, 1H, J = 4.0, 11.0 Hz), 3.81−3.85 (dd, 1H, J = 7.0, 11.0 Hz), 2.31 (s, 3H), 1.81 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 144.7, 139.7, 129.7, 128.4, 127.2, 126.5, 126.2, 122.1, 117.0, 111.0, 67.1, 59.3, 17.2. IR (Nujol): 3302, 2922, 1605, 1376, 1048, 747, 699 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{18}NO$ $(M + H)^+$ 228.1388, found 228.1384.

Synthesis of 44. Prepared as per procedure A using **6** (74.8 mg, 1.75 mmol), **39** (246 μL, 1.75 mmol), CH_2Cl_2 (93 μL), and **4** (100 μL, 0.877 mmol). The reaction was stirred for 147 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.5) yielded **44** (206 mg, 92%) as a pale yellow oil. ^{1}H NMR (DMSO-d_6) δ 7.32−7.34 (d, 2H, J = 7.0 Hz), 7.24−7.28 (app t, 2H, J = 7.5 Hz), 7.17−7.21 (app t, 1H, J = 7.0 Hz), 6.67 (s, 2H), 4.81−4.84 (app t, 1H, J = 5.0 Hz), 4.08 (s, 2H), 3.69 (m, 2H), 2.08 (m, 9H). ^{13}C NMR (DMSO-d_6) δ: 143.2, 142.9, 129.1, 128.9, 128.5, 127.8, 127.3, 126.5, 65.0, 63.0, 20.1, 18.7. IR (neat): 3368, 2920, 1484, 1026, 854, 700 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{17}H_{22}NO$ $(M + H)^+$ 256.1701, found 256.1691.

Synthesis of 45. Prepared as per procedure A using **6** (37.4 mg, 0.0877 mmol), **40** (283 μL, 1.75 mmol), CH_2Cl_2 (340 μL), and **4** (100 μL, 0.877 mmol). The reaction was stirred for 71 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.7) yielded **45** (207 mg, 84%) as a yellow solid, mp 79−81 °C. ^{1}H NMR ($CDCl_3$) δ 7.31−7.42 (m, 5H), 6.66 (s, 1H), 6.44 (s, 2H), 4.46−4.49 (app t, 1H, J = 5.0 Hz), 3.98−4.01 (dd, 1H, J = 4.0, 11.0 Hz), 3.79−3.83 (dd, 1H, J = 6.0, 11.0 Hz). ^{13}C NMR ($CDCl_3$) δ: 148.7, 138.7, 135.2, 128.9, 127.9, 126.4, 117.4, 111.8, 67.0, 59.3. IR (neat): 3431, 2930, 1593, 1451, 1316, 1069, 703 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{14}H_{14}NOCl_2$ $(M + H)^+$ 282.0452, found 282.0461.

Synthesis of 47. Prepared as per procedure A using **6** (86.9 mg, 0.20 mmol), **36** (186 μL, 2.04 mmol), CH_2Cl_2 (324 μL), and **46** (200 mg, 1.02 mmol). The reaction was stirred for 142 h at 30 °C. Column chromatography of the reaction mixture (1:1 CH_2Cl_2/hexane, R_f 0.1) yielded **47** (270 mg, 92%) as a pale pink solid, mp 126−127 °C (lit.[39] 122−124 °C). ^{1}H NMR ($CDCl_3$) δ 7.26−7.31 (m, 6H), 7.07−7.18 (m, 6H), 6.67−6.70 (app t, 1H, J = 7.3 Hz), 6.54−6.56 (d, 2H, J = 7.5 Hz), 5.09−5.10 (d, 1H, J = 6.8 Hz), 4.69−4.70 (d, 1H, J = 5.0 Hz), 4.49 (br s, 1H), 2.33 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 146.3, 139.5, 138.0, 128.7, 127.9, 127.8, 127.6, 127.5, 127.2, 126.1, 117.5, 113.5, 76.7, 63.2. NMR spectral data are consistent with that in the literature.[39] IR (Nujol): 3345, 3255, 1601, 1057, 752, 690, 624 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{20}H_{20}NO$ $(M + H)^+$ 290.1545, found 290.1552.

Synthesis of 49. Prepared as per procedure A using **6** (58.7 mg, 0.138 mmol), **48** (141 μL, 1.38 mmol), and **18** (103.3 mg, 0.69 mmol). The reaction was stirred for 20 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.6) yielded **49** (153 mg, 85%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.37−7.40 (m, 2H), 7.24−7.30 (m, 5H), 6.91−6.96 (m, 2H), 4.85−4.88 (app t, 1H, J = 6.5 Hz), 3.89−3.98 (m, 2H), 3.87 (s, 3H), 2.12 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 156.4, 134.2, 131.6, 128.4, 128.3, 127.9, 126.7, 126.6, 120.3, 110.4, 64.1, 55.2, 48.8. IR (neat): 3429, 2937, 1584, 1491, 1246, 1026, 739 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{15}H_{16}O_2NaS$ $(M + Na)^+$ 283.0769, found 283.0769.

Synthesis of 51. Prepared as per procedure A using **6** (58.7 mg, 0.138 mmol), **50** (143 μL, 1.38 mmol), and **19** (103.3 mg, 0.69 mmol). The reaction was stirred for 20 h. Column chromatography of the reaction mixture (CH_2Cl_2, R_f 0.2) yielded **51** (146 mg, 82%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.31−7.40 (m, 7H), 6.95−6.97 (d, 2H, J = 6.0 Hz), 4.55−4.57 (d, 1H, J = 11.5 Hz), 4.51−4.53 (dd, 1H, J = 4.0, 9.0 Hz), 4.34−4.36 (d, 1H, J = 11.5 Hz), 3.85 (s, 3H), 3.75−3.79 (dd, 1H, J = 9.0, 11.5 Hz), 3.62−3.65 (m, 1H), 2.31 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 159.6, 138.0, 130.4, 128.4, 128.3, 127.9, 127.8, 114.1, 81.7, 70.5, 67.4, 56.3. IR (neat): 3435, 2932, 1610, 1512, 1247, 1099, 1034, 832, 698 cm^{-1}. HRMS (ESI, *m*/*z*) calcd for $C_{16}H_{18}O_3Na$ $(M + Na)^+$ 281.1154, found 281.1160.

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Supporting Information Available: Complete reference for Gaussian 03, details of computational results (PDB files of final optimized complexes), general experimental details, and ^{1}H and ^{13}C NMR spectra of catalyst **6** and all adducts prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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