JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

A Dual-Catalysis Anion-Binding Approach to the Kinetic Resolution of Amines: Insights into the Mechanism via a Combined Experimental and Computational Study

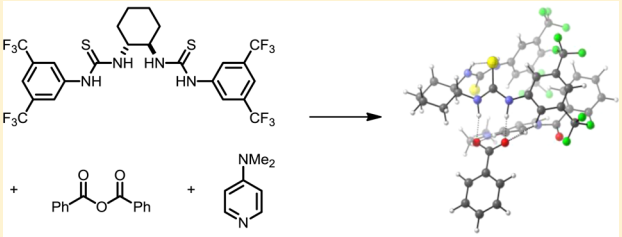
Nisha Mittal,[‡] Katharina M. Lippert,[#] Chandra Kanta De,[‡] Eric G. Klauber,[‡] Thomas J. Emge,[‡] Peter R. Schreiner,*[,#] and Daniel Seidel*[,‡]

[‡]Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States

[#]Institute of Organic Chemistry, Justus-Liebig University, Heinrich-Buff-Ring 58, 35392 Giessen, Germany

Supporting Information

ABSTRACT: Racemic benzylic amines undergo kinetic resolution via benzoylation with benzoic anhydride in the presence of a dual catalyst system consisting of a readily available amide-thiourea catalyst and 4-dimethylaminopyridine (DMAP). An evaluation of various experimental parameters was performed in order to derive a more detailed understanding of what renders this process selective. The catalyst's aggregation behavior and anion-binding ability were evaluated in regard to their relevance for the catalytic process. Alternate scenarios, such as catalyst deprotonation or the in situ formation of a neutral chiral acylating reagent were ruled out. Detailed computational studies at the M06/6-31G(d,p) level of theory including solvent modeling utilizing a polarized continuum model provide additional insights into the nature of the ion pair and reveal a range of important secondary interactions that are responsible for efficient enantiodiscrimination.

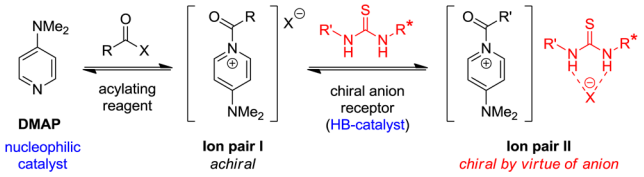


INTRODUCTION

Enantiopure amines are important building blocks with a plethora of applications.[1] While enantioselective methods for the synthesis of chiral amines continue to be developed at a rapid pace,[1] the classic separation of racemic amines via their diastereomeric salts remains a frequently used approach, especially in large scale preparations.[2] Although often highly reliable, a disadvantage of this strategy is that it requires the use of stoichiometric amounts of chiral acids as resolving reagents.[2,3] An attractive alternative is the use of chiral catalysts that facilitate the kinetic resolution of racemic amines via acylation and other methods.[4] In contrast to their enzymatic counterparts,[4y,5] the kinetic resolution of racemic amines via small-molecule-based approaches has remained challenging. Solutions to this problem have started to appear only recently and still lag behind the advances that have been achieved in the corresponding kinetic resolutions of alcohols.[4,6] This is at least in part due the inherent nucleophilicity of amines and their resulting propensity to react with common acylating reagents without the need for intervention by a catalyst.

We have recently reported a new concept for asymmetric nucleophilic catalysis and demonstrated its applicability in the kinetic resolution of various classes of amines,[7] the desymmetrization of *meso*-diamines,[8] and other asymmetric acyl-transfer reactions.[9] As outlined in Scheme 1, a chiral acylating reagent is generated in situ via the interplay of three components: 4-dimethylaminopyridine (DMAP),[10] an achiral acylating reagent,

Scheme 1. Anion-Binding Concept for Asymmetric Acyl Transfer

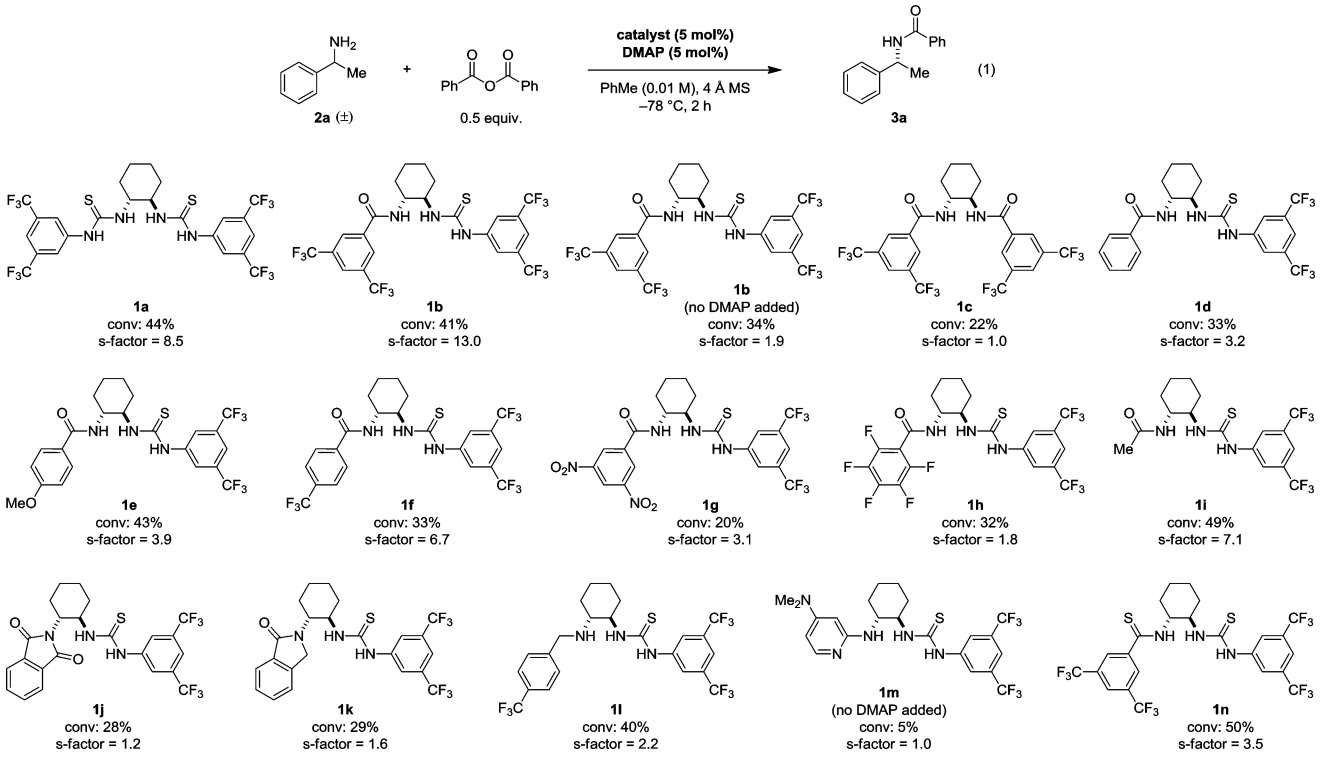


and a chiral anion receptor/hydrogen bonding (HB) catalyst.[11−13] Mixtures of DMAP and various acylating reagents are known to exist in equilibrium with their corresponding acylpyridinium salts (e.g., ion pair I).[14] These acylpyridinium salts are rendered chiral upon interaction of the counteranion with a chiral anion receptor such as a thiourea catalyst to form ion pair II.[15,16] Furthermore, the chiral anion receptor is thought to impact the equilibrium between DMAP and its acylpyridinium salt. Ion pair II is expected to be more electrophilic and/or soluble than ion pair I. Consequently, reactions with substrates such as amines should more readily occur with ion pair II than with ion pair I. While the applicability of this concept to the kinetic resolution of amines has been demonstrated as mentioned above, questions remain as to the exact nature of ion pair II and the role of all reaction

Received: January 7, 2015
Published: April 14, 2015

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

Scheme 2. Evaluation of Catalysts in the Kinetic Resolution of a Benzylic Amine



components in the enantiodetermining step of the reaction. In fact, it has thus far remained unclear whether a species corresponding to ion pair II is actually involved in the catalytic process. Here we report the results of experiments and computations that shed light on these questions.

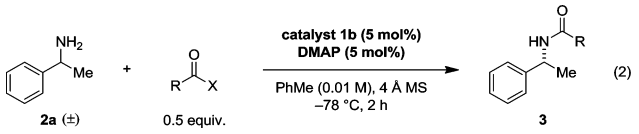
RESULTS AND DISCUSSION

Evaluation of Catalysts. In our original study on the kinetic resolution of benzylic amines via benzoylation, the Nagasawa bis-thiourea **1a**,[17] used in combination with DMAP, was identified as an effective catalyst system.[7a] Catalyst loadings of 20 mol % of each, **1a** and DMAP, provided a selectivity factor (s-factor) of 10 for the benzoylation of racemic 1-phenylethanamine (not shown).[18] To determine which structural catalyst components are important for efficient catalysis, a range of potential catalysts was tested in the resolution of 1-phenylethanamine **2a** (Scheme 2). To amplify potentially subtle differences between the catalysts, reactions were performed at a 5 mol % catalyst loading, using 0.5 equiv of benzoic anhydride as the acylating reagent (50% maximum conversion). All reactions were conducted in the presence of 4 Å molecular sieves at −78 °C in toluene (0.01 M concentration) and quenched after 2 h. Under these conditions, **1a** provided an s-factor of 8.5 (44% conversion). Amide-thiourea catalyst **1b** displayed improved performance (s-factor = 13 at 41% conversion). Importantly, the presence of DMAP was found to be crucial. Although **1b** displayed catalytic activity in the absence of DMAP, a significantly reduced s-factor of 1.9 resulted. A 3,5-bis(trifluoromethyl)phenyl thiourea moiety was found to be a crucial component of any catalyst.[19] For instance, structurally related diamide **1c** was completely ineffective. A comparison of catalysts **1d**−**f** illustrates that the presence of substituents (in particular electron withdrawing groups) on the para-position of the aryl-amide ring is preferable to an unsubstituted phenyl ring. While compound **1g** contains the most electron-deficient aryl ring studied, the low solubility of this species likely accounts for its poor performance. Interestingly, simple acetamide **1i** performed relatively better than most of the aryl-amide catalysts. The presence of a free amide NH-proton was found to be essential, as replacement for an imide or an *N*-alkyl amide led to inferior performance (cf., **1d**, **1j**, and **1k**). Similarly, replacement of amide for the corresponding amine led to a significant drop in catalyst efficiency (cf., **1f** and **1l**). Catalyst **1m**, containing both thiourea and DMAP moieties, was essentially inactive. Thioamide-thiourea **1n** was considered to be a promising candidate for improved catalysis due to its more acidic NH-proton. However, **1n** was found to be inferior to catalyst **1b**. This implies an important role for the amide-carbonyl group which may be involved in secondary interactions.

Impact of the Acylating Reagent. An evaluation of various acylating reagents as summarized in Table 1 provides compelling support for the intermediacy of a type II ion pair (Scheme 1). Benzoylation with benzoyl fluoride, chloride, or bromide showed a clear trend favoring the smallest halide while establishing a strong counteranion effect (Table 1, entries 1−3). However, these results were inferior to those of benzoic anhydride (entry 4). Substituted benzoic anhydrides, without exception, provided poorer results without showing a discernible trend with regard to electronics (entries 5−9). Acetyl chloride and acetic anhydride were also tested (entries 10, 11). Although acetic anhydride performed relatively better, both were inferior to benzoic anhydride. Consistent with the better leaving group ability of benzoate vs acetate, acylation with the mixed acetic benzoic anhydride provided exclusively acetylated product **3g** (eq 3). The s-factor was substantially lower than in the case of benzoic anhydride (6.8 vs 13). In agreement with the computational results (vide infra), this observation illustrates not only the importance of the

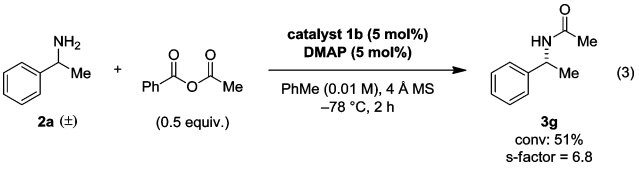
DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

Table 1. Evaluation of Different Acylating Reagents[a]



entry	acylating reagent	product	conversion (%)	s-factor
1	PhCOF	**3a**	34	3.1
2	PhCOCl	**3a**	50	2.4
3	PhCOBr	**3a**	39	1.0
4	$(PhCO)_2O$	**3a**	41	13
5	$(4\text{-}CF_3\text{–}PhCO)_2O$	**3b**	47	7.5
6	$(4\text{-Br-}PhCO)_2O$	**3c**	24	1.2
7	$(4\text{-F-}PhCO)_2O$	**3d**	50	12.9
8	$(4\text{-Me-}PhCO)_2O$	**3e**	38	12.8
9	$(4\text{-MeO-}PhCO)_2O$	**3f**	3.6	4.8
10	MeCOCl	**3g**	43	1.4
11	$(MeCO)_2O$	**3g**	43	6.7

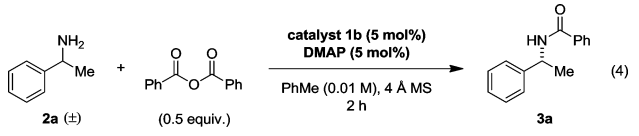
[a]Reactions were performed on a 0.2 mmol scale. The s-factors were determined by HPLC analysis; see Supporting Information for details.



counteranion but also the nature of the substituent on the acylpyridinium cation.

Impact of the Reaction Temperature. To exclude the possibility of unusual temperature dependence, the title reaction was conducted at various temperatures (Table 2). As anticipated, lower s-factors were obtained upon increasing the reaction temperature from the optimal −78 to −40 °C.

Table 2. Evaluation of Reaction Temperature[a]

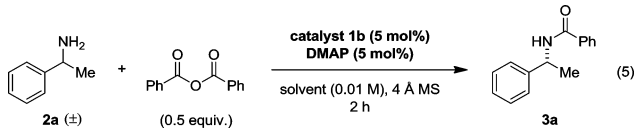


entry	temperature (°C)	conversion (%)	s-factor
1	−78	41	13
2	−60	50	10
3	−40	50	7.5

[a]See footnote in Table 1.

Impact of the Reaction Medium. Toluene appears to hold a privileged place in catalytic enantioselective reactions that proceed via catalyst–substrate ion pairing.[15,4m] This is consistent with the notion that the nature of an ion pair strongly depends on the reaction medium, with nonpolar solvents favoring tight (contact) ion pairs whereas more polar solvents result in solvent-shared or solvent-separated ion pairs.[15i] Different solvents were evaluated as part of the present study (Table 3). A reaction performed in hexanes resulted in poor conversion and no measurable degree of selectivity (entry 2). This is likely attributable to the poor solubility of catalyst **1b** in hexanes, and the increased tendency toward self-association of polar substrates such as **1b** in nonpolar solvents. In an effort to restore catalyst solubility and still reduce the dielectric

Table 3. Evaluation of Solvent[a]



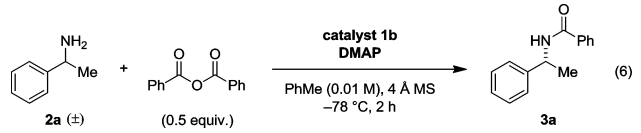
entry	solvent	conversion (%)	s-factor
1	toluene	41	13
2	hexanes	17	1.0
3	toluene/hexanes (1:1)	50	12
4	mesitylene/hexanes (1:1)	42	5.6
5	EtOAc	19	1.5
6	MTBE	38	1.4

[a]See footnote in Table 1.

constant of the reaction medium, a 1:1 mixture of toluene and hexanes was evaluated. The outcome was nearly identical to that in neat toluene (entry 3). A 1:1 mixture of toluene and mesitylene resulted in a markedly reduced s-factor (entry 4). Neat mesitylene could not be evaluated due to its melting point of −44.8 °C. As anticipated, the more polar solvents ethyl acetate (EtOAc, entry 5) and methyl *tert*-butyl ether (MTBE, entry 6) provided inferior results.

Impact of the Catalyst Loading. Upon studying the effect of catalyst loading on the resolution of **2a** (Table 4), we made

Table 4. Evaluation of Catalyst Loading[a]



entry	**1b** (mol %)	DMAP (mol %)	time (h)	conversion (%)	s-factor
1	10	10	2	50	8.6
2	5	5	2	41	13
3	2	2	4	48	8.6
4	1	1	4	43	5.1

[a]See footnote in Table 1.

the intriguing discovery that a reduction in catalyst loading from 10 to 5 mol % led to an improvement in s-factor from 8.6 to 13 (entries 1 and 2). While such a phenomenon is not without precedent,[20] it is quite rare to achieve improved selectivities upon reduction of the catalyst loading. Interestingly, a catalyst loading of 2 mol % provided a nearly identical result to that obtained with 10 mol % (compare entries 1 and 3). A catalyst loading of 1 mol % led to a further drop in selectivity although an appreciable level of selectivity was maintained (entry 4). The trend in going from 5 over 2 to 1 mol % of catalyst loading is readily rationalized by an increasingly competitive background reaction. On the other hand, the reduction in s-factor at higher catalyst loadings is consistent with catalyst aggregation[20b,21] (vide infra).

Catalyst Aggregation Behavior. Two sets of single crystals of catalyst **1b** suitable for X-ray crystallography could be obtained. The first solid-state structure of **1b** is depicted in Figure 1 (crystals obtained by diffusion of hexanes into a dichloromethane solution of **1b**) and is characterized by a chain-type aggregation with multiple intra- and intermolecular H-bonding interactions.

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748–5758

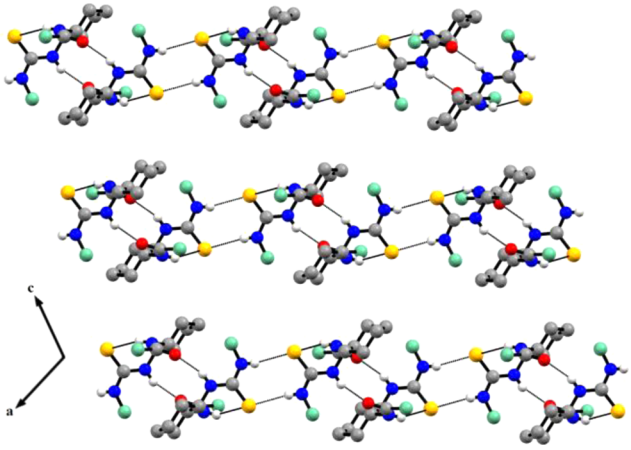


Figure 1. Aggregation scheme in the crystal structure of **1b**, characterized by a 1D array of molecules arranged in the crystallographic *ac* plane. The **1b** molecules are oriented left−right across the page and engage in two distinct and alternating H-bonding motifs across the page: (A) pairwise NH···O H-bonding interactions to form a dimer, (B) pairwise NH···S H-bonding interactions to bridge adjacent dimers. The HNCNH group is in the exo conformation and allows one intramolecular NH···S interaction. The van der Waals, vdW, radii used are 1.80, 1.52, and 1.2 Å for S (yellow), O (red), and H (white), respectively. The C atoms are gray and the N atoms are blue. For clarity, the H atoms of the cyclohexyl ring are omitted and the 3,5-bis(trifluoromethyl)phenyl group is depicted by a green ball.

The solid-state structure of **1b** as depicted in Figure 2 is markedly different (crystals obtained in the presence of ethyl acetate) in that it contains two slightly different catalyst dimers. Catalyst dimerization occurs via bifurcated hydrogen bonding of both thiourea NH-protons with the amide carbonyl group of a second molecule. Two such interactions are present in each dimer. In one type of dimer, the NH-protons of the amide are engaged in NH···S H-bonding interaction with thioureas from neighboring dimers. The NH-protons of the amide of the second dimer are involved in NH···O H-bonding interactions with ethyl acetate.

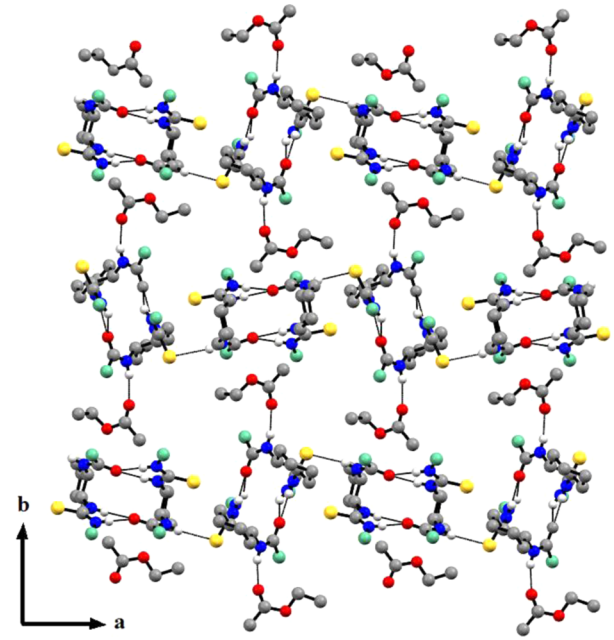


Figure 2. Aggregation scheme in the crystal structure of **1b**·EtOAc, characterized by a 1D array of molecules arranged in the crystallographic ab plane. The vdW radii and atom and 3,5-bis-(trifluoromethyl)phenyl group representations are as in Figure 1

To determine whether catalyst aggregation also occurs in solution,[22] ^{1}H NMR spectra of **1b** were recorded at varying concentrations. This study was initially conducted in $CDCl_3$. Due to the low solubility of **1b**, 0.04 M was the highest possible concentration at which spectra could be recorded. Figure 3

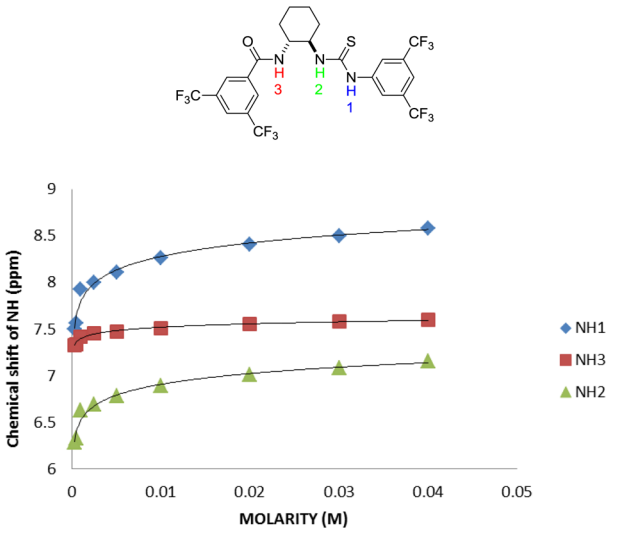


Figure 3. Graphical representation of chemical shift dependence of NH-protons of catalyst **1b** in $CDCl_3$. A more limited dilution study of catalyst **1b** was also performed in toluene, the solvent used in the reaction. Here the signal corresponding to the NH1-proton was not readily observable.[23]

shows the dependence of the concentration on the chemical shift of the three different types of NH-protons. Upon decreasing the concentration of **1b**, the NH1 and NH2 thiourea protons experience a significant upfield shift. An upfield shift is also observed for the NH3 proton, albeit to a much lesser extent. These observations are consistent with aggregation via H-bonding at higher concentrations, and a significant degree of deaggregation at lower concentrations.[19] Interestingly, the NH3 proton does not appear to be involved directly (via HB) in the aggregation process which points to isolated catalyst dimers (cf., dimers in Figure 2).

With regard to the aggregation behavior of the Nagasawa catalyst (**1a**), Eckert-Maksić, Friščić, and co-workers have previously obtained an X-ray crystal structure of **1a**·2(*i*-PrOH).[24] For comparison purposes, this structure is shown in Figure 4. Its main characteristic is the presence of bifurcated H bonds of both thiourea NH-protons with the thiourea sulfur atom of a neighboring bisthiourea molecule.

We also studied the aggregation behavior of **1a** by ^{1}H NMR (Figure 5). Due to partial overlap of NH-signals with aromatic protons in deuterated toluene, C_6D_6 was selected for this study. Similar to what was seen for **1b**, both types of thiourea protons of **1a** experience an upfield shift upon lowering of the solvent molarity. The magnitude of this shift was found to be roughly equal for NH1 and NH2 and is consistent with the type of aggregation observed in the solid state (cf., Figure 4). The corresponding study in $CDCl_3$ provided a similar result.[23] Importantly, these studies indicate that the catalysts should exist largely in their nonaggregated forms at the concentrations

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

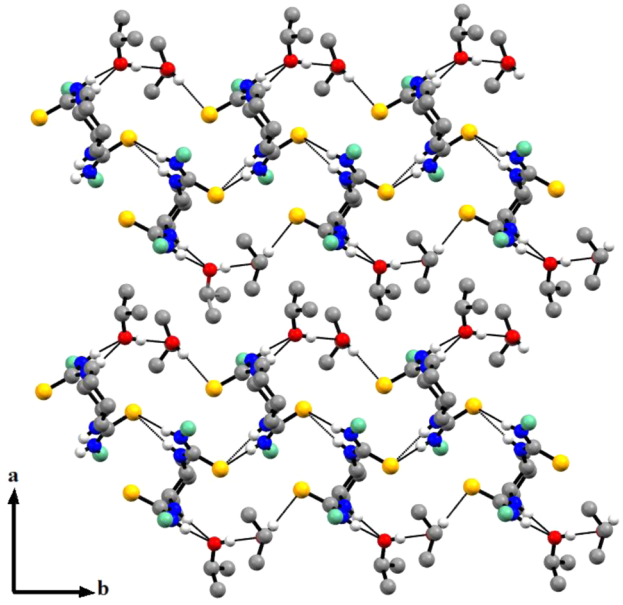


Figure 4. Aggregation scheme in the crystal structure of **1a**·2(*i*-PrOH),[24] characterized by a 1D array of molecules arranged along the crystallographic *b* axis with adjacent **1a** molecules oriented in a head-up/head-down fashion, so that both S atoms can accept H-bonds: one from one HNCNH group of an adjacent molecule of **1a**, and one from the first *i*-PrOH solvate. The other HNCNH group of the molecule terminates connectivity through H-bonding to the second unique *i*-PrOH solvate. Because of the involvement of two unique *i*-PrOH molecules, the overall motif is that of a 1D polymeric array. The vdW radii and atom and 3,5-bis(trifluoromethyl)phenyl group representations are as in Figure 1

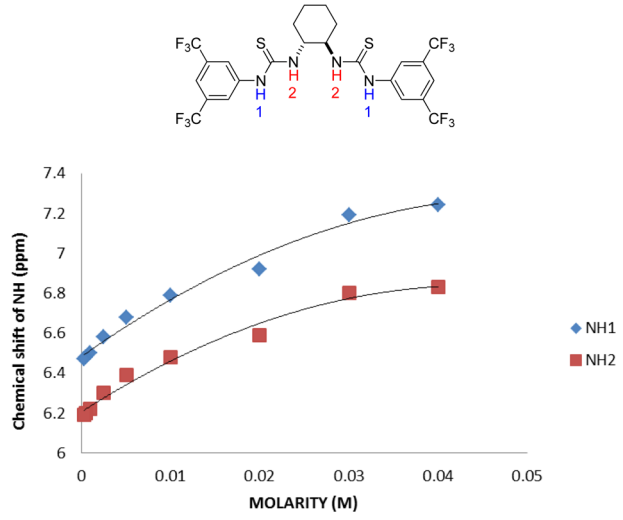


Figure 5. Graphical representation of chemical shift dependence of NH-protons of catalyst **1a** in C_6D_6.

relevant for catalysis. It should be noted that in a related study by Miller et al. on the kinetic resolution of alcohols with a peptide catalyst, poorer catalyst performance at higher than optimal concentrations was attributed in part to catalyst aggregation.[25]

Catalyst Anion Binding. Numerous attempts were undertaken to cocrystallize catalysts **1a** and **1b** with various carboxylate or acylpyridinium salts in order to obtain insights into how these species interact.[26] While these efforts met with limited success, X-ray quality crystals were obtained from a solution containing **1a**, triethylamine, and benzoic acid in a 1:1:1 ratio. The resulting X-ray crystal structure is shown in Figure 6.

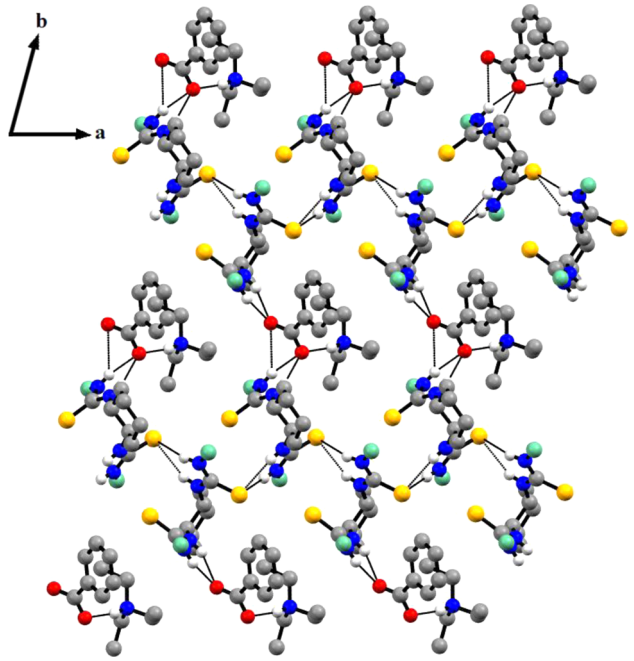


Figure 6. Aggregation scheme in the crystal structure of the triethylammonium benzoate cocrystal of $(\mathbf{1a})_2$·$(HNEt_3^+PhCO_2^-)$, characterized by a 2D array of molecules arranged in the crystallographic *ab* plane. The **1a** molecules are oriented up−down across the page and engage in HNCNH···S H-bonding as in the bis-2-propanol solvate of **1a** (Figure 4). Contrasting the motif in Figure 4: (A) the two O atoms of the benzoate ion act as acceptors for three H-bonds each, bridging one linear array of **1a** molecules to the adjacent ones in the *b* axis direction, and (B) one of the two S atoms per **1a** molecule does not engage in H-bonding. The vdW radii and atom and 3,5-bis(trifluoromethyl)phenyl group representations are as in Figure 1.

Catalyst/anion interactions were also studied in solution and monitored by ^{1}H NMR. The results of the titration of **1b** with tetrabutylammonium benzoate (TBAB) are shown in Figure 7. A substantial shift was seen for all three NH-signals upon increasing the mole fraction of benzoate. However, the NH-signals of the thiourea functionality (NH1 and NH2) experienced a more substantial downfield shift than that of NH3. This is consistent with the results obtained from the computational analysis (vide infra), which suggest intramolecular hydrogen bonding of NH3 to the thiourea sulfur atom, but no direct involvement of NH3 in anion binding. The data indicate 1:1 binding of the catalyst to the benzoate anion based on the observation that the chemical shifts for all three NH's remains nearly constant upon reaching a mole ratio of one. A 1:1 binding stoichiometry was confirmed via a UV−vis titration and Job plot analysis.[23] A related study with tetrabutylammonium acetate provided qualitatively similar results.[23]

Catalyst Deprotonation Study. In light of recent thiourea deprotonation studies,[27] it appeared plausible that different types of ion pairs could play a role in the resolution process (Scheme 3). Given the presence of relatively basic substrates, deprotonation of the proposed ion pair **4** could result in alternate ion pair **5**. To determine the likelihood of **5** being

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

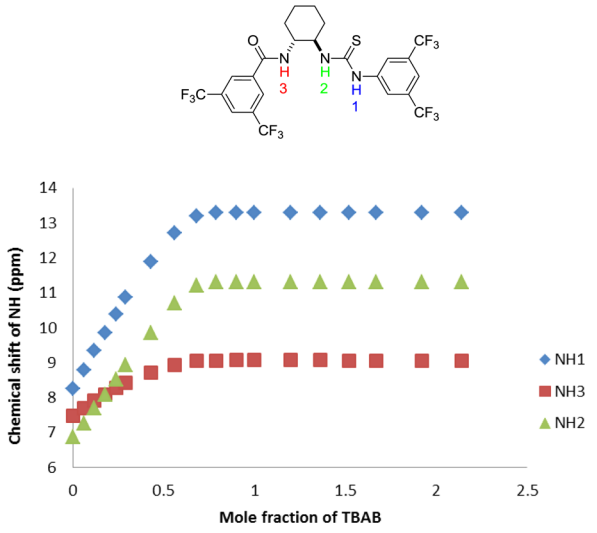
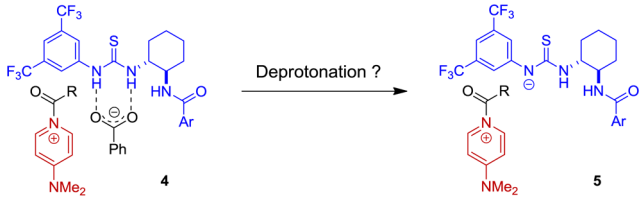


Figure 7. Graphical representation of chemical shift dependence of NH-protons on the mole ratio of TBAB/**1b** in $CDCl_3$.

Scheme 3. Different Ion Pairs of Potential Relevance

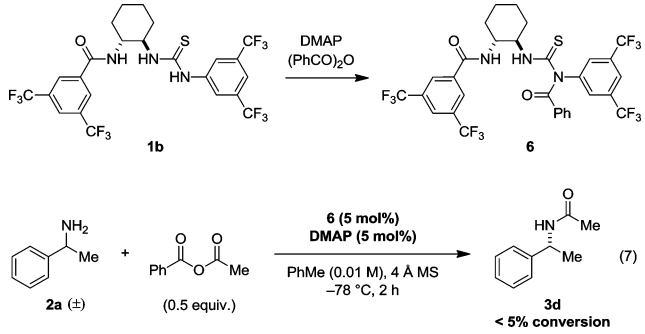


involved in the catalytic process, **1b** was exposed to a number of different bases, including triethylamine, DMAP, Hünig's base, and 1-phenylethanamine. While in some cases the apparent disappearance of one of the thiourea NH-signals in the ^{1}H NMR was noted, virtually no change was observed in the corresponding ^{13}C and ^{19}F NMR spectra. Since significant changes in the ^{13}C NMR were observed upon deprotonation of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea,[27] we conclude that the observed changes in the ^{1}H NMR spectra are due to hydrogen bonding and/or a fast exchange process.

When the stronger base BEMP was added to a solution of **1b** in deuterated toluene, a significant change in the ^{13}C NMR spectrum was noted. Due to the poor solubility of **1b** in toluene, an identical experiment was performed in THF-d_8 (Figure 8). Again, significant spectral changes were observed, consistent with the deprotonation of the thiourea moiety. In particular, the downfield shift of C6 and the upfield shift of C9 support this notion. Considering that strongly basic conditions are required for the deprotonation of **1b** and that its pK_a value is approximately 17−18,[27b] we rule out the involvement of the conjugate base of **1b** in the catalytic process.

Acylation of the Catalyst. Upon studying potential interactions between catalyst **1b** with DMAP and benzoic anhydride, we observed the slow benzoylation of **1b** at room temperature to give **6** (Scheme 4). Since **6** could conceivably

Scheme 4. Acylation of 1b



act as a chiral acylating reagent, we decided to evaluate its potential role in the catalytic cycle. Thus, **6** was used in place of catalyst **1b** in the kinetic resolution of **2a** under standard conditions (eq 7). Less than five percent conversion was observed, which can be attributed to background reactivity. Consequently, neutral acylating reagents such as **6** appear to play no role in the catalytic cycle.

COMPUTATIONAL METHODS

We employed the M06 density functional[28] in conjunction with a double-ζ basis set [6-31G(d,p)], a level of theory which has proven to be quite suitable for the description of ion pairs and hydrogen binding interactions owing to the inclusion of medium-range correlation effects.[19] Interaction energies are not corrected for basis set superposition errors because this often leads to overcorrections.[29] All stationary structures were characterized by computing analytical second derivatives to define minima (number of imaginary frequencies = 0) on the respective potential energy hypersurface and to compute zero-

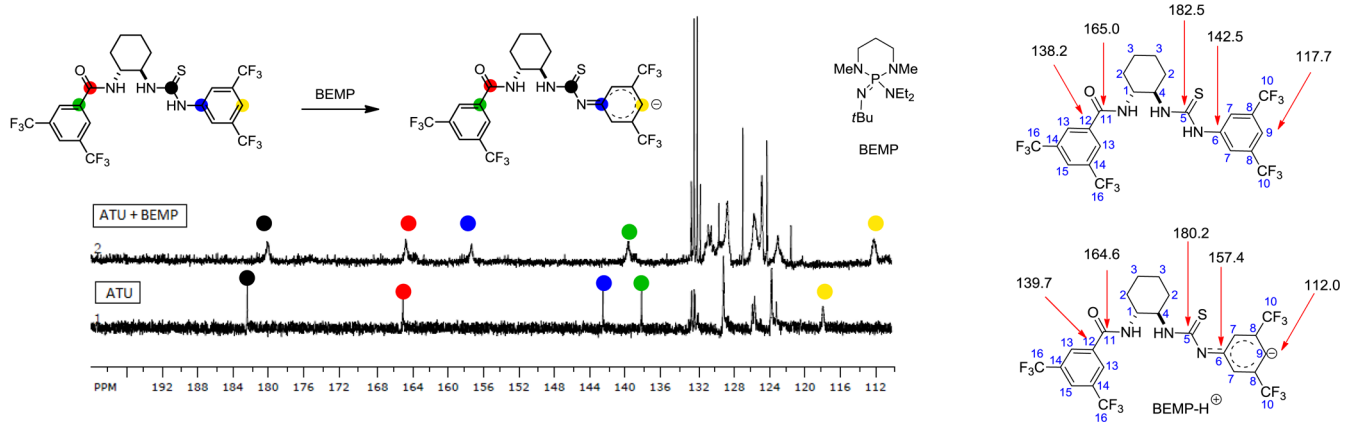


Figure 8. Changes in the ^{13}C NMR of **1b** in THF-d_8 upon addition of 2 equiv of BEMP.

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

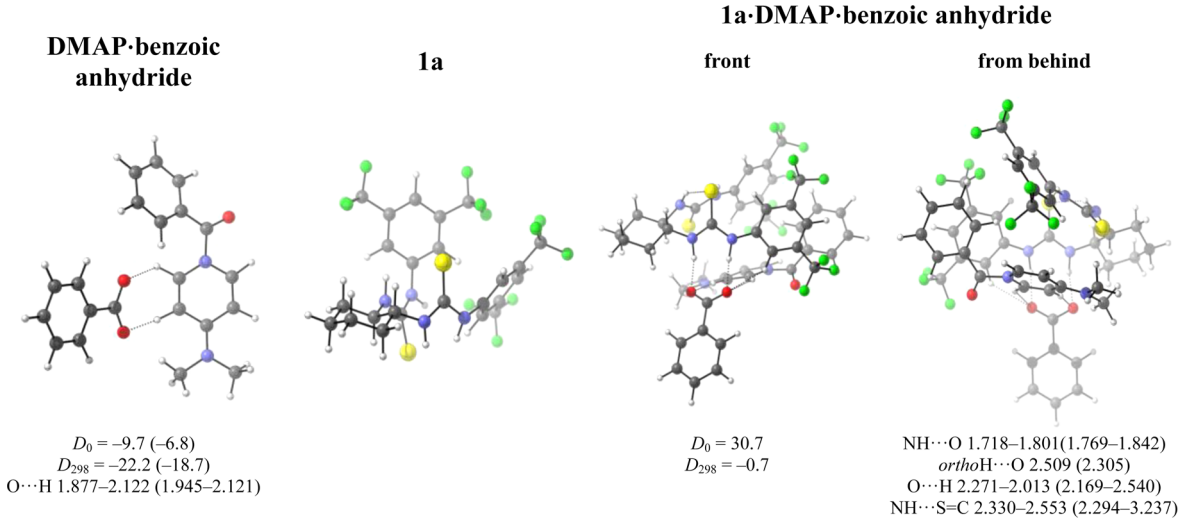


Figure 9. Overview of the lowest-lying complexes and conformers of **2** computed at the M06/6-31G(d,p) level of theory. Energies are given in kcal mol^{-1}; distances are given in Å. Values in parentheses were computed with the PCM model for toluene, employing UAHF radii.

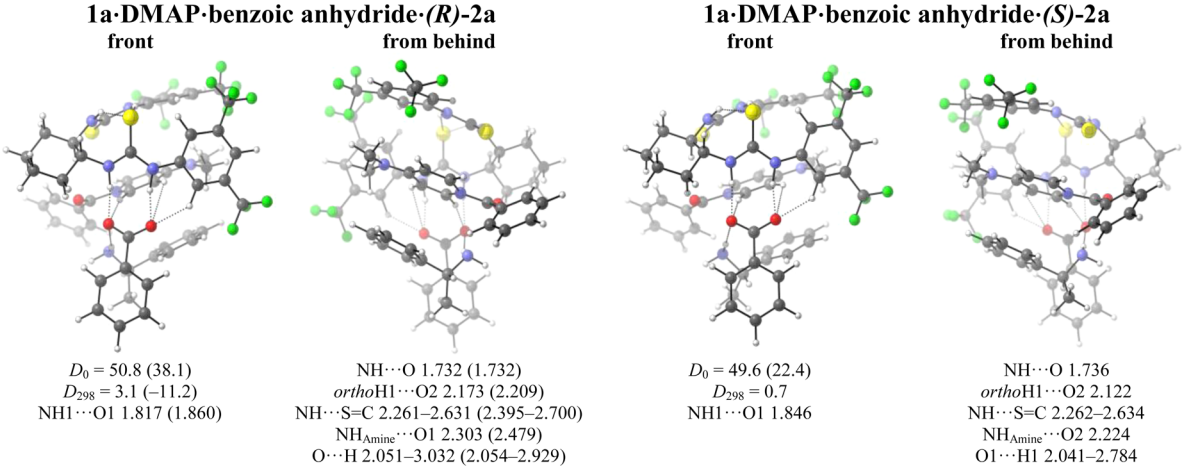


Figure 10. Overview of the lowest-lying quaternary complexes computed at the M06/6-31G(d,p) level. Energies are given in kcal mol^{-1}; distances are given in Å. Values in parentheses were computed with the PCM model for toluene, employing UAHF radii. Despite numerous attempts, the PCM computations did not converge for **1a**·DMAP·benzoic anhydride (*S*)-**2a**.

point vibrational energy (ZPVE) differences. Solvent effects were included using the polarized-continuum model (PCM) within the self-consistent reaction-field (SCRF) model by optimizing the stationary structures in a particular solvent, and frequency computations for the determination of solvent effects were also performed using the M06/6-31G(d,p) method using a self-consistent reaction-field (SCRF) model.[30] The PCM used the United Atom Topological (UAHF) Model applied on radii optimized at the HF/6-31G(d) level of theory.[30b,31] All ΔH_0 values are ZPVE-corrected. We utilized the Gaussian09 program package for all computations.[32] All structures were visualized with CYLview.[33]

Computations and Comparisons with 2D-NMR Experiments. We computed a large series of ion pair configurations for benzoic anhydride interacting with DMAP (Figure 9). The lowest-lying complex corresponds to a pyridinium salt with the benzoate and benzoyl rings on the pyridine's nitrogen on the same side. The dissociation energies of the complex are substantial and negative at rt as well as at 195 K. Thus, the formation of the DMAP salt with benzoic anhydride is likely to be unfavorable[14f] as also evident from the absence of NOE signals in toluene-d_8 at rt; however, this could also be due to long proton−proton distances and fast exchange. DOSY NMR-spectroscopy also did not reveal evidence of ion pair formation.[34]

The lowest-lying conformer of Nagasawa's catalyst **1a**[17a] (Figure 9) displays *Z*,*Z*- and *Z*,*E*-orientations of the NH-bonds of the two thiourea moieties. The preferred conformation in solution remains difficult to determine due to the inseparability of the NH and *o*-protons in the ^{1}H NMR-spectra. The lowest-lying ternary complex shows a clear preference for complex formation of the bis(thiourea) with the DMAP salt in **1a**·DMAP·benzoic anhydride (Figure 9): The *Z*,*Z*-oriented NH protons of one thiourea moiety coordinate through double hydrogen-bonding to the oxygen of benzoate. The acidified *o*-proton of the thiourea's aryl-ring also coordinates to oxygen,[19] while the second thiourea motif binds to the sulfur atom of the other thiourea moiety. Additionally, the oxygens coordinate to the phenyl protons of DMAP in ortho- and para-positions. The benzoyl group is stereochemically fixed through $\pi-\pi$ stacking with one of the thiourea aryl rings. The **1a**·DMAP·benzoic anhydride complex is favored at lower temperatures because of

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

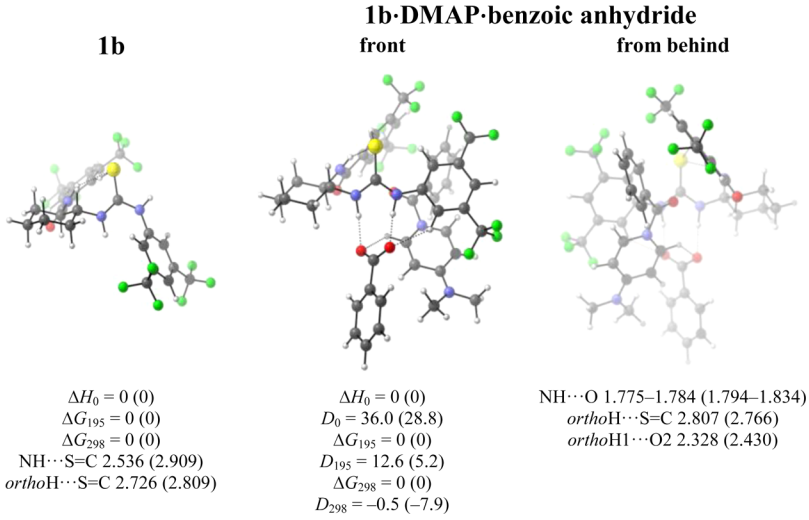


Figure 11. Conformer **1b** and the lowest-lying ternary complex of **1b**·DMAP·benzoic anhydride computed at the M06/6-31G(d,p) level. Energies are given in kcal mol^{-1}; distances are given in Å. Values in parentheses were computed with PCM model for toluene, employing UAHF radii.

a positive dissociation energy D_{195} = +10.4 kcal mol^{-1} (D_{195} = +3.6 kcal mol^{-1} in solution). The analysis of the 2D-NMR spectra of these ternary complexes was complicated by the appearance of new signals. A ^{1}H, ^{15}N HSQC spectrum (60.8 MHz) of complex **1a**·DMAP·benzoic anhydride (each compound c = 10 mM) in toluene-d_8 at 298 K) revealed no signals for the N−H bonds probably due to fast exchange.

Adding the (*R*)-configured amine (Figure 10), the lowest-lying quaternary complex **1a**·DMAP·benzoic anhydride (*R*)-**2a** displays *Z*,*Z*-oriented NH-protons; one thiourea moiety coordinates to benzoate through double hydrogen-bonding. The second thiourea function coordinates to the first thiourea moiety also through double hydrogen-bonding. At the same time, benzoate binds to the *o*- and *p*-protons of the pyridinium cation, which now prefers an orientation that is *opposite* to that of **1a**·DMAP·benzoic anhydride. The alternative orientation allows 3-fold $\pi-\pi$ stacking of one thiourea aryl, DMAP's pyridine, and the phenylethylamine ring. This quaternary complex structurally precedes the transfer of the benzoyl group in the transition state. The computations show that the quaternary complex is more favored at 195 K as at rt (D_{195} = 19.0 kcal mol^{-1} vs D_{298} = 3.1 kcal mol^{-1} in gas phase). With the (*S*)-configured amine, the quaternary complex is energetically *less* favorable.

In contrast to **1a**, catalyst **1b**, which bears a thiourea and an amide function, prefers both in the gas phase and in toluene an *E*,*Z*-orientation of the thiourea moiety (Figure 11). The lowest lying ternary complex **1b**·DMAP·benzoic anhydride contains a *Z*,*Z*-oriented thiourea moiety, which binds to the oxygens of benzoate with its acidified *o*-proton in a double hydrogen-bonding fashion (Figure 11). Simultaneously, the amide function binds through the NH-bond to the sulfur atom of the thiourea moiety. Benzoate coordinates with the oxygens to the *o*-proton of DMAP's pyridine ring, and the two aryl groups of the catalyst stereochemically fix DMAP and the benzoyl moiety. The dissociation energy is negative at rt but positive at 195 K (+12.6 kcal mol^{-1} in the gas phase and +5.2 kcal mol^{-1} in toluene).

The computations thus reveal that the quaternary complexes configured (*R*) in the amine, which are likely to precede the corresponding transition structures, are energetically favored, which is in excellent agreement with the experimental findings. Of course, it would be highly desirable to actually determine the transition structures for these reactions, but this is currently technically not possible owing to the enormous number of possible configurations of the various complexes, especially when considering their large number of rotational degrees.

■ CONCLUSIONS

Examination of multiple reaction parameters in the kinetic resolution of a benzylic amine via benzoylation has provided important insights into the mechanism of this transformation. The catalyst pair, consisting of a bis-thiourea (or an amide-thiourea) catalyst and DMAP, upon interaction with benzoic anhydride, forms a chiral ion pair that acts as the acyl-transfer reagent. A key feature of this ion pair is the binding of a catalyst thiourea subunit to the benzoate counteranion of the DMAP-derived *N*-benzoylpyridinium salt. This notion is corroborated by the demonstrated ability of the catalyst to bind benzoate in 1:1 fashion. The potential involvement of neutral chiral acylating reagents or alternative ion pairs (e.g., those resulting from deprotonation of the thiourea catalyst) were ruled out. Catalyst aggregation, as observed in the solid state and in solution, is responsible, at least in part, for the fact that reduced catalyst loadings provide better selectivities in some instances.

Computational investigations provided detailed insights into the nature of the chiral ion pairs. In addition, evaluation of the two diastereomeric quaternary complexes helped rationalize the experimental observation that the *R*-enantiomer of 1-phenylethanamine is benzoylated preferentially over the corresponding *S*-enantiomer. Interestingly, for both the bis-thiourea and the amide-thiourea catalyst, dual intramolecular hydrogen bonding to the sulfur atom of a thiourea subunit was found to activate this moiety for anion binding via acidification of the two N−H bonds. While the closely related intramolecular activation of a thiourea by another urea unit has already been exploited by others,[35] our results suggest that this mode of activation may be more prevalent than previously considered and could in fact become an important design element in the development of new organocatalysts.

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

■ ASSOCIATED CONTENT

Supporting Information

EExperimental procedures, characterization data, and CIF files. Cartesian coordinates, energies, and thermodynamic corrections for all calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*prs@org.chemie.uni-giessen.de.
*seidel@rutchem.rutgers.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under grant no. CHE-1300382 to D.S. D.S. is grateful to the Alexander-von-Humboldt-Foundation for a research fellowship for experienced researchers. We thank Mr. Chenfei Zhao (Rutgers University) for performing a number of experiments for Table 1.

■ REFERENCES

(1) Nugent, T. C., Ed. *Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH: Weinheim, 2010.

(2) See: (a) Ferreira, F. C.; Ghazali, N. F.; Cocchini, U.; Livingston, A. G. *Tetrahedron: Asymmetry* **2006**, *17*, 1337. (b) Synoradzki, L.; Bernas, U.; Ruskowski, P. *Org. Prep. Proced. Int.* **2008**, *40*, 165. (c) Tan, H.; Cui, S.; Gahm, K.; Luu, V.; Walker, S. D. *Org. Process Res. Dev.* **2010**, *15*, 53 and references cited therein.

(3) Selected examples of amine resolution with chiral acylating reagents: (a) Yokomatsu, T.; Arakawa, A.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 3506. (b) Kondo, K.; Kurosaki, T.; Murakami, Y. *Synlett* **1998**, 725. (c) Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119. (d) Maezaki, N.; Furusawa, A.; Uchida, S.; Tanaka, T. *Tetrahedron* **2001**, *57*, 9309. (e) Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 257. (f) Arseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3314. (g) Arseniyadis, S.; Subhash, P. V.; Valleix, A.; Mathew, S. P.; Blackmond, D. G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* **2005**, *127*, 6138. (h) Karnik, A. V.; Kamath, S. S. *Tetrahedron Asymmetry* **2008**, *19*, 45. (i) Kolleth, A.; Christoph, S.; Arseniyadis, S.; Cossy, J. *Chem. Commun.* **2012**, *48*, 10511. (j) Kreituss, I.; Murakami, Y.; Binanzer, M.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10660. (k) Kolleth, A.; Cattoen, M.; Arseniyadis, S.; Cossy, J. *Chem. Commun.* **2013**, *49*, 9338. (l) Hsieh, S.-Y.; Wanner, B.; Wheeler, P.; Beauchemin, A. M.; Rovis, T.; Bode, J. W. *Chem.—Eur. J.* **2014**, *20*, 7228.

(4) Selected reviews covering various aspects of asymmetric nucleophilic catalysis, acyl-transfer, and kinetic resolution: (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (b) Spivey, A. C.; Maddaford, A.; Redgrave, A. *J. Org. Prep. Proced. Int.* **2000**, *32*, 331. (c) Eames, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 885. (d) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (e) Vedejs, E.; Daugulis, O.; MacKay, J. A.; Rozners, E. *Synlett* **2001**, 1499. (f) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (g) Dehli, J. R.; Gotor, V. *Chem. Soc. Rev.* **2002**, *31*, 365. (h) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron Asymmetry* **2003**, *14*, 1407. (i) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985. (j) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291. (k) Murugan, R.; Scriven, E. F. V. *Aldrichim. Acta* **2003**, *36*, 21. (l) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542. (m) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601. (n) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (o) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (p) Fogassy, E.; Nogradi, M.; Palovics, E.; Schindler, J. *Synthesis* **2005**, 1555. (q) Fogassy, E.; Nogradi, M.; Kozma, D.; Egri, G.; Palovics, E.; Kiss, V. *Org. Biomol. Chem.* **2006**, *4*, 3011. (r) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570. (s) Spivey, A. C.; McDaid, P. *Enantiosel. Organocatal.* **2007**, 287. (t) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 248. (u) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (v) Wills, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4264. (w) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563. (x) Palomo, C.; Oiarbide, M.; Lopez, R. *Chem. Soc. Rev.* **2009**, *38*, 632. (y) Azov, V. A. *Sci. Synth.* **2009**, *40a*, 419. (z) Spivey, A. C.; Arseniyadis, S. *Top. Curr. Chem.* **2010**, *291*, 233. (aa) Marion, N.; Fu, G. C. *Chiral Ferrocenes Asymmetric Catal.* **2010**, 307. (ab) Kumar, R. R.; Kagan, H. B. *Adv. Synth. Catal.* **2010**, *352*, 231. (ac) Mueller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012. (ad) Seidel, D. *Sci. Synth.* **2012**, *21*, 427. (ae) Taylor, J. E.; Bull, S. D.; Williams, J. M. J. *Chem. Soc. Rev.* **2012**, *41*, 2109. (af) Krasnov, V. P.; Gruzdev, D. A.; Levit, G. L. *Eur. J. Org. Chem.* **2012**, 1471.

(5) Selected reviews on enzymatic amine acylation: (a) Höhne, M.; Bornscheuer, U. T. *ChemCatChem.* **2009**, *1*, 42. (b) Turner, N. J. *Nat. Chem. Biol.* **2009**, *5*, 567. (c) Gotor-Fernandez, V.; Gotor, V. *Curr. Opin. Drug Discovery Dev.* **2009**, *12*, 784. (d) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999.

(6) Selected examples of small-molecule catalysis approaches to the kinetic resolution of amines: (a) Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234. (b) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (c) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264. (d) Anstiss, M.; Nelson, A. *Org. Biomol. Chem.* **2006**, *4*, 4135. (e) Arnold, K.; Davies, B.; Herault, D.; Whiting, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2673. (f) Hou, X. L.; Zheng, B. H. *Org. Lett.* **2009**, *11*, 1789. (g) Reznichenko, A. L.; Hampel, F.; Hultzsch, K. C. *Chem.—Eur. J.* **2009**, *15*, 12819. (h) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 2870. (i) Charville, H.; Jackson, D.; Hodges, G.; Whiting, A. *Chem. Commun.* **2010**, *46*, 1813. (j) Yang, X.; Bumbu, V. D.; Birman, V. B. *Org. Lett.* **2011**, *13*, 4755. (k) Binanzer, M.; Hsieh, S. Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698. (l) Yang, X.; Bumbu, V. D.; Liu, P.; Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, W.; Jiang, X.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2012**, *134*, 17605. (m) Hsieh, S.-Y.; Binanzer, M.; Kreituss, I.; Bode, J. W. *Chem. Commun.* **2012**, *48*, 8892. (n) Allen, S. E.; Hsieh, S.-Y.; Gutierrez, O.; Bode, J. W.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 11783.

(7) (a) De, C. K.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 17060. (b) Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624. (c) Klauber, E. G.; Mittal, N.; Shah, T. K.; Seidel, D. *Org. Lett.* **2011**, *13*, 2464. (d) Mittal, N.; Sun, D. X.; Seidel, D. *Org. Lett.* **2012**, *14*, 3084. (e) Min, C.; Mittal, N.; De, C. K.; Seidel, D. *Chem. Commun.* **2012**, *48*, 10853. (f) Seidel, D. *Synlett* **2014**, *25*, 783.

(8) De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 14538.

(9) De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 16802.

(10) Selected reviews on catalysis with DMAP: (a) Hoefle, G.; Steglich, W.; Vorbrueggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436. (c) De Rycke, N.; Couty, F.; David, O. R. P. *Chem.—Eur. J.* **2011**, *17*, 12852.

(11) Selected reviews on hydrogen bonding catalysis: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (e) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (f) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (g) Yu, X.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516. (h) Pihko, P. M., Ed. *Hydrogen Bonding in Organic Synthesis*; Wiley-VCH: Weinheim, 2009. (i) Schenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem.* **2011**, 2209.

(12) Selected reviews on anion receptor chemistry: (a) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465. (b) Kang, S. O.; Begum, R. A.; Bowman-James, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7882. (c) Sessler, J. L.; Gale, P. A.; Cho, W.-S. *Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, UK, 2006. (d) Li, A. F.; Wang, J. H.; Wang, F.; Jiang, Y. B. *Chem. Soc. Rev.* **2010**, *39*, 3729. (e) Amendola, V.;

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

Fabbrizzi, L.; Mosca, L. *Chem. Soc. Rev.* **2010**, *39*, 3889. (f) Bowman-James, K.; Bianchi, A.; García-España, E., Eds. *Anion Coordination Chemistry*; Wiley-VCH: Weinheim, 2011. (g) Wenzel, M.; Hiscock, J. R.; Gale, P. A. *Chem. Soc. Rev.* **2012**, *41*, 480.

(13) Selected reviews on cooperative catalysis: (a) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655. (b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (c) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999. (d) Rueping, M.; Koenigs, R. M.; Atodiresei, I. *Chem.—Eur. J.* **2010**, *16*, 9350. (e) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6216. (f) Briere, J. F.; Oudeyer, S.; Dalla, V.; Levacher, V. *Chem. Soc. Rev.* **2012**, *41*, 1696. (g) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (h) Wende, R. C.; Schreiner, P. R. *Green Chem.* **2012**, *14*, 1821.

(14) Selected reports on the formation, nature, and reactivity of acylpyridinium salts: (a) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4826. (b) Xu, S.; Held, I.; Kempf, B.; Mayr, H.; Steglich, W.; Zipse, H. *Chem.—Eur. J.* **2005**, *11*, 4751. (c) Held, I.; Villinger, A.; Zipse, H. *Synthesis* **2005**, 1425. (d) Fischer, C. B.; Xu, S. J.; Zipse, H. *Chem.—Eur. J.* **2006**, *12*, 5779. (e) Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem.—Eur. J.* **2007**, *13*, 336. (f) Lutz, V.; Glatthaar, J.; Würtele, C.; Serafin, M.; Hausmann, H.; Schreiner, P. R. *Chem.—Eur. J.* **2009**, *15*, 8548. (g) Larionov, E.; Achrainer, F.; Humin, J.; Zipse, H. *ChemCatChem.* **2012**, *4*, 559. (h) Larionov, E.; Mahesh, M.; Spivey, A. C.; Wei, Y.; Zipse, H. *J. Am. Chem. Soc.* **2012**, *134*, 9390.

(15) Selected reviews on chiral anion catalysis: (a) Lacour, J.; Hebbe-Viton, V. *Chem. Soc. Rev.* **2003**, *32*, 373. (b) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073. (c) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (d) Beckendorf, S.; Asmus, S.; Mancheno, O. G. *ChemCatChem.* **2012**, *4*, 926. (e) Avila, E. P.; Amarante, G. W. *ChemCatChem.* **2012**, *4*, 1713. (f) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603. (g) Woods, P. A.; Smith, A. D. *Supramol. Chem.: Mol. Nanomater.* **2012**, *4*, 1383. (h) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. (i) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534.

(16) Examples of catalytic processes that likely involve anion-binding: (a) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434. (b) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (d) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686. (e) Martínez-García, H.; Morales, D.; Pérez, J.; Coady, D. J.; Bielawski, C. W.; Gross, D. E.; Cuesta, L.; Marquez, M.; Sessler, J. L. *Organometallics* **2007**, *26*, 6511. (f) Weil, T.; Kotke, M.; Kleiner, C. M.; Schreiner, P. R. *Org. Lett.* **2008**, *10*, 1513. (g) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (h) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887. (i) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358. (j) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (k) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (l) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (m) Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286. (n) Singh, R. P.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2010**, *132*, 9558. (o) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U. S. A* **2010**, *107*, 20678. (p) Birrell, J. A.; Desrosiers, J.-N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 13872. (q) Opalka, S. M.; Steinbacher, J. L.; Lambiris, B. A.; McQuade, D. T. *J. Org. Chem.* **2011**, *76*, 6503. (r) Zhang, Z. G.; Lippert, K. M.; Hausmann, H.; Kotke, M.; Schreiner, P. R. *J. Org. Chem.* **2011**, *76*, 9764. (s) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578. (t) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564. (u) Beck, E. M.; Hyde, A. M.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 4260. (v) Wang, Y.; Yu, T. Y.; Zhang, H. B.; Luo, Y. C.; Xu, P. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12339. (w) Lin, S.; Jacobsen, E. N. *Nat. Chem.* **2012**, *4*, 817. (x) Beckendorf, S.; Asmus, S.; Muck-Lichtenfeld, C.; Mancheno, O. G. *Chem.—Eur. J.* **2013**, *19*, 1581. (y) Sawamura, Y.; Nakatsuji, H.; Sakakura, A.; Ishihara, K. *Chem. Sci.* **2013**, *4*, 4181. (z) Schafer, A. G.; Wieting, J. M.; Fisher, T. J.; Mattson, A. E. *Angew. Chem., Int. Ed.* **2013**, 11321. (aa) Kumar, V.; Mukherjee, S. *Chem. Commun.* **2013**, *49*, 11203. (ab) Borovika, A.; Tang, P.-I.; Klapman, S.; Nagorny, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 13424. (ac) Min, C.; Mittal, N.; Sun, D. X.; Seidel, D. *Angew. Chem.* **2013**, *52*, 14084. (ad) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 1891.

(17) (a) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (b) Sohtome, Y.; Takemura, N.; Takagi, R.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron* **2008**, *64*, 9423.

(18) S-factor = rate of faster reacting enantiomer/rate of slower reacting enantiomer. S-factors were calculated according to: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(19) For a study on the role of the 3,5-bis(trifluoromethyl)phenyl group, see: Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.; Schreiner, P. R. *Eur. J. Org. Chem.* **2012**, 5919.

(20) Examples of organocatalytic processes that provide higher ee's at reduced catalyst loadings: (a) Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593. (b) Jang, H. B.; Rho, H. S.; Oh, J. S.; Nam, E. H.; Park, S. E.; Bae, H. Y.; Song, C. E. *Org. Biomol. Chem.* **2010**, *8*, 3918. (c) Rulli, G.; Duangdee, N.; Baer, K.; Hummel, W.; Berkessel, A.; Gröger, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 7944. (d) Mao, H.; An, S. L.; Kim, S. M.; Yang, J. W. *Bull. Korean Chem. Soc.* **2011**, *32*, 4408. (e) Kumar, A.; Chimni, S. S. *Tetrahedron* **2013**, *69*, 5197. For a review on organocatalysis at low catalysts loadings, see: (f) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406.

(21) For a study on the aggregation behavior of a bifunctional catalyst, see: Tárkányi, G.; Király, P.; Soós, T.; Varga, S. *Chem.—Eur. J.* **2012**, *18*, 1918.

(22) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.

(23) See Supporting Information for details.

(24) Štrukil, V.; Igrc, M. D.; Eckert-Maksić, M.; Friščić, T. *Chem.—Eur. J.* **2012**, *18*, 8464.

(25) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638.

(26) For an X-ray crystal structure of an acylpyridinium salt of a chiral DMAP catalyst, see: Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091.

(27) (a) Hrdina, R.; Müller, C. E.; Wende, R. C.; Lippert, K. M.; Benassi, M.; Spengler, B.; Schreiner, P. R. *J. Am. Chem. Soc.* **2011**, *133*, 7624. (b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.

(28) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2008**, *41*, 157.

(29) Risthaus, T.; Grimme, S. *J. Chem. Theory Comput.* **2013**, *9*, 1580.

(30) (a) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999. (b) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210.

(31) Camaioni, D. M.; Dupuis, M.; Bentley, J. *J. Phys. Chem. A* **2003**, *107*, 5778.

(32) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*; Gaussian, Inc., Wallingford, CT, 2009.

(33) Legault, C. Y. *CYLview, 1.0b*; Université de Sherbrooke, 2009 (http://www.cylview.org).

(34) Conditions for the NOESY spectrum of DMAP and benzoic anhydride (each c = 10 mM) with a 600 MHz NMR spectrometer and

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758

a mixing time of 1 s in toluene-d_8 at 298 K. The DOSY spectrum of the same sample was measured with a diffusion delay of 50 ms.
(35) (a) Jones, C. R.; Pantos, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 7391. (b) Probst, N.; Madarasz, A.; Valkonen, A.; Papai, I.; Rissanen, K.; Neuvonen, A.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8495.

DOI: 10.1021/jacs.5b00190
J. Am. Chem. Soc. 2015, 137, 5748−5758