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Phase-Transfer Catalysis via a Proton Sponge: A Bifunctional Role for Biscyclopropenimine

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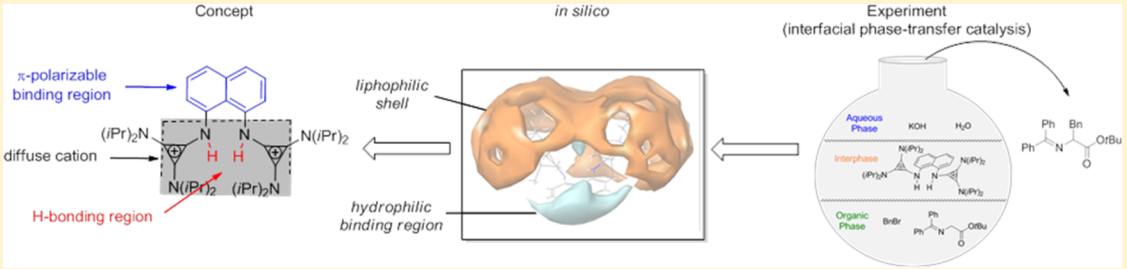
Supporting Information



ABSTRACT: The use of a bis(diisopropylamino)cyclopropenimine-substituted bis-protonated proton sponge as a bifunctional phase-transfer catalyst is reported. Experimental studies and DFT calculations suggest it operates simultaneously as a hydrogen bond donor and a phase-transfer catalyst, facilitating the movement of charged intermediates from the interface to the organic phase via favorable partitioning of hydrophilic/hydrophobic surface areas, resulting in high catalytic activity.

INTRODUCTION

The interest in bis(dialkylamino)cyclopropenimine (DAC) motifs has markedly increased in recent years, due in large part to their emerging use in organocatalysis[1] and phase-transfer catalysis,[2] in addition to applications as ionic liquids[3] and nitrogen-based ligands.[4] Accompanying the practical interests in DACs has been an avid curiosity among physical organic chemists and theoreticians alike in their strong Brønsted–Lowry basicity, which arguably derives from an intrinsic kinetic propensity to form stable aromatic bis(dialkylamino)cyclopropeniminium cations upon protonation. Not surprisingly, this fascinating link between basicity and aromaticity, compounded with the status of DACs as so-called "superbases" has served as an impetus for continued study into the underlying electronic nature and chemical reactivity of this intriguing class of heterocycles.

In this light, our recently synthesized superbases, DACN (**1**)[5] and Janus (**2**),[6] further explored the nature of DACs in the context of freebase strain and intramolecular hydrogen bonding, within the historically relevant proton sponge scaffold. Our group has also reported the first use of a DAC derivative (**3**) as a phase-transfer catalyst (PTC) for benzylation and fluorination reactions (Figure 1).[2a] From an experimental standpoint, phase-transfer protocols are particularly advantageous as they are, in general, operationally simple, amenable to both large- and small-scale synthetic protocols, involve mild reaction conditions, and use inexpensive reagents and solvents. As a result, it is perhaps not surprising that the scope of phase-transfer catalysis has continued to evolve at an accelerated pace, resulting in a number of new catalysts and protocols offering complementary and/or distinct modes of reactivity.[7] In building upon earlier works exploring multisite PTCs (catalysts

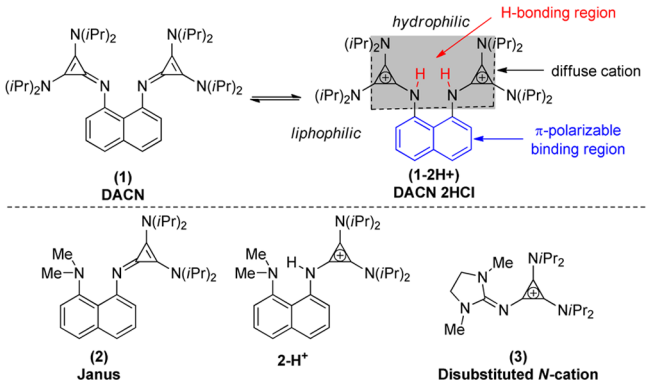


Figure 1. Reported cyclopropinimine compounds by Dudding et al.

with more than one active site),[8] particular emphasis has recently been placed on bifunctional catalysts combining both hydrogen bonding and phase-transfer motifs.[9] Among this class of PTCs, the predominant approach involves combining positively charged quaternary ammonium cations as the phase-transfer functionality and urea or thiourea as the hydrogen bond donor.

As part of our continued interest in phase-transfer reactions and hydrogen bonding, we were particularly interested to investigate the use of protonated DACs as hydrogen bond donors in phase-transfer catalysis. We envisioned the use of **1**-2H$^+$ (Figure 1) as a unique, bifunctional phase-transfer catalyst. DACs are unique phase-transfer motifs, considering that their

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positive charges are highly diffuse in nature, which stands in contrast to the localized point charges of widely employed quaternary ammonium (or occasionally phosphonium) cations. With the application of **1**-2H$^+$ as a PTC, this report demonstrates that protonated DACs can be compatible hydrogen bond donors for phase-transfer chemistry. Thus, DACs have a unique ability to play a bifunctional role, as both the phase-transfer motif and hydrogen bonding donor.

The functional utility of **1**-2H$^+$ in phase-transfer catalysis was projected to benefit from a distinct partitioning of lipophilic and hydrophilic surface areas (Figure 1), which could be subdivided into a (1) π-polarizable naphthyl ring that would allow for $\pi-\pi$ stacking interactions, (2) a pair of highly diffuse cations that would facilitate the transport of anions into a lipophilic organic phase, and (3) a H-bonding region for molecular recognition. As a corollary, it was foreseen that in situ derived freebase, **1**, might serve a further role, acting as an organic base to facilitate the deprotonation of pronucleophiles, thus providing another mechanistic dimension to phase-transfer catalysis.

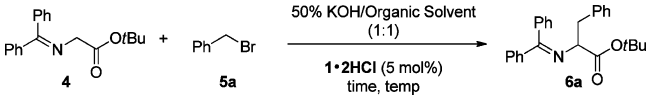
RESULTS AND DISCUSSION

At the outset of this study, to explore the potential of the bisprotonated salt of DACN (**1**-2H$^+$) in PTC as a bifunctional and/or multisite phase-transfer catalyst, we chose the well-established alkylation of O'Donnell's glycine imines[10] given its historical significance and the numerous mechanistic investigations using this substrate. However, it was initially uncertain if **1**-2H$^+$ would undergo N-alkylation, as it would presumably be in equilibrium with **1** under basic conditions, or if the sterically encumbered environment of **1** would impede alkylation. To investigate this possibility, 100 mg of **2** was mixed with excess benzyl bromide in a 1:1 mixture of DCM and 50% aqueous KOH and stirred at room temperature for 8 h. Encouragingly, there was no evidence of the alkylated catalyst, and the catalyst could be easily recovered in near quantitative yield. Although there was no evidence of catalyst alkylation, it was shown that deprotonation under the reaction conditions did indeed occur, as established by dissolution of **1**-2H$^+$ in a 50% solution of KOH in D_2O at room temperature. In terms of catalyst stability, it is notable that when a sample of **1**-2H$^+$ was left in an aqueous 50% KOH solution at ambient temperature there was no noticeable decomposition after 2 weeks, as determined by ^{1}H NMR.

Given this promising preliminary result, reaction conditions were subsequently screened for the alkylation of benzophenone imine **4** with benzyl bromide **5a** (Table 1). To this end, the polar aprotic solvent acetonitrile (MeCN) was optimal, resulting in complete consumption of the starting material in only 20 min at room temperature and a 92% product yield. Comparatively, the use of slightly less polar dichloromethane (DCM) provided a similar outcome to that of MeCN, with full consumption of the starting material occurring in 45 min at room temperature. Meanwhile, the use of toluene, on the other hand, resulted in a slight background rate, extended reactions times, and poor overall product yield.

At that stage, to investigate the hypothesis that the bisprotonated, dicationic moiety of **1**-2H$^+$ was critical for catalysis, three additional compounds all sharing structural similarities with **1**-2H$^+$ were employed as potential catalysts under the same reaction conditions (Figure 2). Namely, phase-transfer alkylation was performed in the presence of 5 mol % of the hydrochloride salts of Janus sponge (**2**-H$^+$),[6] Alder's proton

Table 1. Optimized Reaction Conditions with 1-2H$^+$



entry	solvent	temp (°C)	time	conversion[a] (%)	yield[b,c] (%)
1	MeCN	25	20 min	100	92
2	MeCN	0	1 h	100	91
3	DCM	25	45 min	100	92
4	DCM	0	1.5 h	100	89
5	toluene	25	8 h[d]	51	36
6	toluene	50	8 h[d]	67	51

[a]Based on ^{1}H NMR spectroscopy. [b]Isolated yield after column chromatography. [c]In the absence of the catalyst, no conversion was observed except 6% for entry 6 based on ^{1}H NMR. [d]Noticeable background reaction observed longer than 8 h.

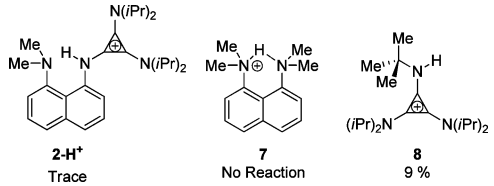


Figure 2. Alternative compounds screened for PTC activity.

sponge (**7**),[11] and *t*-butyl(bisdiisopropylamino)-cyclopropenimine (**8**).[1a] To this end, the use of **2**-H$^+$ afforded only trace amounts of the benzylated product, while **7** resulted in no reaction, indicating that the protonated 1,8-diaminonaphthyl ring system was not the only structural feature of **1**-2H$^+$ leading to PTC catalysis. Conversely, **8** catalyzed the reaction to a small extent, providing 9% of the desired product along with small amounts of alkylated byproduct.[12] The failure of **2**-H$^+$, **7**, and **8** to impart any appreciable catalytic activity, despite their partial structural similarity to **1**-2H$^+$, is notable, as it provides strong evidence that **1**-2H$^+$ acts uniquely as a phase-transfer catalyst.

In view of the dramatic differences in reactivity between these compounds, the ability of **1**-2H$^+$ as a phase-transfer catalyst was further explored using other electrophiles under the conditions applied for entry 3 in Table 1 with the reaction time extended to 1 h (Scheme 1). Along these lines, naphthalene bromide (**5b**) was comparable in reactivity to benzyl bromide, resulting in 92% isolated yield, while perhaps more interestingly, the more sterically hindered secondary bromide **5c** afforded **6c** in 91% yield, demonstrating that substitution at the benzylic carbon was tolerated under the reaction conditions. Alternatively, the use of less reactive benzyl chlorides **5d** and 4-methoxybenzyl chloride **5e** led to lower product yields, providing **6d** and **6e** in 60 and 54% yields, respectively. In contrast, 4-methyl benzyl bromide (**5f**) substrate afforded a yield comparable to that of benzyl bromide, with **6f** isolated in 92% yield. Furthermore, the use of resonance-donating electron-withdrawing 4-chloro-substituted and strongly electron-withdrawing 4-nitro-functionalized benzyl bromides **5g** and **5h** provided high product yields. Based on these trends, it would appear that the enhanced leaving group ability of a benzylic bromide relative to that of a chloride effectively supersedes subtle electronic perturbations on reactivity introduced by the inclusion of a *p*-substituent. These results are consistent with a mechanistic scenario involving halide dissociation and C–C bond formation

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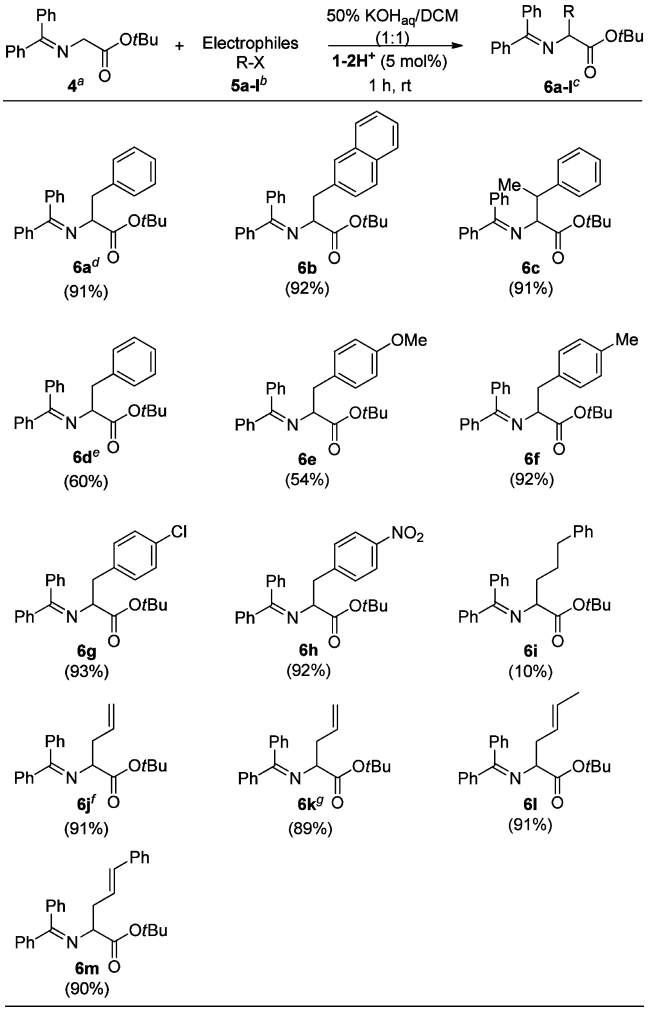
Scheme 1. Electrophile Screen

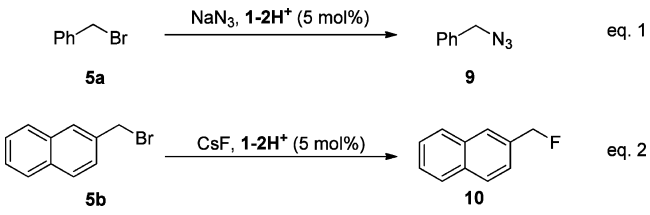


[a]With 1 equiv. [b]With 1.2 equiv. [c]Yields based on isolated product obtained after column chromatography. No product was formed in any reaction in the absence of catalyst **1**-2H$^+$. [d]**5a** = benzyl bromide. [e]**5d** = benzyl chloride. [f]**5j** = allyl bromide. [g]**5k** = allyl chloride.

occurring via a transition state involving S_N2 displacement or conceivably even backside nucleophilic addition to a short-lived benzylic cation$^+$X$^-$ tight ion pair. Meanwhile, substrate 3-benzyl-1-bromopropane (**5i**) having an aliphatic chain proved to be a far less reactive electrophile, yielding only 10% of the desired product **6i**, though the reaction does reach completion with longer reaction times. Lastly, allyl bromide (**5j**), crotyl bromide (**5l**), allyl chloride (**5k**), and cinnamyl bromide (**5m**) were all reactive, though allyl chloride gave a slightly lower yield, while the regiochemical outcome with **5l** and **5m** indicated that a S_N2' displacement of the bromide was not a competing process.

Having demonstrated that **1**-2H$^+$ was a competent catalyst for interfacial PTC, we next applied it to nucleophilic fluorination and sodium azide substitution reactions, which are PTC processes generally believed to occur by extraction-based mechanisms (Scheme 2).[13] Emerging from these studies was the instructive finding that in stark contrast to the ability of **1**-2H$^+$ to facilitate interfacial PTC, it was a markedly less effective catalyst for extraction PTC, which is interesting given that our recently reported cyclopropeniminium-containing pnictogen N-centered cation **3** was an effective phase-transfer

Scheme 2. Extraction-Type PTC Reactions (See Supporting Information for Details)



catalyst for both hydroxide-initiated interfacial and extraction-based PTC.[2a] For instance, even under optimized conditions, **1**-2H$^+$ provided only moderate rate enhancement in the benzylic fluorination of **5b** with CsF in MeCN (eq 1) with respect to the noncatalyzed background reaction (see Supporting Information). Furthermore, **1**-2H$^+$ had no effect on catalyzing the bromide displacement of **5a** by azide under PTC conditions (eq 2). See Supporting Information for details.

While PTC reactions are renowned for being dynamic processes, wherein product formation is oftentimes complicated by "off-cycle" pre-equilibria, there is little doubt that the alkylation of O'Donnell's imine in this work proceeds by way of an interfacial hydroxide-initiated mechanism.[10] Granted this fact, the more relevant question relates to the underlying source of the high catalytic activity of **1**-2H$^+$. In part, it is thought to derive from the tendency of the catalyst to concentrate at the interfacial space, which is known to be an important factor in hydroxide-initiated PTC reactions.[14] Presumably, the innate organophilicity of **1**-2H$^+$ also plays a critical role in enhancing the transport rate of anions from the interfacial phase to the organic layer, leading to faster reactions.[15] Though conjectural, a third aspect of **1**-2H$^+$-mediated PTC is the likelihood that the catalyst stabilizes the benzophenone imine enolate (**4**$^-$) via a set of heteronuclear positive-charge-assisted hydrogen bonds ((+)CAHB).[16] Lastly, it is reasoned that **1** undergoes a rapid protonation/deprotonation event at the organic/aqueous interface, given its basicity and the basicity of the aqueous phase.[15] This would in turn toggle the solubility characteristics of the catalyst between that of a charged hydrophilic **1**-2H$^+$ dication with H-bonding residues to that of more a lipophilic **1** or **1**-1H$^+$ species, which would be prone to reside in the organic layer. In essence, the dynamics of this system would establish a scenario where the catalyst would be held at the interface by rapid protonation/deprotonation processes.

Modeling of the hydrophobic/hydrophilic surface areas of **1**-2H$^+$ and the corresponding hydrogen-bound complex **1**-2H$^+$·4$^-$ supported this conjecture, as revealed by the hydrophobic/hydrophilic surface area plots depicted in Figure 3. Apparent from these plots was a distinct amphipathic division of

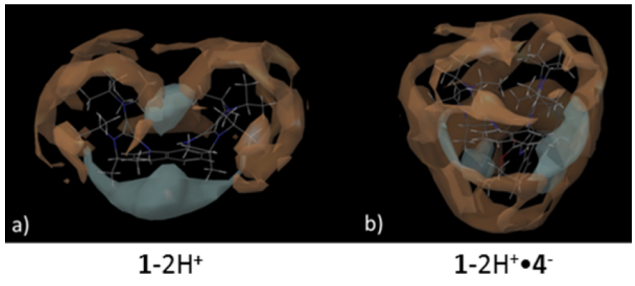


Figure 3. Hydrophobic (orange)/hydrophilic (blue) surfaces of **1**-2H$^+$ (left) and the **1**-2H$^+$·4$^-$ complex (right) generated using Macromodel.

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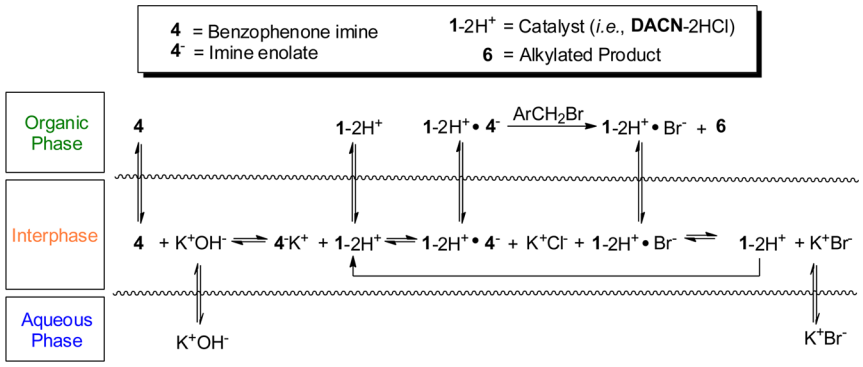

Figure 4. Proposed hydroxide-initiated interfacial PTC mechanism for alkylation of imine **4** to afford **6**.

hydrophobic/hydrophilic surface volumes in **1**-2H$^+$ that suggested it would be prone to accumulate at organic/aqueous interfaces (Figure 3a), while in **1**-2H$^+$·**4**$^-$, the hydrophilic surface density was localized at the *re* and *si* faces of the enolate ester carbon and the oxyanion was buried within the interior of this complex (Figure 3b). Notably, this encasing of the oxyanion can be likened to that of the role played by hydrophilic/hydrophobic amino acid residues in protein folding/function.[17] Yet more importantly, this discrete arrangement of hydrophilic/hydrophobic surfaces and positioning of H-bond donor sites both stabilize and protect the reactive enolate intermediate, presumably prolonging its lifetime in the organic phase and thereby increasing the probability of reaction with an electrophile.

As for the PTC cycle of these alkylation reactions, it is envisioned that a series of pre-equilibrium steps generate an effective concentration of a reactive benzophenone imine enolate **1**-2H$^+$·**4**$^-$ complex in the interphase (Figure 4). A preliminary model derived from DFT calculations suggests that the computed 34.9 kcal/mol binding affinity for this complex was driven by the formation of a bifurcated ((+)CAHB) H-bond/Coulombic interaction, akin to a salt bridge which is a common motif found in enzymes (Figure 5).

Migrating into the bulk of the organic phase, **1**-2H$^+$·**4**$^-$ then engages in C−C bond formation via a transition state assembly such as **TS1** with an activation barrier of 10.7 kcal/mol (2.2 kcal/mol lower than that of the uncatalyzed transition state; see Supporting Information) and elongated 2.46 Å C−C bond forming distance, which is suggestive of an early transition state leading to alkylated product **6** (Figure 5).

CONCLUSIONS

In closure, we have demonstrated that DACs can be used as hydrogen bond donors in phase-transfer chemistry and have introduced the first bifunctional DAC-based PTC, **1**-2H$^+$. The bis-protonated salt of DACN (i.e., **1**-2H$^+$), a shelf-stable salt easily prepared from commercially and/or readily available reagents, was shown to be an effective catalyst for hydroxide-initiated interfacial PTC alkylations, while it was a poor catalyst for PTC processes occurring by extraction-based mechanisms. Evidence was presented that suggests **1**-2H$^+$ has a tendency to reside at the aqueous/organic interphase and the ability to enclose reactive hydrophilic intermediates in a hydrophobic shell, thus facilitating their transport to the organic phase. Ongoing studies geared toward the development and application of related PTC protocols with chiral DAC-derived catalysts is underway in our lab and will be reported in due course.

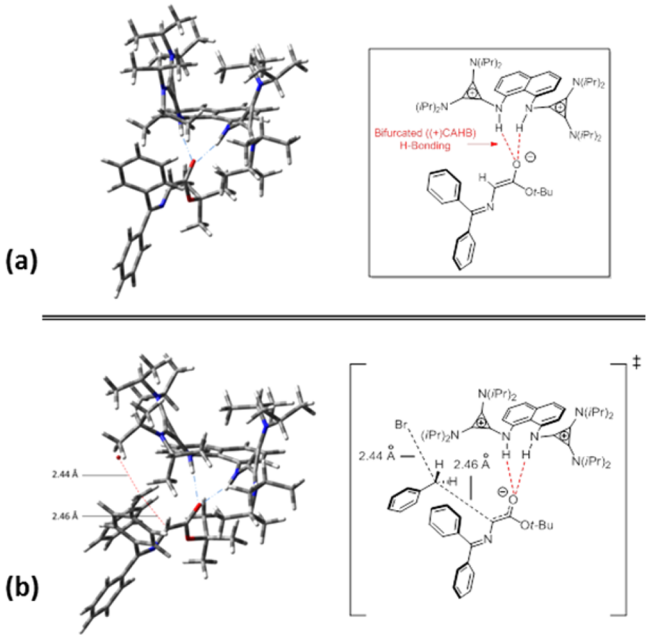

Figure 5. (a) Computed complex **1**-2H$^+$·**4**$^-$ (left). Two-dimensional rendering of favorable binding interaction in **1**-2H$^+$·**4**$^-$ (right). (b) Computed benzylation transition state, **TS1** (left). Two-dimensional rendering of TS1 (right). Computations performed at the wb97xd/6-31g(d)/def2sv (scrf = dichloromethane) level.

EXPERIMENTAL SECTION

Calculations were carried out at the Kohn−Sham hybrid DFT wb97xd/6-31g(d)/def2sv level of theory at standard temperature and pressure using the Gaussian 09 and GaussView v5.0.8 programs. To account for solvent effects, the integrated equation formalism polarized continuum solvation model (IEFPCM) was used throughout the computations with default parameters for dichloromethane. A number of transition state configurations were computed and were confirmed by the presence of a single imaginary frequency, though only the lowest energy transition states for the catalyzed and uncatalyzed reactions are reported (see Supporting Information). The intrinsic reaction coordinate (IRC) methodology was then implemented to identify the corresponding minima, which were confirmed by the presence of only real vibrational frequencies.

Materials and Methods. Materials were obtained from commercial suppliers and were used without further purification, unless otherwise specified. Reactions were monitored by thin layer chromatography (TLC) using TLC silica gel 60 F254. NMR spectra were obtained with a 300 MHz spectrometer (^{1}H 300 MHz, ^{13}C 75.5 MHz or ^{13}C 150.9 MHz, ^{19}F 292.4 MHz, ^{11}B 96.3 MHz). The chemical shifts are reported as δ values (ppm) relative to tetramethylsilane.

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General Phase-Transfer Catalysis Procedure. *N*-(Diphenylmethylene)glycine *tert*-butyl ester **4** (25 mg, 0.0846 mmol, 1 equiv), DACN 2HCl (3 mg, 0.00428 mmol, 5 mol %), and electrophile (0.01 mmol, 1.2 equiv) was dissolved in 0.5 mL of dichloromethane in a 10 mL vial with a stir bar, followed by the addition of 0.5 mL of 50% aqueous potassium hydroxide. The vial was closed, and the reaction was allowed to stir at room temperature for 1 h. The reaction was extracted with three aliquots of 2 mL of dichloromethane; the organic layer was dried with magnesium sulfate and concentrated in vacuo. Products were isolated using flash column chromatography 9:1 (hexane/ethyl acetate).

tert-Butyl-2-(diphenylmethyleneamino)-3-(phenyl)propanoate (**6a**):[18] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as white crystals in 92% yield (0.0778 mmol, 30 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (s, 9H), 3.19−3.28 (m, J = 8.9, 4.4 Hz, 2H), 4.12−4.16 (dd, J = 9.6, 4.0 Hz, 1H), 6.62−6.64 (d, J = 7.0 Hz, 2H), 7.07−7.10 (m, 2H), 7.19−7.21 (m, 2H), 7.27−7.39 (m, 5H), 7.51−7.53 (t, J = 7.8 Hz, 1H), 7.59−7.62 (d, J = 7.4 Hz, 2H), 7.82−7.85 (d, J = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 170.2, 139.7, 138.3, 137.6, 132.4, 130.0, 129.8, 128.7, 128.2, 128.0, 127.96, 127.69, 126.1, 81.1, 67.9, 39.6, 28.0.

tert-Butyl-2-(diphenylmethyleneamino)-3-(naphthalen-2-yl)-propanoate (**6b**):[18] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as yellow oil in 92% yield (0.0778 mmol, 34 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.48 (s, 9H), 3.35−3.42 (m, 2H), 4.24−4.29 (dd, J = 9.0, 4.4 Hz, 1H), 6.55−6.57 (d, J = 7.2 Hz, 2H), 7.16−7.24 (m, 2H), 7.29−7.35 (m, 3H), 7.41−7.44 (m, 2H), 7.51−7.60 (m, 4H), 7.67−7.70 (d, J = 7.8 Hz, 2H), 7.77−7.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 170.4, 139.5, 137.7, 136.3, 135.9, 133.4, 132.4, 132.1, 130.0, 128.7, 128.4, 128.2, 128.0, 127.9, 127.6, 127.5, 127.4, 125.7, 125.2, 81.2, 67.9, 39.7, 28.0.

tert-Butyl-2-(diphenylmethyleneamino)-3-(phenyl)butanoate (**6c**):[10] Compound was purified via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as yellow oil 91% yield (0.0769 mmol, 31 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.45 (s, 9H), 3.49−3.61 (m, 1H), 3.99−4.02 (d, J = 8.2 Hz, 1H), 6.75−6.78 (d, J = 6.8 Hz, 2H), 7.14−7.25 (m, 5H), 7.30−7.40 (m, 5H), 7.50−7.53 (d, J = 7.0 Hz, 2H), 7.65−7.68 (d, J = 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.7, 170.4, 143.8, 143.4, 136.6, 136.4, 132.4, 130.1, 130.0, 129.97, 128.9, 128.8, 128.6, 128.3, 128.27, 128.23, 128.14, 128.14, 128.0, 127.9, 127.88, 127.82, 127.7, 126.2, 81.0, 80.8, 72.8, 71.9, 43.5, 28.0, 27.8, 18.0, 16.82.

tert-Butyl-2-(diphenylmethyleneamino)-3-(phenyl)propanoate (**6d** = **6a**):[18] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as white crystals in 60% yield (0.0508 mmol, 19 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (s, 9H), 3.19−3.28 (m, J = 8.9, 4.4 Hz, 2H), 4.12−4.16 (dd, J = 9.6, 4.0 Hz, 1H), 6.62−6.64 (d, J = 7.0 Hz, 2H), 7.07−7.10 (m, 2H), 7.19−7.21 (m, 2H), 7.27−7.39 (m, 5H), 7.51−7.53 (t, J = 7.8 Hz, 1H), 7.59−7.62 (d, J = 7.4 Hz, 2H), 7.82−7.85 (d, J = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 170.2, 139.7, 138.3, 137.6, 132.4, 130.0, 129.8, 128.7, 128.2, 128.0, 127.96, 127.69, 126.1, 81.1, 67.9, 39.6, 28.0.

tert-Butyl-2-(diphenylmethyleneamino)-3-(4-methylphenyl)-propanoate (**6e**):[19] Compound was purified via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as clear oil in 92% yield (0.0778 mmol, 31 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (s, 9H), 2.31 (s, 3H), 3.09−3.25 (m, 2H), 4.09−4.13 (dd, J = 9.0, 4.0 Hz, 1H), 6.60−6.71 (d, J = 7.0 Hz, 2H), 6.94−7.03 (dt, J = 8.7, 7.5 Hz, 4H), 7.27−7.39 (m, 6H), 7.58−7.61 (dd, J = 8.0, 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.9, 170.1, 139.6, 136.4, 135.5, 135.2, 130.0, 129.7, 128.7, 128.2, 128.1, 128.0, 127.9, 127.7, 81.05, 68.0, 39.1, 28.0, 21.0.

tert-Butyl-2-(diphenylmethyleneamino)-3-(4-chlorophenyl)-propanoate (**6f**):[20] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as clear oil in 91% yield (0.0770 mmol, 32 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (s, 9H), 3.10−3.24 (m, 2H), 4.08−4.13 (dd, J = 8.7, 4.2 Hz, 1H), 6.68−6.70 (d, J = 7.0 Hz, 2H), 6.99−7.02 (d, J = 8.3 Hz, 2H), 7.16−7.19 (d, J = 6.8 Hz, 2H), 7.30−7.40 (m, 6H), 7.57−7.60 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.6, 170.5, 139.4, 137.6, 136.2, 132.4, 132.0, 131.2, 130.7, 130.2, 130.0, 128.7, 128.4, 128.2, 81.3, 67.6, 38.9, 28.0.

tert-Butyl-2-(diphenylmethyleneamino)-3-(4-nitrophenyl)-propanoate (**6g**):[21] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as white crystals in 93% yield (0.0787 mmol, 34 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (s, 9H), 3.30−3.33 (m, 2H), 4.17−4.21 (dd, J = 8.0, 2.3 Hz, 1H), 6.72−6.74 (d, J = 6.9 Hz, 2H), 7.25−7.36 (m, 8H), 7.57−7.60 (d, J = 6.9 Hz, 2H), 8.07−8.10 (d, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.9, 170.1, 146.6, 146.5, 139.1, 136.0, 130.6, 130.4, 128.7, 128.6, 128.3, 128.1, 127.5, 123.2, 81.7, 67.0, 39.4, 28.0.

tert-Butyl-2-(diphenylmethyleneamino)-3-(4-methoxyphenyl)-propanoate (**6h**):[19] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as clear oil in 54% yield (0.0457 mmol, 19 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (s, 9 H), 3.10−3.25 (m, 2 H), 3.77 (s, 3 H) 4.10−4.14 (t, J = 4.0 Hz, 1H), 7.02 (d, J = 6.0 Hz, 2 H), 7.38 (d, J = 4.0 Hz, 2H), 7.47−7.85 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.9, 170.2, 160.1, 136.4, 132.4, 130.8, 130.1, 129.4, 128.7, 128.5, 128.2, 128.0, 127.8, 127.7, 81.0, 68.1, 55.2, 38.7, 28.0.

tert-Butyl-2-(diphenylmethyleneamino)-5-(phenyl)pentanoate (**6i**):[9c] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as clear oil in 10% yield (0.0085 mmol, 4 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (s, 9H), 1.59−1.69 (m, 2H), 1.94−2.01 (m, 2H), 2.56−2.61 (t, J = 7.8 Hz, 2H), 3.95−3.99 (t, J = 6.4 Hz, 1H), 7.14−7.19 (m, 5H), 7.32−7.41 (m, 4H), 7.44−7.46 (m, 3H), 7.66−7.68 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.5, 169.9, 142.2, 139.7, 136.7, 130.1, 128.8, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 125.7, 80.8, 65.9, 35.6, 33.3, 28.1, 27.8.

tert-Butyl-2-(diphenylmethyleneamino)pent-4-enoate (**6j**):[18] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as clear oil in 91% yield (0.0769 mmol, 26 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (s, 9H), 2.62−2.69 (m, 2H), 4.00−4.05 (dd, J = 7.7, 2.0 Hz, 1H), 5.01−5.12 (m, 2H), 5.69−5.79 (m, 1H), 7.17−7.21 (m, 2H), 7.31−7.46 (m, 6H), 7.64−7.67 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 170.1, 139.7, 136.6, 134.7, 132.4, 130.1, 130.0, 128.8, 128.5, 128.2, 117.2, 81.0, 65.8, 38.1, 28.0.

tert-Butyl-2-(diphenylmethyleneamino)pent-4-enoate (**6k** = **6j**):[22] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as clear oil in 89% yield (0.0753 mmol, 25 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (s, 9H), 2.62−2.69 (m, 2H), 4.00−4.05 (dd, J = 7.7, 2.0 Hz, 1H), 5.01−5.12 (m, 2H), 5.69−5.79 (m, 1H), 7.17−7.21 (m, 2H), 7.31−7.46 (m, 6H), 7.64−7.67 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.8, 170.1, 139.7, 136.6, 134.7, 132.4, 130.1, 130.0, 128.8, 128.5, 128.2, 117.2, 81.0, 65.8, 38.1, 28.0.

tert-Butyl-2-(diphenylmethyleneamino)hex-4-enoate (**6l**):[18] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine). The final product was obtained as clear oil in 91% yield (0.0769 mmol, 27 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.46 (s, 9H), 1.63−1.65 (d, J = 6.1 Hz, 3H), 2.53−2.62 (m, 2H), 3.95−4.00 (dd, J = 7.6, 2.0 Hz, 1H), 5.31−5.33 (m, 2H), 7.16−7.19 (m, 2H), 7.34−7.46 (m, 6H), 7.64−7.67 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.1,

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169.8, 139.8, 136.8, 130.1, 128.8, 128.4, 128.3, 128.0, 127.95, 127.93, 127.8, 127.1, 126.1, 80.8, 66.4, 36.9, 28.0, 17.9.

*(E)-tert-Butyl 2-((diphenylmethylene)amino)-5-phenylpent-4-enoate (**6m**):*[23] Purified compound was eluted via gravity column chromatography, using a mixture of 97:2:1 hexanes/ethyl acetate/triethylamine. The final product was obtained as a viscous white oil in 90% yield (0.0694 mmol, 24 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (s, 9H), 2.77−2.85 (m, 2H), 4.09−4.13 (m, 1H), 6.08−6.16 (m, 1H), 6.40−6.46 (m, 1H), 7.16−7.45 (m, 13H), 7.31−7.46 (m, 6H), 7.67−7.69 (d, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.9, 170.3, 139.7, 137.5, 136.7, 132.4, 130.2, 128.8, 128.5, 128.4, 128.0, 127.9, 127.0, 126.5, 126.0, 81.1, 66.2, 37.3, 28.1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02395.

Coordinate and thermochemical data for all structures and NMR spectra for all reported compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 5552−5555. (b) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799−11802. (c) Wilde, M. M. D.; Gravel, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12651−12654. (d) Mirabdolbaghi, R.; Dudding, T. *Org. Lett.* **2015**, *17*, 1930−1933.

(2) (a) Mirabdolbaghi, R.; Dudding, T.; Stamatatos, T. *Org. Lett.* **2014**, *16*, 2790−2793. (b) Bandar, J. S.; Tanaset, A.; Lambert, T. A. *Chem. - Eur. J.* **2015**, *21*, 7365−7368.

(3) (a) Curnow, O. J.; MacFarlane, D. R.; Walst, K. *Chem. Commun.* **2011**, *47*, 10248−10250. (b) Curnow, O. J.; Holmes, M. T.; Ratten, L. C.; Walst, K. J.; Yunis, R. *RSC Adv.* **2012**, *2*, 10794−10797.

(4) (a) Bruns, H.; Patil, M.; Carreras, J.; Vazquez, A.; Thiel, W.; Goddard, R.; Alcarazo, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3680−3683. (b) Kozma, Á.; Gopakumar, G.; Farès, C.; Thiel, W.; Alcarazo, M. *Chem. - Eur. J.* **2013**, *19*, 3542−3546.

(5) Belding, L.; Dudding, T. *Chem. - Eur. J.* **2014**, *20*, 1032−1037.

(6) Belding, L.; Stoyanov, P.; Dudding, T. *J. Org. Chem.* **2015**, DOI: 10.1021/acs.joc.5b01743.

(7) (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656−5682. (b) Denmark, S. E.; Gould, N. D.; Wolf, L. M. *J. Org. Chem.* **2011**, *76*, 4260−4336. (c) Yang, X.; Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 5225−5228. (d) Woźniak, Ł.; Murphy, J. J.; Melchiorre, P. *J. Am. Chem. Soc.* **2015**, *137*, 5678−5681.

(8) (a) Jayachandran, P.; Wang, M.-L. *Synth. Commun.* **1999**, *29*, 4101−4112. (b) Balakrishnan, T.; Jayachandran, P. J. *Synth. Commun.* **1995**, *25*, 3821. (c) Balakrishnan, T.; Jayachandran, J. P. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2081.

(9) (a) Bernal, P.; Fernandez, R.; Lassaletta, J. M. *Chem. - Eur. J.* **2010**, *16*, 7714−7718. (b) Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492−2495. (c) Novacek, J.; Waser, M. *Eur. J. Org. Chem.* **2013**, *2013*, 637−648 and references therein. (d) Wang, B.; Liu, Y.; Sun, C.; Wei, Z.; Cao, J.; Liang, D.; Lin, Y.; Duan, H. *Org. Lett.* **2014**, *16*, 6432−6435. (e) Shirakawa, S.; Koga, K.; Tokuda, T.; Yamamoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2014**, *53*, 6220−6223. (f) Parvez, Md. M.; Haraguchi, N.; Itsuno, S. *Macromolecules* **2014**, *47*, 1922−1928. (g) Li, M.; Woods, P. A.; Smith, M. D. *Chem. Sci.* **2013**, *4*, 2907−2911.

(10) O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, *19*, 4625−4628.

(11) Alder, R. W.; Bowman, P. S.; Steele, W. R. S.; Winterman, D. R. *Chem. Commun.* **1968**, *452*, 723−724.

(12) During the preparation of this paper, Lambert reported that **10** decomposed under PTC conditions. See ref 2b.

(13) Hydroxide-initiated PTC alkylations of O'Donnell's imine are generally believed to occur by an interfacial mechanism, while S_N2 displacements with small, charged nucleophiles (e.g., N_3^- and F^-) are generally believed to occur by an extraction mechanism. See ref 7b and references therein.

(14) Makosza, M.; Lasek, W. *J. Phys. Org. Chem.* **1993**, *6*, 412−420.

(15) Herriott, A.; Picker, D. *J. Am. Chem. Soc.* **1975**, *97*, 2345−2349.

(16) Belding, L.; Taimoory, S. M.; Dudding, T. *ACS Catal.* **2015**, *5*, 343−349.

(17) Meirovitch, H.; Scheraga, H. A. *Macromolecules* **1980**, *13*, 1406−1414.

(18) Kumar, S.; Sobhia, M. E.; Ramachandran, U. *Tetrahedron: Asymmetry* **2005**, *16*, 2599−2605.

(19) Siva, A.; Murugan, E. *Synthesis* **2005**, *2005*, 2927−2933.

(20) Peng, W.; Wan, J.; Xie, B.; Ma, X. *Org. Biomol. Chem.* **2014**, *12*, 8336−8345.

(21) Wang, X.; Yin, L.; Yang, T.; Wang, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 108−114.

(22) Nun, P.; Perez, V.; Calmes, M.; Martinez, J.; Lamaty, F. *Chem. - Eur. J.* **2012**, *18*, 3773−3779.

(23) Lee, J. H.; Yoo, M. S.; Jung, J. H.; Jew, S. s.; Park, H. g.; Jeong, B. S. *Tetrahedron* **2007**, *63*, 7906−7915.

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