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Basicities and Nucleophilicities of Pyrrolidines and Imidazolidinones Used as Organocatalysts

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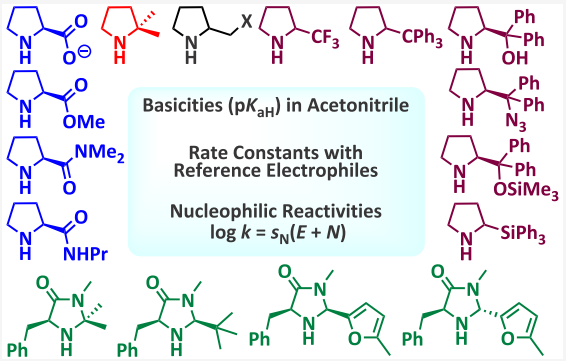
Supporting Information

ABSTRACT: The Brønsted basicities pK_{aH} (i.e., pK_a of the conjugate acids) of 32 pyrrolidines and imidazolidinones, commonly used in organocatalytic reactions, have been determined photometrically in acetonitrile solution using CH acids as indicators. Most investigated pyrrolidines have basicities in the range $16 < pK_{aH} < 20$, while imidazolidinones are significantly less basic ($10 < pK_{aH} < 12$). 2-(Trifluoromethyl)pyrrolidine (**A14**, pK_{aH} 12.6) and the 2-imidazoliummethyl-substituted pyrrolidine **A21** (pK_{aH} 11.1) are outside the typical range for pyrrolidines with basicities comparable to those of imidazolidinones. Kinetics of the reactions of these 32 organocatalysts with benzhydrylium ions (Ar_2CH^+) and structurally related quinone methides, common reference electrophiles for quantifying nucleophilic reactivities, have been measured photometrically. Most reactions followed second-order kinetics, first order in amine and first order in electrophile. More complex kinetics were observed for the reactions of imidazolidinones and several pyrrolidines carrying bulky 2-substituents, due to reversibility of the initial attack of the amines at the electrophiles followed by rate-determining deprotonation of the intermediate ammonium ions. In the presence of 2,4,6-collidine or 2,6-di-*tert*-butyl-4-methyl-pyridine, the deprotonation of the initial adducts became faster, which allowed the rate of the attack of the amines at the electrophiles to be determined. The resulting second-order rate constants k_2 followed the correlation $\log k_2(20\ °C) = s_N(N + E)$, where electrophiles are characterized by one parameter (E) and nucleophiles are characterized by the two solvent-dependent parameters N and s_N. In this way, the organocatalysts **A1**−**A32** were integrated in our comprehensive nucleophilicity scale, which compares n-, π-, and σ-nucleophiles. The nucleophilic reactivities of the title compounds correlate only poorly with their Brønsted basicities.



INTRODUCTION

Chiral pyrrolidines and imidazolidinones play a key role as organocatalysts in modern organic synthesis.[1−3] Numerous mechanistic investigations on organocatalytic transformations via intermediate enamines[4] and iminium ions[5] have been performed, mostly in water, DMSO, and acetonitrile. The rate of the initial step, commonly the nucleophilic attack of the secondary amine at the carbonyl group, depends on the nature of the carbonyl group as well as on the basicity and nucleophilicity of the amine. Whereas Brønsted basicities of several pyrrolidines and imidazolidinones have been reported in aqueous solution,[6] investigations of protonation equilibria in aprotic solvents are rare,[7] and we are not aware of any systematic determinations of their nucleophilic reactivities. Since knowledge of these thermodynamic and kinetic data is crucial for the systematic optimization of organocatalytic transformations, we have now determined the Brønsted basicities of the amines **A1**−**A32** (Chart 1) in acetonitrile and the kinetics of their reactions with reference electrophiles.

RESULTS

Syntheses for Amines A1−A32. Compounds synthesized from L-proline or L-phenylalanine were obtained as enantiopure compounds, and others were synthesized as racemates, generally following literature procedures. Major variations were the cyclization step in the synthesis of 2-isopropylpyrrolidine (**A4**) and the synthesis of potassium prolinate (K-**A1**). Since the purification of the amines has been modified in several cases, full experimental details of all syntheses are given in the Supporting Information.

Brønsted Basicities in Acetonitrile. In order to avoid confusion, basicities of the amines are always expressed by their pK_{aH} values, which equal the pK_a values of the conjugate ammonium ions. Since acetonitrile proved to be a suitable solvent for our kinetic investigations, we also used acetonitrile as the solvent for comparing the Brønsted basicities of **A1**−**A32**. Extensive previous work by Leito and associates on acidities in acetonitrile included the determination of pK_a values for the CH acids **C1**H−**C6**H (Chart 2), which were suitable as indicators for our studies, since their deprotonation yields the colored carbanions **C1**$^-$−**C6**$^-$.[8]

As illustrated in Figure 1 for the deprotonation of **C4**H with **A24**, spectrophotometric titrations were performed by record-

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Chart 1. Pyrrolidines and Imidazolidinones Investigated in This Work

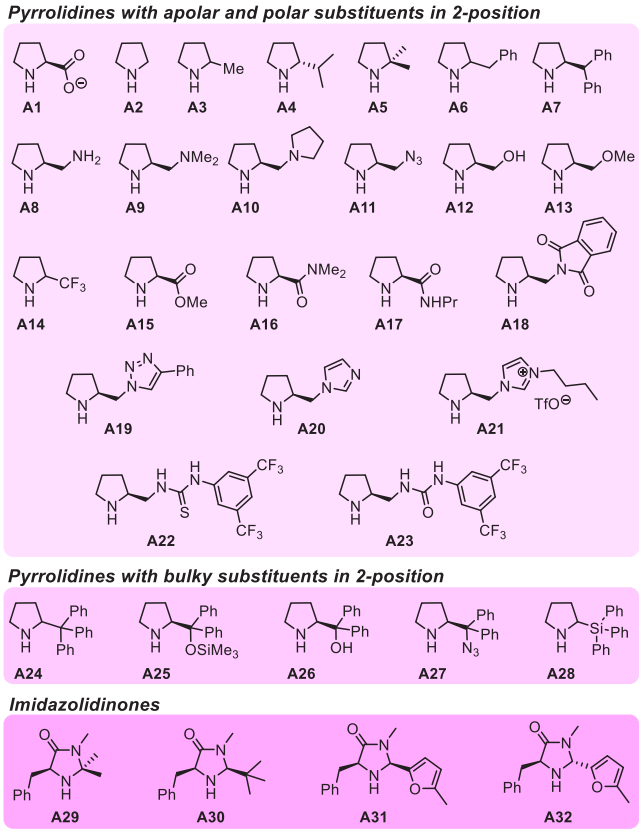
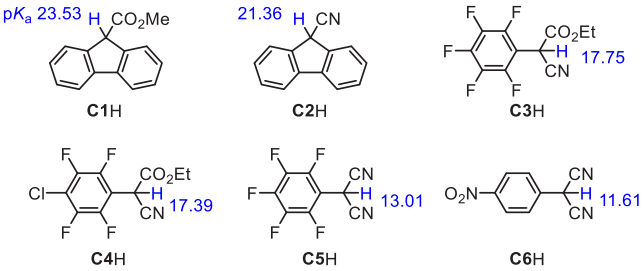


Chart 2. Indicator Acids and Their pK_a Values in Acetonitrile (25 °C)[8]



ing the UV−vis spectra in the range from 250 to 600 nm (stock solutions of the amines **A** were added to solutions of the indicator acids **CH**). Since we wanted to compare the equilibrium constants with kinetic data at 20 °C, also the titrations were carried out at 20 °C.

For each step of the titration, the equilibrium constant K for the reaction in eq 1 can be calculated by eq 2.

$$\mathbf{A} + \mathbf{CH} \overset{K}{\rightleftharpoons} \mathbf{AH}^+ + \mathbf{C}^- \tag{1}$$

$$K = \frac{[\mathbf{AH}^+][\mathbf{C}^-]}{[\mathbf{A}][\mathbf{CH}]} \tag{2}$$

According to the Lambert−Beer law, the equilibrium concentrations $[\mathbf{C}^-]$, $[\mathbf{A}]$, and $[\mathbf{CH}]$ required to calculate K in eq 2 were obtained by applying eqs 3−5, in which V_0 and V_f are the initial and final volumes of the acetonitrile solutions, respectively, and $[\mathbf{A}]_{0,i}$ is the initial concentration of the added amine **A** at a certain step i of the titration. Furthermore, the experimentally measured absorbance after each step i of the titration (A) and the final absorbance (A_f) reached after quantitative deprotonation of the indicator acids **CH** by adding the strong Brønsted bases 1,5,7-triazabicyclo[4.4.0]-dec-5-ene (TBD, pK_{aH} 26.02[7c]) or 1,8-diazabicyclo(5.4.0)-undec-7-ene (DBU, pK_{aH} 24.31[7c]) in the final step of the titration are used in eq 3.

$$[\mathbf{C}^-] = [\mathbf{AH}^+] = [\mathbf{CH}]_0(A/A_f)(V_0/V_f) \tag{3}$$

$$[\mathbf{A}] = [\mathbf{A}]_{0,i} - [\mathbf{C}^-] \tag{4}$$

$$[\mathbf{CH}] = [\mathbf{CH}]_0(V_0/V) - [\mathbf{C}^-] \tag{5}$$

According to eq 2 and because $[\mathbf{AH}^+] = [\mathbf{C}^-]$, the individual equilibrium constants $\log K$ were then determined from the slopes of a linear plot of $[\mathbf{C}^-]^2$ vs $[\mathbf{A}][\mathbf{CH}]$. The basicity of amine **A** (pK_{aH}) is then given by eq 6:

$$\mathrm{p}K_{aH}(\mathbf{A}) = \mathrm{p}K_a(\mathbf{CH}) + \log K \tag{6}$$

Since the free amines **A18** and **A23** are only stable in highly dilute solutions, their basicities were determined by adding stock solutions of the stable ammonium salts **A18**H$^+$ and **A23**H$^+$ to solutions of the colored indicator anions **C**$^-$.

As shown in Chart 2, the indicator acids **C1**H−**C6**H cover an acidity range from 11.6 < pK_a < 23.5, which allowed us to compare amines of widely differing basicity. In several cases (**A7**, **A11**, **A15**−**A20**, **A22**−**A29**), basicities were determined with two different indicators, and the agreement was typically within 0.03 pK_{aH} units. Deviations of pK_{aH} determined by using different indicators never exceeded 0.1 pK_{aH} units.

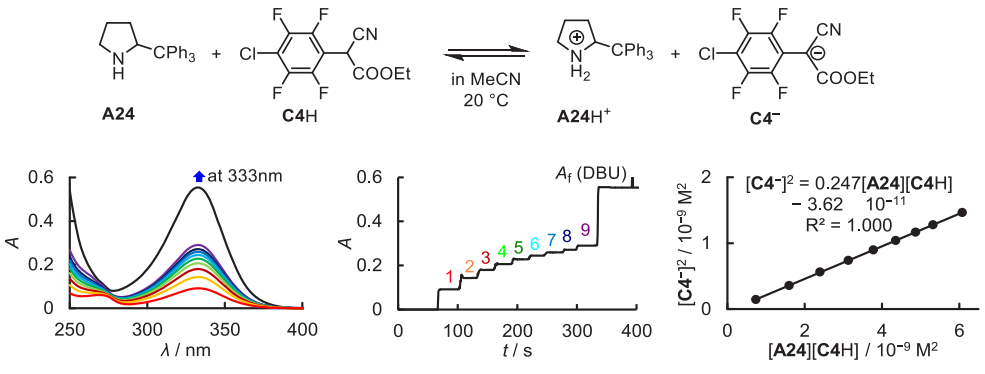


Figure 1. Determination of the pK_{aH} of **A24** by portionwise (steps 1−9) addition of **A24** (2.27×10^{-3} M) to the solution of **C4**H (8.13×10^{-5} M) in acetonitrile at 20 °C. DBU was added in the final step to achieve quantitative deprotonation of **C4**H.

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Individual and averaged Brønsted basicities pK_{aH} of all investigated cyclic secondary amines **A1**−**A32** are listed in Table 1.

Table 1. Basicities (pK_{aH}) of Proline (A1), the Pyrrolidines A2−A28, and the Imidazolidinones A29−A32 (in MeCN)

amine	indicator	K[a]	individual pK_{aH}	averaged pK_{aH}
A1	**C1H**	3.07	24.02	24.02
A2	**C2H**	3.35×10^{-2}	19.89	19.89[b]
A3	**C2H**	1.62×10^{-2}	19.57	19.57
A4	**C2H**	8.92×10^{-3}	19.31	19.31
A5	**C2H**	1.30×10^{-2}	19.47	19.47
A6	**C2H**	2.04×10^{-3}	18.67	18.67
A7	**C2H**	5.59×10^{-4}	18.11	18.13
	C3H	2.47	18.14	
A8	**C2H**	3.19×10^{-2}	19.86	19.86
A9	**C2H**	2.82×10^{-2}	19.81	19.81
A9H$^+$	**C6H**	3.46×10^{-4}	8.15	8.15
A10	**C2H**	4.81×10^{-2}	20.04	20.04
A11	**C3H**	7.65×10^{-1}	17.63	17.66
	C4H	1.93	17.68	
A12	**C2H**	4.28×10^{-3}	18.99	18.99
A13	**C2H**	3.28×10^{-3}	18.88	18.88
A14	**C5H**	4.21×10^{-1}	12.63	12.63
A15	**C3H**	7.56×10^{-2}	16.63	16.63
	C4H	1.72×10^{-1}	16.63	
A16	**C2H**	1.14×10^{-3}	18.42	18.38
	C3H	6.11	18.34	
A17	**C3H**	2.72×10^{-1}	17.18	17.18
	C4H	6.19×10^{-1}	17.18	
A18	**C3$^-$**	2.28[c]	18.11	18.12
	C4$^-$	5.53[c]	18.13	
A19	**C3H**	1.72×10^{-1}	16.99	16.94
	C4H	3.13×10^{-1}	16.89	
A20	**C3H**	9.78×10^{-2}	16.74	16.74
	C4H	2.26×10^{-1}	16.75	
A21	**C6H**	3.38×10^{-1}	11.14	11.14
A22	**C3H**	3.97×10^{-1}	17.35	17.31
	C4H	7.64×10^{-1}	17.27	
A22$^-$	*d*	7.04	25.16	25.16
A23	**C3$^-$**	2.14×10^{1}[c]	19.08	19.13
	C4$^-$	6.12×10^{1}[c]	19.18	
A24	**C3H**	1.12×10^{-1}	16.80	16.79
	C4H	2.47×10^{-1}	16.78	
A25	**C3H**	7.21×10^{-1}	17.61	17.61
	C4H	1.68	17.62	
A26	**C3H**	4.36×10^{-1}	17.39	17.39
	C4H	9.82×10^{-1}	17.38	
A27	**C3H**	1.14×10^{-2}	15.81	15.79
	C4H	2.46×10^{-2}	15.78	
A28	**C3H**	1.17	17.82	17.81
	C4H	2.57	17.80	
A29	**C5H**	6.72×10^{-2}	11.84	11.83
	C6H	1.64	11.83	
A30	**C6H**	1.06×10^{-1}	10.63	10.63
A31	**C6H**	8.61×10^{-2}	10.54	10.54
A32	**C6H**	1.22×10^{-1}	10.70	10.70

[a] K as defined in eq 2. [b] Leito and co-workers reported pK_{aH}(**A2**) 19.62 in MeCN (ref 7c). [c] Obtained by titrating **AH$^+$** into solutions of deprotonated indicators **C$^-$** (see text). [d] By following the absorbance of **A22$^-$** in the titration with DBU (pK_{aH} 24.31).

As illustrated in Figure 2, the basicity constants in acetonitrile cover the range $10 < pK_{aH} < 24$; while most pyrrolidines are in the range $16 < pK_{aH} < 20$, the imidazolidinones are in the range $10 < pK_{aH} < 12$. Thus, steric and electronic effects of the 2-substituents generally reduce the basicity of the parent pyrrolidine **A2** (pK_{aH} 19.89) by less than 4 pK units. If one disregards the slightly higher basicity of the diamine **A10**, 2-(trifluoromethyl)pyrrolidine **A14** is the only neutral pyrrolidine outside this range with a basicity constant pK_{aH} of 12.63, that is, 7 pK_a units smaller than that of the parent pyrrolidine. On the other hand, charged substituents have a large effect on the basicity. Thus, the negative charge of the carboxylate group in prolinate (**A1**) increases the basicity of the pyrrolidine by 4 orders of magnitude, while the positive charge of the imidazolium group in **A21** (pK_{aH} 11.14) reduces the pyrrolidine basicity by almost 9 pK_{aH} units.

Kinetic Investigations. It is obvious that a single reference electrophile is not sufficient for comparing nucleophiles of widely varying reactivities. Hence, we have used a set of previously characterized *p*- and *m*-substituted benzhydrylium ions and structurally related quinone methides (Chart 3) as reference electrophiles, which differ widely in reactivity while the steric surroundings of the reaction center are kept constant.

All kinetic investigations were performed photometrically at 20 °C by following the disappearance of the colored electrophiles (346 nm $\leq \lambda_{max} \leq$ 646 nm). A sufficient excess of the amines **A** (≥10 equiv) over the electrophiles **E** was used in all reactions to achieve pseudo-first-order kinetics. As a consequence, in most cases a monoexponential decay of the absorbances of the electrophiles was observed, from which the first-order rate constants k_{obs} (s^{-1}) were derived by least-squares fitting of the function $A_t = A_0 \exp(-k_{obs}t) + C$ to the observed time-dependent absorbances. Since the first-order rate constants k_{obs} did not always increase linearly with the concentration of the amines, let us first consider the mechanism of these reactions (Scheme 1): The reaction of a secondary amine **A** with a benzhydrylium ion **E** generates the ammonium ion **F**, which will generally be deprotonated by **A**, because **A** and **G** can be assumed to have similar basicities but **A** is present in high excess under the conditions of the kinetic experiments. If **A** is a strong Lewis base and **E** is a strong Lewis acid, the combination of **A** with **E** to give **F** is irreversible, and the reactions follow second-order kinetics, first order in **E** and first order in **A**. Second-order kinetics will also be encountered, if the formation of **F** is endergonic, but deprotonation of **F** is much faster than the reverse reaction ($k_T[\mathbf{A}] \gg k_{-2}$). If the retroaddition of **F** is faster than its deprotonation, the second step of Scheme 1 is rate-determining, and in the case of $k_T[\mathbf{A}] \ll k_{-2}$, third-order kinetics will result, first order in **E** and second order in **A**.

Since all reactions of the reference electrophiles **E** from Chart 3 with pyrrolidines **A** give rise to analogous products, we studied a few of the possible combinations to confirm this assumption. As exemplified in Scheme 2 for the reactions of the benzhydrylium tetrafluoroborate **E13** with the 2-methyl-, 2-trifluoromethyl-, 2-trityl-, and 2-triphenylsilyl-substituted pyrrolidines **A3**, **A14**, **A24**, and **A28**, respectively, in acetonitrile at 20 °C, N-benzhydrylated pyrrolidines were isolated and characterized by spectroscopic methods. Recrystallization of 4,4′-((2-tritylpyrrolidin-1-yl)methylene)-bis(*N*,*N*-dimethylaniline) delivered crystals, which were

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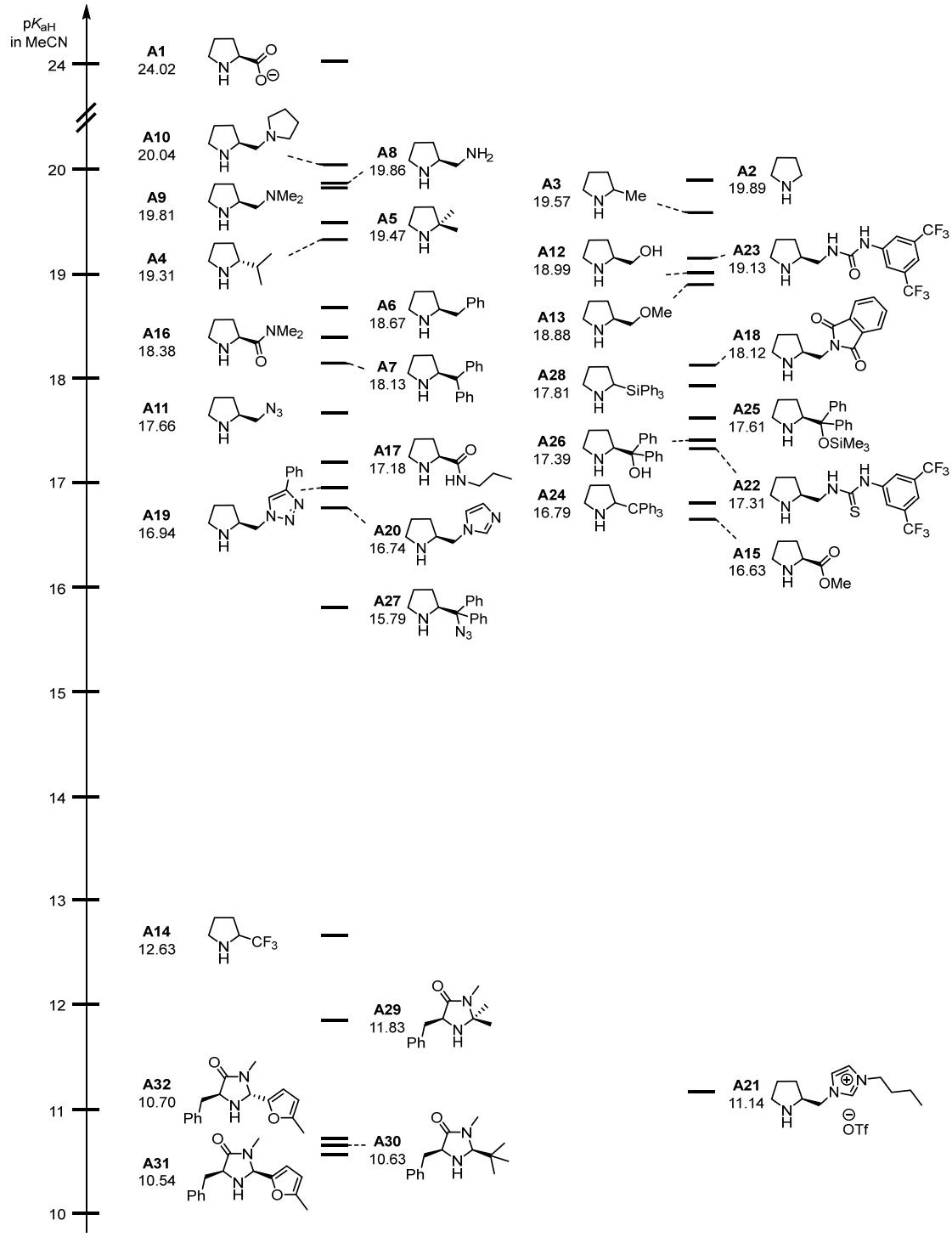

Figure 2. Basicity scale (pK_{aH} in MeCN) for the cyclic secondary amines **A1**−**A32**.

investigated by single crystal X-ray analysis,[10] showing that even the installation of the bulky trityl group in the 2-position leaves enough space at the adjacent nucleophilic nitrogen of the pyrrolidine to allow the attack of the benzhydrylium ions used as reference electrophiles in this study.

As explicitly described in section 2.3 of the Supporting Information, our initial attempts to follow the reactions of amines **A** with the benzhydrylium ions **E** in dichloromethane were hampered by the fact that deprotonation of the initially formed ammonium ions **F** was often found to be rate-determining. Hence, in many cases, rate constants for the initial attack of amines **A** at benzhydrylium ions **E** could not be derived from these measurements. Fortunately, the reactions in acetonitrile generally followed second-order kinetics even for combinations of pyrrolidines with weak electrophiles, as illustrated for the reaction of **A13** with **E9** in Figure 3. Therefore, acetonitrile was selected as the standard solvent for the further investigations.[11,12]

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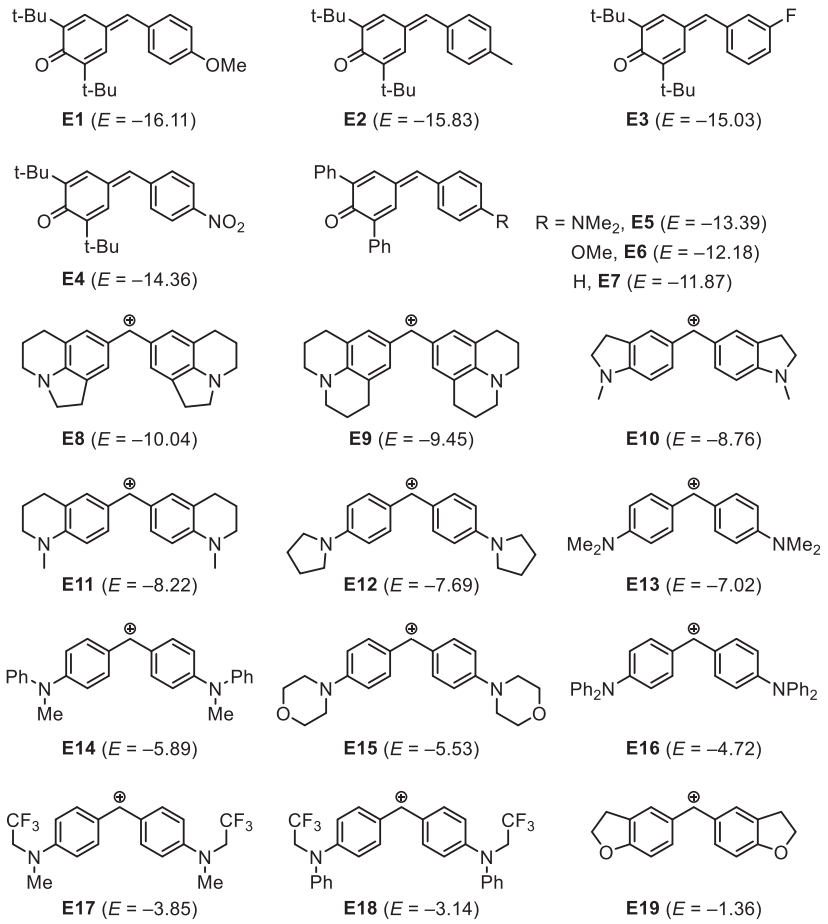
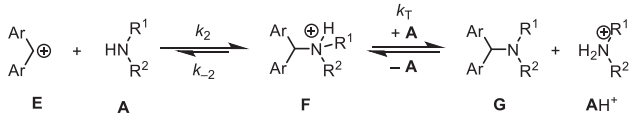
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

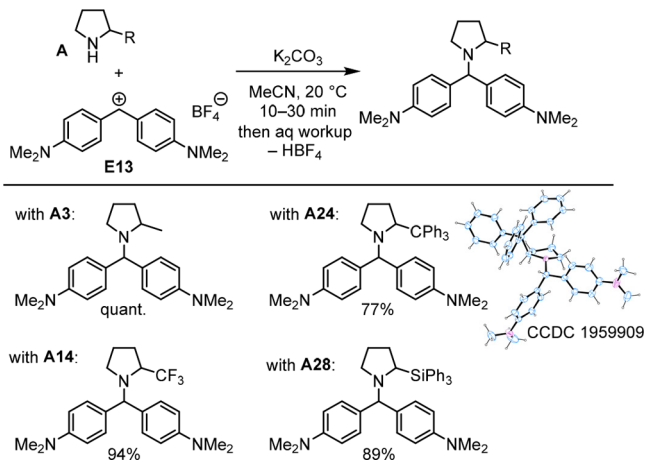
Chart 3. Electrophilicity Parameters of Benzhydrylium Ions (Counterions: BF_4^-) and Quinone Methides Used as Reference Electrophiles in This Study[9]



Scheme 1. Mechanism for the Reactions of Amines A with Benzhydrylium Ions E8–E19



Scheme 2. Reactions of Pyrrolidines with E13



However, pyrrolidines with bulky substituents deviated from this behavior also in acetonitrile solution. The upper graph of Figure 4 shows, for example, that the benzhydrylium ion **E13** was consumed by less than 10% when combined with 10 equiv of the sterically shielded pyrrolidine **A27**. Attempts to shift this equilibrium toward the product side by adding more basic aliphatic tertiary amines (trimethylamine, dimethylethylamine, diisopropylethylamine) were unsuccessful, because these amines reacted with **E13** (probably via hydride transfer)[13] with similar rates as **A27**. The 2,4,6-trialkylated pyridines **D1** and **D2**, however, did not react with **E13**, and Figure 4 illustrates that the reaction of **A27** with **E13** can be shifted more and more to the product side when increasing quantities of 2,4,6-collidine (**D2**) were added.

Accordingly, a higher order of **A27** was observed for the reaction of **A27** with **E13** in the absence of an additive, in line with a reversible nucleophilic attack of **A27** at **E13** (left graph of Figure 5). On the other hand, clear-cut second-order reactions, first order with respect to **E13** and first order with respect to **A27**, were found when sufficient amounts of collidine (**D2**) or 2,6-di-*tert*-butyl-4-methyl-pyridine (**D1**) were present (Figure 5, middle and right). Since the same rate constants within experimental error were obtained when **D2** or **D1** were used as additives, one can conclude that these reactions proceed with rate-determining formation of an ammonium ion **F** (Scheme 1), which is rapidly deprotonated by the pyridines **D1** or **D2**.

Deviations from second-order kinetics were also observed in reactions with the CF_3-substituted pyrrolidine **A14**. While the reaction of **A14** with the highly electrophilic and Lewis acidic

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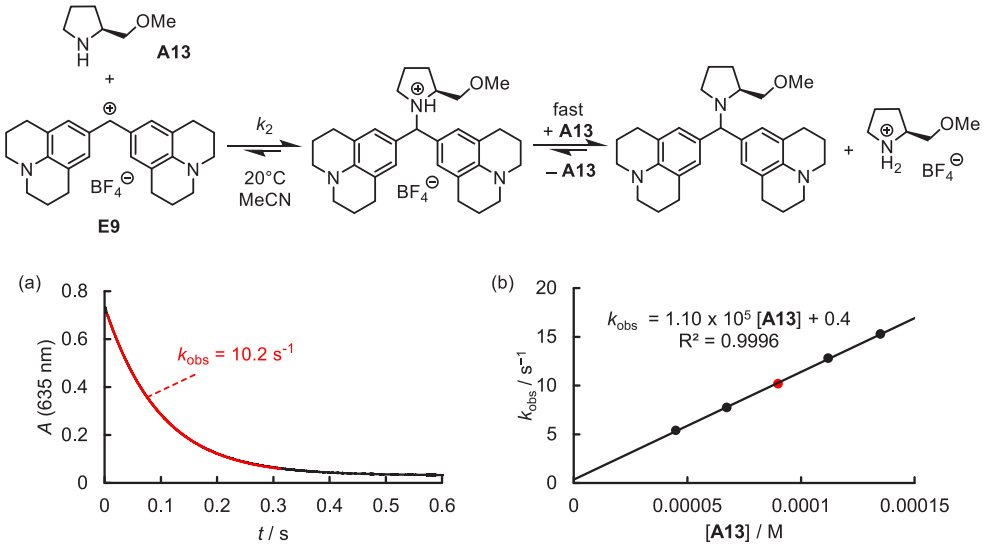

Figure 3. (a) Determination of the pseudo-first-order rate constant for the reaction of **A13** (c_0 = 8.99 × 10^{-5} M) with **E9** (c_0 = 4.28 × 10^{-6} M) in MeCN at 20 °C. (b) Determination of the second-order rate constant for the reaction of **A13** with **E9**.

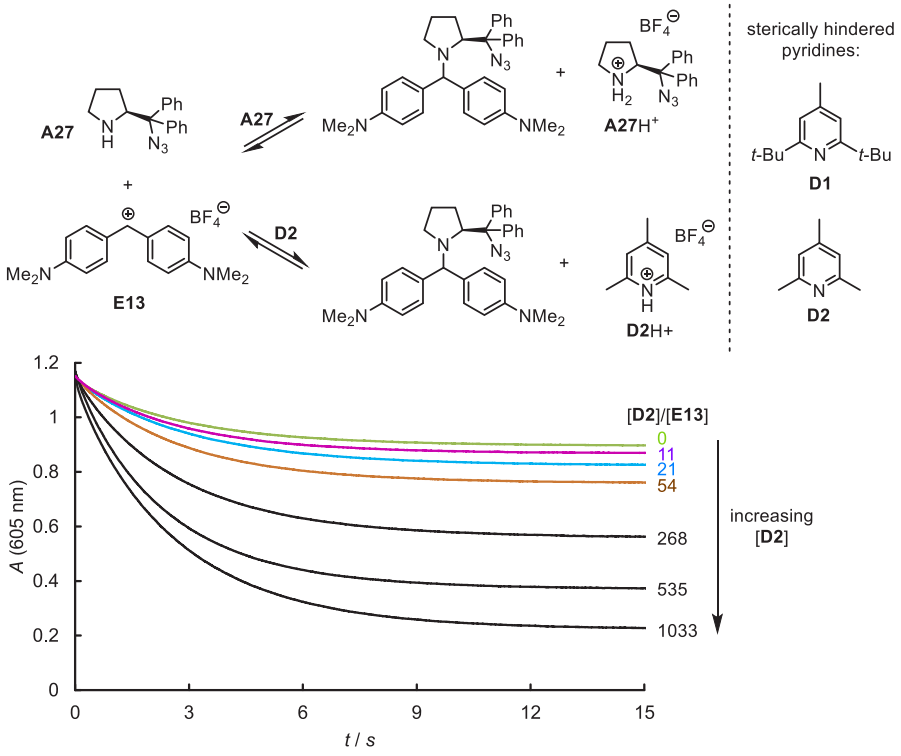

Figure 4. Reaction of **E13** (c_0 = 7.06 × 10^{-6} M) with an excess of **A27** (c_0 = 7.67 × 10^{-5} M) in the presence of increasing concentrations of **D2** (in MeCN, 20 °C).

benzhydrylium ion **E18** followed second-order kinetics in the absence of any additive, the less electrophilic (and less Lewis acidic) benzhydrylium ions **E17** and **E15** only reacted by second-order kinetics when an additional base was present (e.g., 1.23 mM **D1** in the case of **E17** and 2.46 mM **D1** in the case of **E15**). For the reaction of the even further stabilized benzhydrylium ion **E13** with excess **A14**, Figure 6a shows that the pseudo-first-order rate constant k_{obs} did not increase linearly with the concentration of **A14** even when **D1** was present in a concentration of 4.92 mM. For this reaction, also a concentration of 2.25 mM of **D2** was insufficient to achieve a linear correlation between k_{obs} and [**A14**] (Figure 6b). A linear correlation of k_{obs} with [**A14**] was eventually observed in the presence of 4.49 mM **D2** (Figure 6c). With pK_{aH} 15.00,[7c] collidine (**D2**) is a stronger base than **A14** (pK_{aH} 12.63, Table 1), which explains the observation that second-order kinetics for the reaction of **E13** with **A14** were obtained in the presence of **D2** at a concentration of 4.45 mM. Since pyridine **D1** (pK_{aH} 12.8)[14] is only slightly more basic than **A14** in acetonitrile, one can explain why **D1** is ineffective to achieve second-order kinetics.

According to the previous discussion, both steric and electron-withdrawing effects reduce the Lewis basicities of the pyrrolidines and lead to kinetics, in which deprotonation of

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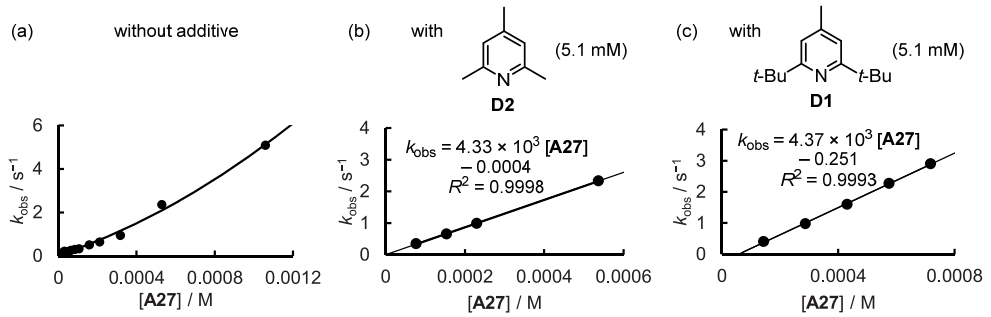

Figure 5. Comparison of (a) the reactions of **A27** with **E13** (c_0 = 2.35 × 10^{-6} M) without additive and (b) with added **D2** (c_0(**E13**) = 5.1 × 10^{-6} M) or (c) with added **D1** (c_0(**E13**) = 5.3 × 10^{-6} M).

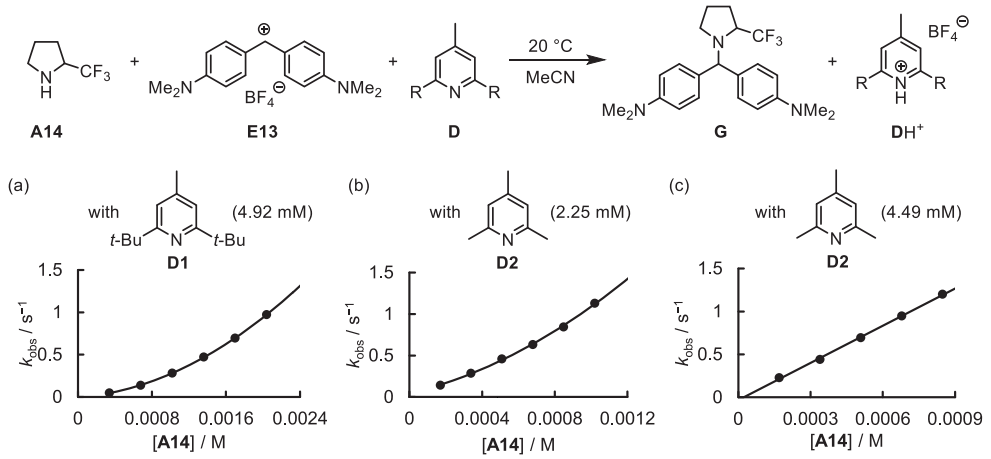

Figure 6. Effect of base additives on the kinetics of the reactions between **A14** and **E13** (4.85 × 10^{-6} M).

the initially formed ammonium ions **F** is rate determining. Imidazolidinones **A29**–**A32** have a reaction center, which is sterically shielded by the vicinal substituents, and they are less basic than all pyrrolidines of this study (exception: cationic base **A21**, Figure 2). As a consequence, even the initial attack of imidazolidinones at the highly reactive benzhydrylium ions **E17** and **E18** is reversible.

Figure 7 shows time-dependent absorption traces for three runs of the reaction of **A29** with **E18** performed under exactly the same conditions (concentrations, etc.), indicating that the kinetics of this reaction was not reproducible in the absence of a base. In the presence of 0.99 mM **D1**, the kinetics of the reaction of **A29** with **E18** became reproducible and a linear correlation between k_{obs} and [**A29**] afforded the second-order rate constant k_2 (Table S186, Supporting Information).

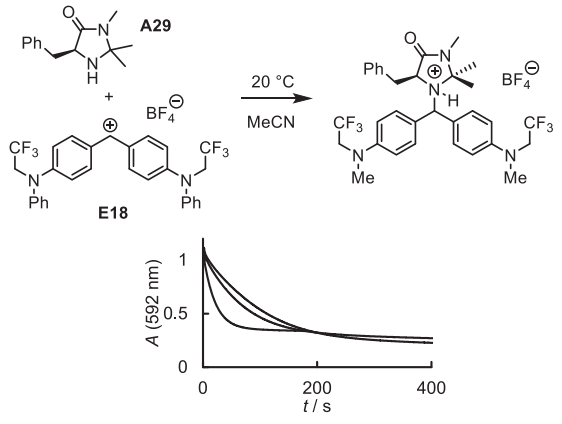

Figure 7. Kinetics of the reactions of **A29** (1.78 × 10^{-4} M) with **E18** (1.36 × 10^{-5} M) were not reproducible in the absence of additional base.

Figure 8a illustrates that the less Lewis acidic benzhydrylium ion **E17** was consumed to only a small extent when combined with 11 equiv of **A29**. Different from the observations in the reaction of **A29** with **E18**, k_{obs} for the reaction of **A29** with **E17** did not increase linearly with the concentration of **A29** in the presence of pyridine **D1** (0.97 mM, Figure 8b). A concentration of 1.18 mM **D2** was also not sufficient to achieve a linear correlation between k_{obs} and [**A29**] (Figure 8c). Clear-cut second-order kinetics were observed for the reaction of **A29** with **E17**, however, when the concentration of collidine **D2** was further increased (Figure 8d).

The quinone methides **E1**–**E7** are weaker electrophiles than the benzhydrylium ions **E8**–**E19** and are, therefore, suitable for characterizing strong nucleophiles. They have been used as reference electrophiles for determining the nucleophilic reactivities of **A1**, **A2**, **A8**, and **A9**. Due to the low Lewis acidities of the quinone methides, the formation of the zwitterions **F** in Scheme 3 will usually be endergonic.

Since the proton transfer, which transforms **F** into the thermodynamically more stable tautomer **G**, cannot proceed intramolecularly for geometrical reasons, base catalysis will be needed. Though both **A** and **G** may catalyze the tautomerization, the amines **A** are the most likely catalysts because of their high concentration. In line with this interpretation, the concave curvature of the k_{obs} vs [**A2**]

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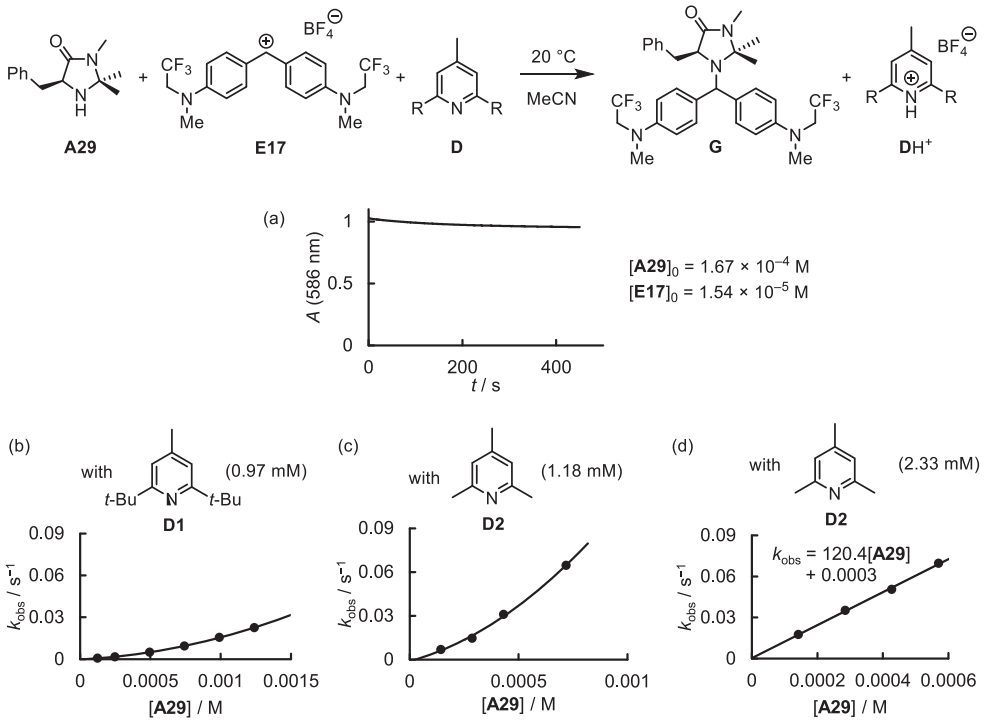
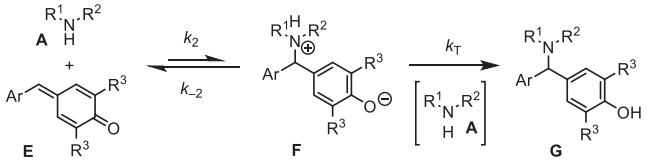


Figure 8. Kinetics of the reaction of **A29** with **E17** ((1.01−1.33) × 10^{-5} M) (a) without additive and (b−d) in the presence of the pyridines **D1** or **D2**.

Scheme 3. Mechanism for the Reactions of Amines A with Quinone Methides E1−E7



plot in Figure 9 indicates a reaction order greater than 1 in amine concentration. Table 2, therefore, does not report second-order rate constants for the reactions of **A2** with the quinone methides **E3** and **E4**. Earlier investigations using much higher concentrations of pyrrolidine (**A2**) allowed second-order rate constants to be derived for its reactions with the less electrophilic quinone methides **E1** and **E2** (Table 2 and ref 11a).

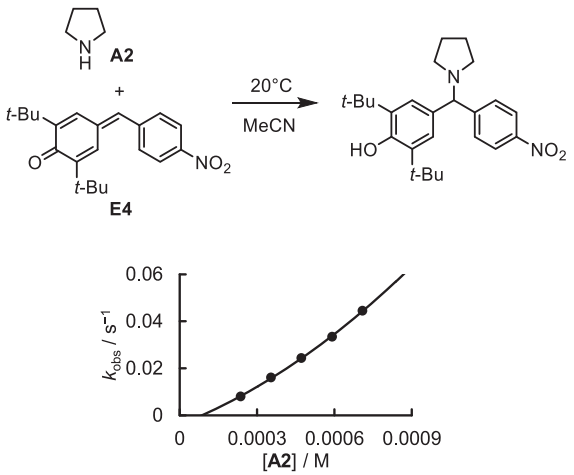


Figure 9. Plot of pseudo-first-order rate constants k_{obs} versus the concentration of pyrrolidine **A2** for the reaction of **A2** with **E4** (2.06 × 10^{-5} M).

Table 2 summarizes that most reactions of the secondary amines with benzhydrylium ions followed second-order kinetics in acetonitrile in the absence of any additive. Footnotes *b* and *c* in Table 2 identify those reactions, in which **D2** or **D1** were added in order to get second-order kinetics with rate-determining attack of the amine at the electrophile.

DISCUSSION

Correlation Analysis. In previous work, we have demonstrated that the linear free energy relationship (eq 7) can be used to describe the rate constants for the reactions of carbocations and Michael acceptors with π-, σ-, and n-nucleophiles.[10,15]

$$\log k_2(20\ ^\circ\mathrm{C}) = s_N(N + E) \quad (7)$$

Figure 10 shows that the second-order rate constants ($\log k_2$) for the attack of the amines **A** at the electrophiles **E7−E13** correlate linearly with the corresponding E parameters according to eq 7, whereby the slopes correspond to the nucleophile-specific parameter s_N and the intercepts on the abscissa ($\log k_2 = 0$, that is, $N = -E$) represent the nucleophilicity parameters N of the amines **A**, which are also listed in Table 2.

The almost parallel correlation lines in Figure 10 (numerically expressed by similar s_N values) illustrate that the relative nucleophilicities of these pyrrolidines are nearly independent of the electrophilicity of the reaction partners. Figure 11 shows, however, that the slopes (s_N) for the pyrrolidines with bulky substituents in 2-position are larger (s_N = 1.39 for **A24**; s_N = 0.98 for **A25**; s_N = 1.22 for **A27**); that is, their reactivities are more affected by variation of the reaction partner than

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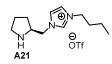
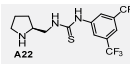
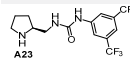
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 2. Second-Order Rate Constants k_2 for the Reactions of the Pyrrolidines and Imidazolidinones A1−A32 with Reference Electrophiles in Acetonitrile at 20 °C

Amines	Electrophiles	k_2 (M^{-1} s^{-1})	N	s_N
 A1	E2	no reaction	19.95	0.68
	E3	2.53×10^3		
	E4	4.77×10^3		
	E5	4.09×10^4		
	E6	1.39×10^5		
	E7	2.31×10^5		
	E8	6.41×10^6		
 A2	E1	3.25×10^{1} [a]	18.58	0.61
	E2	4.82×10^{1} [a]		
	E3	not 2nd order		
	E4	not 2nd order		
	E5	2.12×10^3		
	E6	6.31×10^3		
	E7	1.09×10^4		
	E8	1.18×10^5 [a]		
	E9	3.50×10^5 [a]		
	E10	1.06×10^6		
	E11	2.78×10^6		
 A3	E8	5.53×10^4	16.78	0.71
	E9	1.67×10^5		
	E10	4.22×10^5		
	E11	1.15×10^6		
 A4	E8	3.42×10^4	16.44	0.71
	E9	9.94×10^4		
	E10	2.55×10^5		
	E11	7.18×10^5		
 A5	E9	2.72×10^3	13.96	0.76
	E10	7.89×10^3		
	E11	2.46×10^4		
	E12	7.18×10^4		
	E13	1.78×10^5		
	E14	1.33×10^6		
 A6	E8	7.21×10^4	17.43	0.66
	E9	2.29×10^5		
	E10	4.51×10^5		
	E11	1.33×10^6		
 A7	E8	2.67×10^4	16.61	0.67
	E9	6.08×10^4		
	E10	1.57×10^5		
	E11	4.30×10^5		
	E12	9.80×10^5		
 A8	E7	3.92×10^3	17.24	0.67
	E8	6.03×10^4		
	E9	1.70×10^5		
	E10	4.14×10^5		
	E11	1.12×10^6		
 A9	E8	9.25×10^4	17.41	0.68
	E9	3.32×10^5		
	E10	6.58×10^5		
	E11	1.86×10^6		
 A10	E7	1.31×10^4	18.33	0.64
	E8	1.72×10^5		
	E9	5.48×10^5		
	E10	1.05×10^6		
	E11	2.93×10^6		
 A11	E8	7.54×10^3	15.43	0.73
	E9	2.43×10^4		
	E10	6.38×10^4		
	E11	1.92×10^5		
	E12	4.76×10^5		
	E13	1.13×10^6		
 A12	E8	2.90×10^4	16.74	0.67
	E9	7.89×10^4		
	E10	2.02×10^5		
	E11	4.98×10^5		
 A13	E8	3.60×10^4	16.50	0.71
	E9	1.10×10^5		
	E10	2.63×10^5		
	E11	7.69×10^5		
 A14	E13	1.45×10^3 [b]	11.34	0.73
	E15	1.91×10^4 [c]		
	E17	2.27×10^5 [c]		
	E18	1.21×10^6		
 A15	E8	6.57×10^3	14.75	0.82
	E9	2.47×10^4		
	E10	7.00×10^4		
	E11	2.21×10^5		
 A16	E8	1.08×10^5	17.61	0.67
	E9	3.70×10^5		
	E10	7.67×10^5		
	E11	2.04×10^6		

Amines	Electrophiles	k_2 (M^{-1} s^{-1})	N	s_N
 A17	E9	1.68×10^4	15.20	0.73
	E10	3.87×10^4		
	E11	1.17×10^5		
	E12	3.04×10^5		
 A18	E8	3.33×10^4	15.90	0.77
	E9	8.06×10^4		
	E10	2.77×10^5		
	E11	7.35×10^5		
	E12	2.06×10^6		
 A19	E8	6.16×10^3	15.32	0.72
	E9	1.54×10^4		
	E10	4.42×10^4		
	E11	1.31×10^5		
	E12	3.37×10^5		
	E13	7.81×10^5		
 A20	E8	5.39×10^3	15.55	0.69
	E9	1.83×10^4		
	E10	3.66×10^4		
	E11	1.18×10^5		
	E12	2.77×10^5		
	E13	6.28×10^5		
 A21	E13	2.97×10^3	13.57	0.53
	E14	2.11×10^4 [d]		
	E15	1.49×10^4		
	E16	1.20×10^5 [d]		
	E17	1.33×10^5		
	E18	3.09×10^5		
 A22	E8	2.42×10^3	14.97	0.69
	E9	7.25×10^3		
	E10	1.76×10^4		
	E11	4.11×10^4		
	E12	1.14×10^5		
 A23	E8	5.44×10^4	17.50	0.64
	E9	1.45×10^5		
	E10	3.68×10^5		
	E11	8.11×10^5		
 A24	E11	1.97×10^{1} [c]	9.16	1.39
	E12	1.27×10^2 [c]		
	E13	7.92×10^2 [c]		
	E15	1.16×10^5 [c]		
 A25	E9	2.26×10^2 [c]	12.03	0.98
	E10	2.67×10^3 [c]		
	E11	5.30×10^3 [c]		
	E12	1.63×10^4 [c]		
	E13	9.65×10^4		
	E15	2.05×10^6		
 A26	E9	5.48×10^3	16.18	0.56
	E10	1.22×10^4		
	E11	3.57×10^4		
	E12	7.50×10^4		
	E13	1.72×10^5		
	E15	8.02×10^5 [c]		
 A27	E11	1.26×10^2 [b]	9.90	1.22
	E12	3.29×10^2 [b]		
	E13	4.33×10^3 [b]		
	E15	1.94×10^5		
 A28	E9	4.90×10^3 [c]	14.00	0.84
	E10	3.96×10^4 [c]		
	E11	7.29×10^4		
	E12	1.60×10^5		
	E13	7.15×10^5		
 A29	E15	2.99 [b]	6.04	0.92
	E17	1.20×10^2 [b]		
	E18	3.79×10^2 [c]		
	E19	2.16×10^4		
 A30	E13	1.33×10^{-2} [b]	5.44	1.12
	E15	1.38 [b]		
	E17	3.94×10^{1} [b]		
	E18	4.24×10^2 [c]		
 A31	E13	2.68×10^{1} [b]	8.76	0.89
	E15	1.33×10^3 [b]		
	E17	1.63×10^4 [b]		
	E18	1.10×10^5 [c]		
 A32	E13	1.76 [b]	7.39	1.00
	E15	1.28×10^2 [b]		
	E17	2.48×10^3 [b]		
	E18	1.89×10^4 [c]		

[a] From ref 11a. [b] In the presence of 2,4,6-collidine (**D2**). [c] In the presence of 2,6-di-*tert*-butyl-4-methylpyridine (**D1**). [d] Second-order rate constants k_2 for the reactions of **A21** with **E14** and **E16** were not used for the determination of the N and s_N parameters.

those of ordinary pyrrolidines. All imidazolidinones **A29**−**A32** are less nucleophilic than the investigated pyrrolidines and have s_N values around 1, that is, in between ordinary pyrrolidines and pyrrolidines with bulky substituents.

Comparable to the pK_{aH} scale in Figure 2, Figure 12 shows that, with the exception of a few pyrrolidines with bulky or electron-withdrawing substituents, most pyrrolidines are in a

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J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

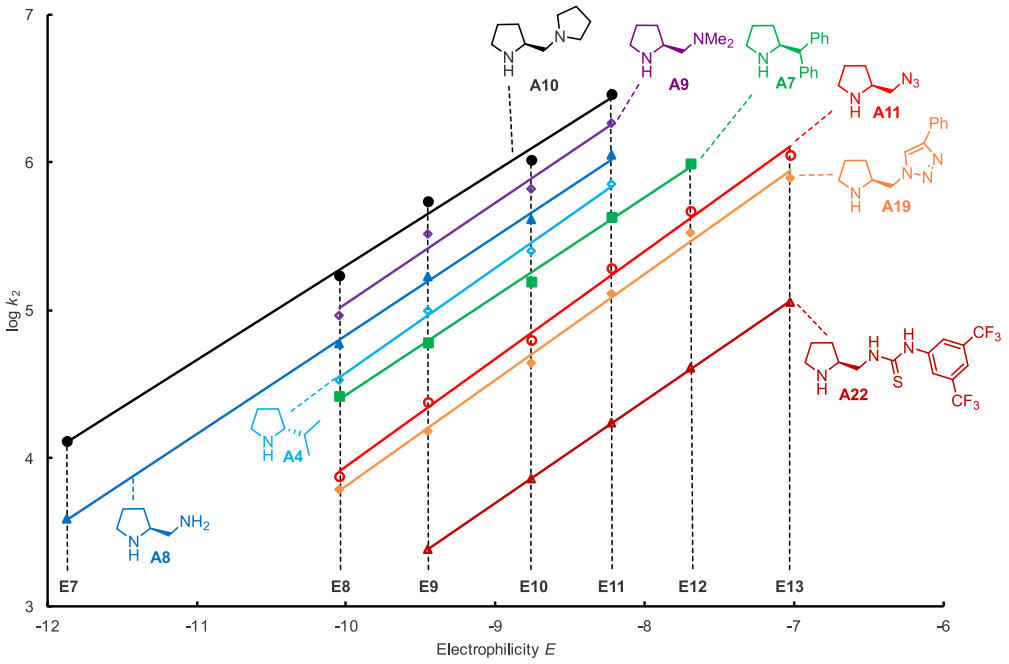

Figure 10. Plot of log k_2 versus E of the reactions of pyrrolidines **A** with reference electrophiles **E** in acetonitrile at 20 °C.

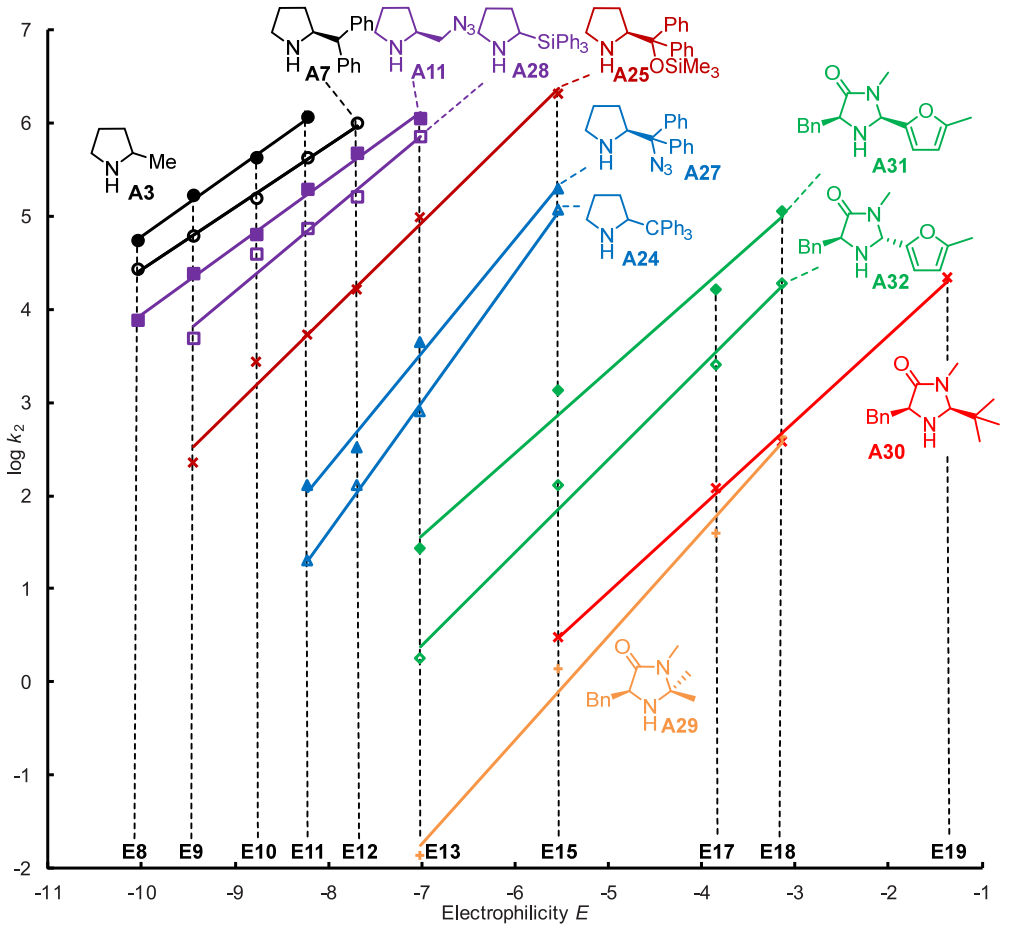

Figure 11. Plot of log k_2 versus E of the reactions of pyrrolidines carrying bulky substituents in the 2-position and of imidazolidinones with reference electrophiles **E** in acetonitrile at 20 °C.

narrow range of nucleophilicity, $13 < N < 18$, significantly more nucleophilic than the imidazolidinones ($5 < N < 9$).

Correlations between nucleophilic reactivities and Brønsted basicities (so-called Brønsted correlations) have been a main

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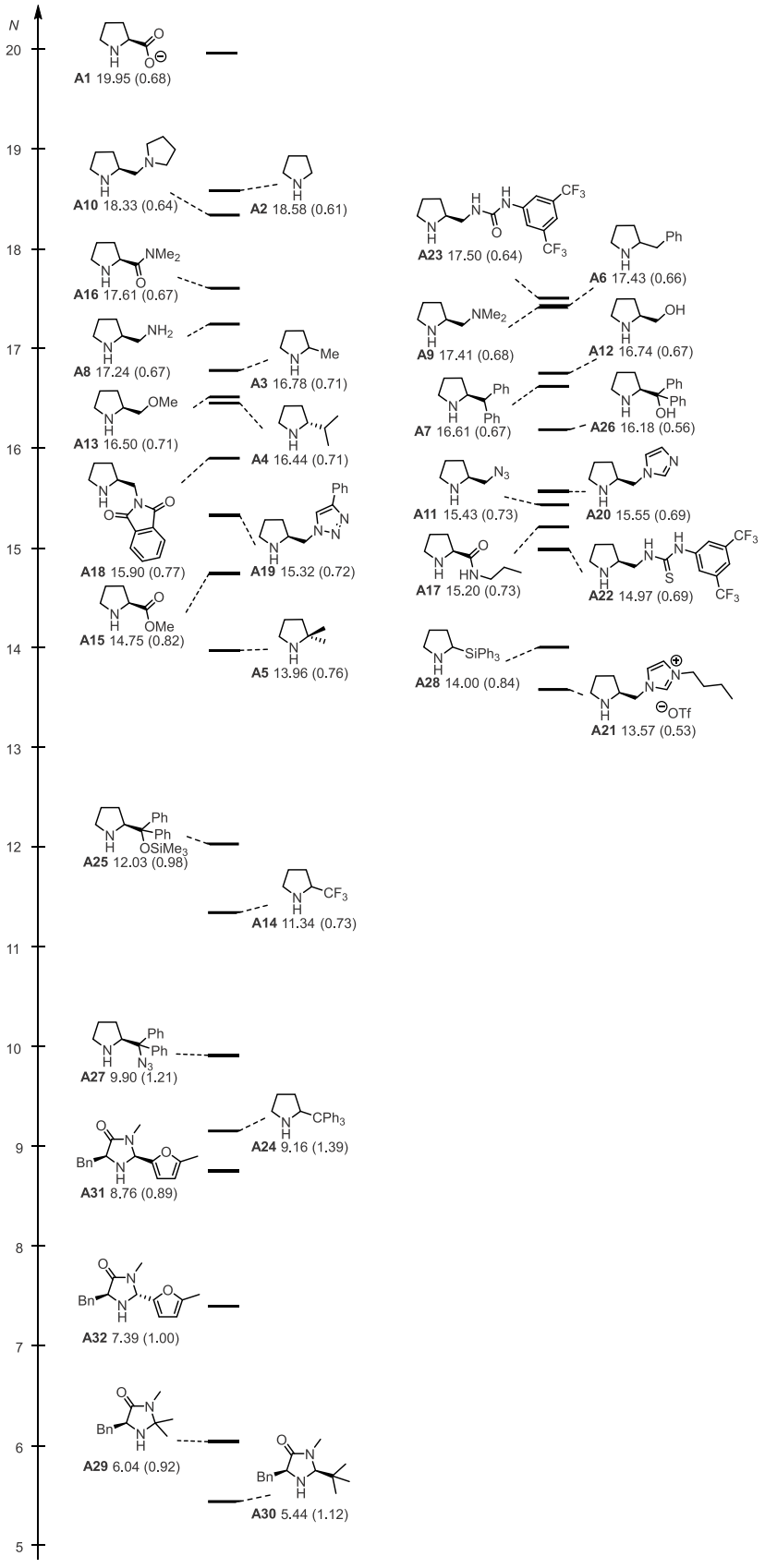

Figure 12. Nucleophilicity scale for pyrrolidines and imidazolidinones in acetonitrile (20 °C) ordered from the bottom to the top according to increasing nucleophilicity parameters N with nucleophile-specific parameters s_N given in parentheses; N and s_N are defined in eq 7.

topic of Physical Organic Chemistry since the 1930s. It is well-known that separate $\log k$ vs pK_{aH} correlations are obtained when the nature of the central atom of the nucleophiles is varied.[16] However, in recent work, we reported

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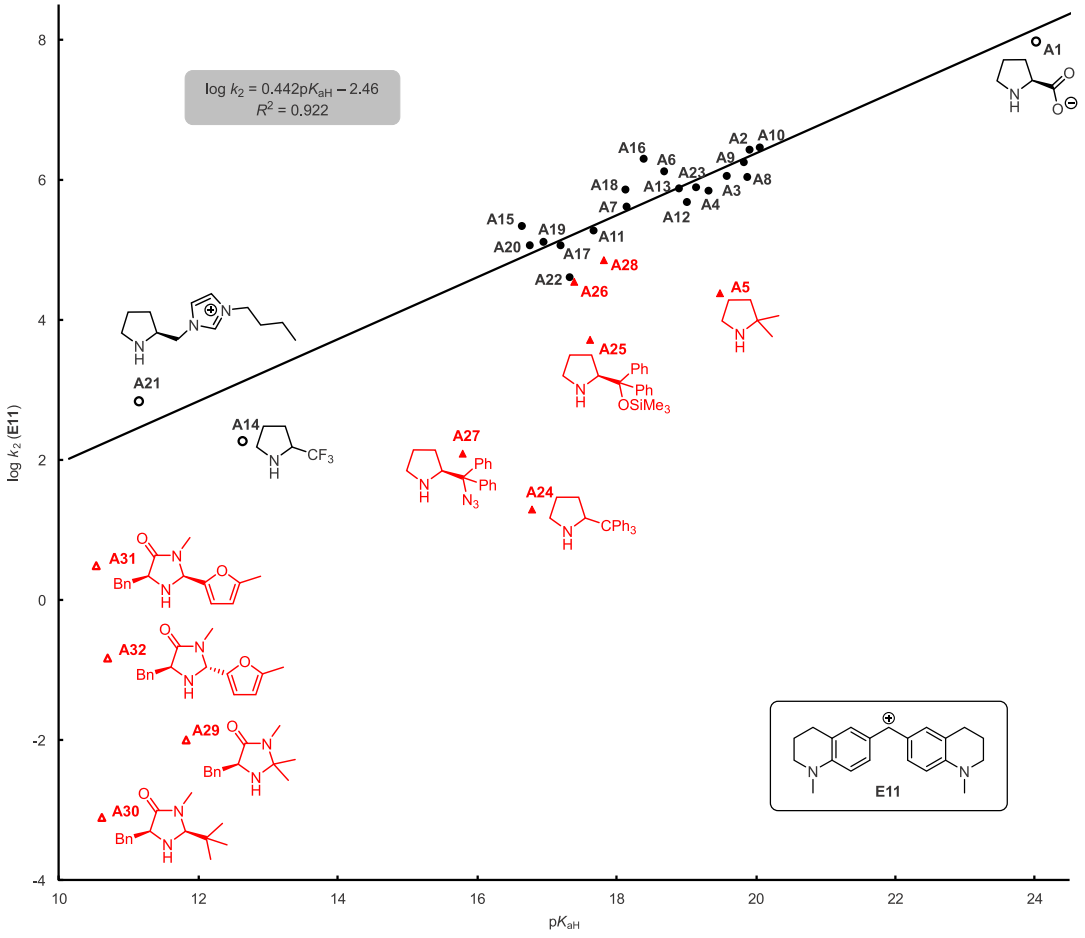

Figure 13. Plot of the rate constants ($\log k_2$) for the reactions of the amines **A1**−**A32** with the benzhydrylium ion **E11** versus the corresponding Brønsted basicities (pK_{aH}) in acetonitrile. The drawn correlation line is based on the reactivities of pyrrolidines identified by circles (i.e., pyrrolidines with bulky substituents and imidazolidinones not included). Rate constants characterized by open symbols were calculated by applying eq 7 because their direct measurement is not possible due to the lacking thermodynamic driving force for reaction with **E11** or their extremely high rate (**A1**).

that $\log k$ vs pK_{aH} correlations may also be poor when a variety of structurally diverse *N*-centered nucleophiles are considered.[11,17]

Because of the wide reactivity range covered by the pyrrolidines **A1**−**A28** and imidazolidinones **A29**−**A32**, there is not a single reference electrophile for which experimental rate constants with all amines **A1**−**A32** are available, which hampers the construction of a Brønsted $\log k$ vs pK_{aH} plot. However, for 25 of the 32 amines, experimental rate constants for their reactions with **E11** have been measured (Table 2). Therefore, rate constants for the reactions of this electrophile with the missing seven amines were calculated by applying the correlation equation (eq 7). The accuracy of the calculated rate constants is certified by the high quality of the correlations in Figures 10 and 11.

A very poor correlation between the rate constants for the reactions of the amines **A1**−**A32** with the electrophiles **E11** and their Brønsted basicities is observed when the whole data set is considered (Figure 13). On the other hand, the drawn correlation line shows a fair correlation (R^2 = 0.92) between the rate constants of the reactions of the benzhydrylium ion **E11** with the 2-substituted pyrrolidines marked by circles, i.e., when pyrrolidines with bulky substituents and imidazolidinones (represented by triangles) are excluded from the correlation. The Brønsted coefficient of this correlation implies that 44% of the differences in basicity are reflected in the transition states of their reactions with **E11**.

Figure 13 furthermore shows that the trityl- and azidodiphenylmethyl-substituted pyrrolidines **A24** and **A27**, respectively, react 2−3 orders of magnitude more slowly than ordinary pyrrolidines of comparable basicity. The steric retardation is much smaller for the Hayashi−Jørgensen catalyst **A25**, which is located only by a factor of 33 below the correlation line. Eventually, the nucleophilicities of diphenylprolinol (**A26**) and 2-(triphenylsilyl)pyrrolidine (**A28**) are only marginally smaller than expected from their Brønsted basicities.

The imidazolidinones **A29**−**A32** (represented by open triangles) react much more slowly than all pyrrolidines studied in this work. This can only partially be due to their lower basicity, since they also react more slowly than pyrrolidine **A21**, which has a similar basicity. As the basicities of **A29**−**A32** are similar, their differences in nucleophilicity are interpreted as steric effects. Obviously, steric retardation is strongest in the reactions of MacMillan generation 2 catalyst **A30**, followed by MacMillan generation 1 catalyst **A29**. Steric effects also retard the reactions of the 2-furyl-substituted imidazolidinones **A31** and **A32**, among which the *trans*-isomer is 20 times less reactive because it carries a shielding substituent on both faces of the five-membered ring.

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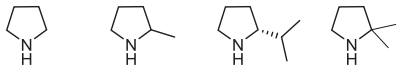
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

The direct comparison of 2-alkyl effects in Scheme 4 shows that the Brønsted basicities K_{aH} differ by less than a factor of 4. While a single alkyl group also reduces nucleophilic reactivity only slightly (**A2**–**A4**), introduction of methyl groups on both faces of the pyrrolidine ring (**A5**) reduces nucleophilicity by 2 orders of magnitude (Scheme 4).

Scheme 4. Comparison of the Brønsted Basicities (pK_{aH}) and Nucleophilic Reactivities (k_{rel}) toward E11 in Acetonitrile at 20 °C



	A2	A3	A4	A5
pK_{aH}	19.89	19.57	19.31	19.47
k_{rel}	1	1/2.4	1/3.9	1/113

Figures 14 and 15 show moderate correlations between the basicities (pK_{aH}) and nucleophilicities ($\log k_2$ vs **E11**) of these pyrrolidines with Hammett's σ_m and Taft's σ^* parameters.[18]

While the reason is presently not understood, there is a good correlation between the basicities of the substituted pyrrolidines and Taft's steric parameters E_s (Figure 16).

As shown in Scheme 5a, the amino-substituted pyrrolidines **A8**–**A10** are slightly stronger Brønsted bases than 2-methylpyrrolidine (**A3**), whereas the hydroxy- and methoxy-substituted pyrrolidines **A12** and **A13** are slightly less basic. Their reactivities toward electrophile **E11** differ only slightly, with the aminomethyl-substituted pyrrolidines somewhat more nucleophilic than their oxy analogues (Scheme 5a).

Scheme 5b shows that the urea-substituted pyrrolidine **A23** has a slightly lower Brønsted basicity and nucleophilic reactivity than 2-methyl-pyrrolidine (**A3**), whereas the change from the urea (**A23**) to the thiourea derivative **A22** reduces the Brønsted basicity by 2 orders of magnitude and the nucleophilic reactivity by a factor of 20. While introduction of the imidazole group in 2-methylpyrrolidine (**A3** → **A20**) reduces the basicity by three pK units, the nucleophilic reactivity decreases by only 1 order of magnitude. N-Butylation of imidazole **A20** to give the positively charged **A21** reduces the Brønsted basicity by 5.6 pK units, while the nucleophilic reactivity decreases only by a factor of 200. Though the imidazolium derivative **A21** is a 31 times weaker base than the 2-(trifluoromethyl)pyrrolidine **A14** (1.5 pK units), **A21** reacts 4 times faster with **E11** than the more basic CF_3-substituted pyrrolidine **A14**. The relative nucleophilic reactivities interconvert, however, due to the difference in s_N, and **A21** reacts 4 times more slowly than **A14** with electrophile **E18** (Table 2).

Figure 17 illustrates that an increasing number of phenyl substituents in the side chain of 2-methyl-pyrrolidine (**A3**) leads to a continuous decrease of basicity (pK_{aH}) with the largest effect between the benzhydryl (**A7**) and trityl groups (**A24**). In contrast, nucleophilicity ($\log k$) stays constant when the first phenyl group is introduced (**A3** → **A6**), drops only slightly with entry of the second phenyl (**A6** → **A7**), but experiences a dramatic decrease on placement of the third phenyl group (**A7** → **A24**).

In previous work, we have demonstrated that enamines, derived from the trityl-substituted pyrrolidine **A24** and the Hayashi–Jørgensen catalyst **A25**, are less nucleophilic than the corresponding enamines derived from the parent pyrrolidine **A2**. Since, on the other hand, iminium ions derived from **A24** and **A25** were even more electrophilic than those derived from **A2**, we concluded that steric effects cannot explain this behavior and deduced an electron-withdrawing effect of the trityl and $CPh_2(OSiMe_3)$ groups through negative hyperconjugation.[2k] We now find the same trend in the pyrrolidines and conclude that the low basicity of the trityl-substituted pyrrolidine **A24** (pK_{aH} 16.79) is predominantly due to negative hyperconjugation of the trityl group. The exceptionally high s_N value of **A24** (s_N = 1.39) accounts for the fact that the reactivity ratio of 2×10^4 for the benzhydryl- (**A7**) and the trityl-substituted (**A24**) pyrrolidines toward **E11** increases to 4×10^5 toward the less electrophilic benzhydrylium ion **E8**.

The prolinate anion **A1** is the strongest Brønsted base as well as the strongest nucleophile of this series. Though carboxylate anions are stronger bases than pyrrolidines in acetonitrile solution (Scheme 6), we assume that the prolinate anion in acetonitrile is preferentially protonated at nitrogen to yield a zwitterion in analogy to the situation in DMSO, where amino acids also exist as zwitterions, though ammonium ions are generally stronger acids in DMSO than carboxylic acids.[7g,19,20] The energy difference between the zwitterion and the tautomer without charge separation is smaller in DMSO than in aqueous solution, however.[21] The preference of the zwitterionic structure of proline in dipolar aprotic solvent may be due to an intramolecular hydrogen bond, as

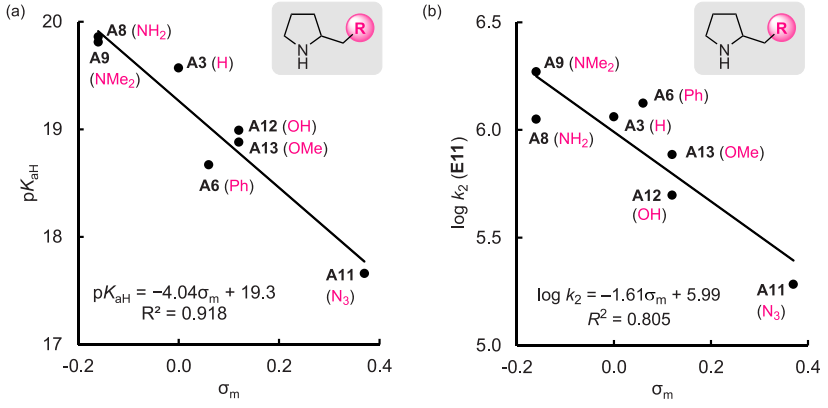


Figure 14. Hammett plots between (a) pK_{aH} and (b) the rate constants for the reactions of **A** with **E11** and σ_m of substituents R at the pyrrolidin-2-ylmethyl position (σ_m from ref 18).

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J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

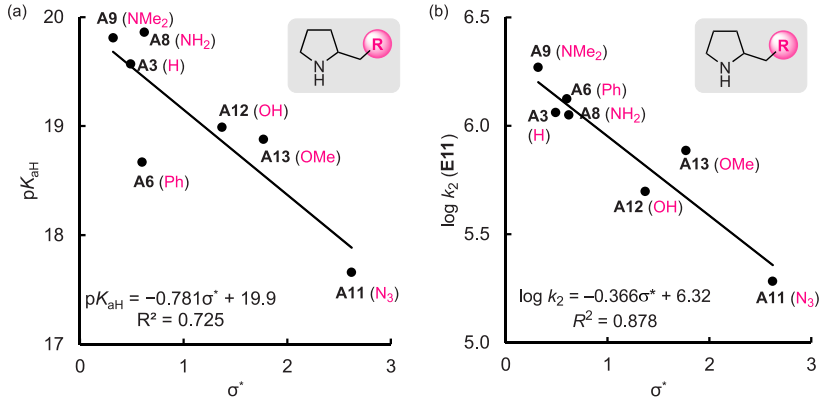


Figure 15. Taft plots between (a) pK_{aH} and (b) the rate constants for the reactions of **A** with **E11** and σ^* of substituents at the pyrrolidin-2-ylmethyl position (σ^* from ref 18).

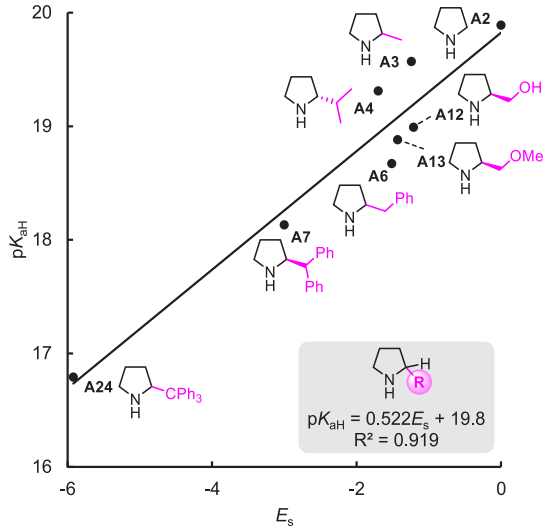


Figure 16. Correlation between Brønsted basicities (pK_{aH}) and Taft's steric parameters E_s of the 2-substituents of pyrrolidines (E_s from ref 18).

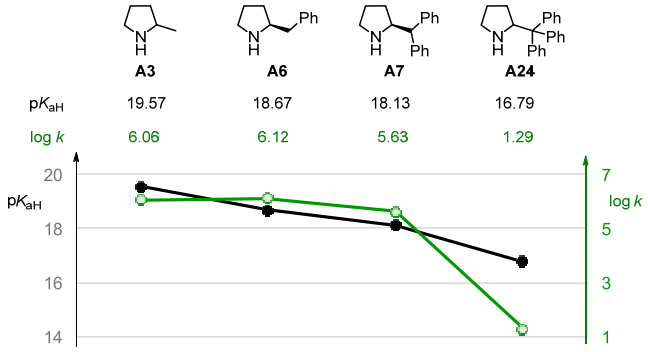
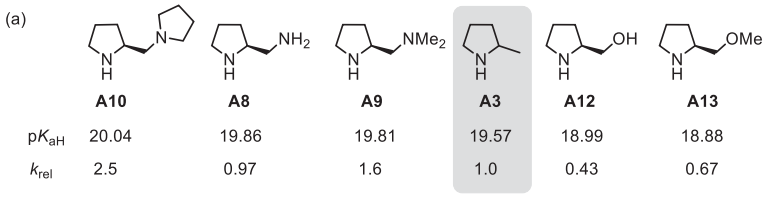


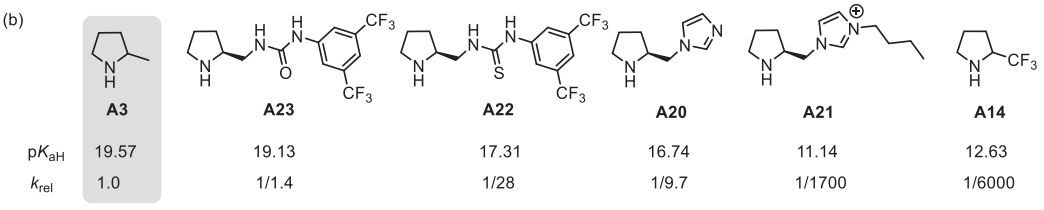
Figure 17. Effect of phenyl groups in the side chain of 2-methylpyrrolidines on Brønsted basicities (black line) and rate constants (green line) of the reactions of the corresponding pyrrolidines with **E11** (in MeCN, 20 °C).

suggested by the X-ray structure of 4-hydroxyproline[22] (Figure 18). Accordingly, the 79-times higher nucleophilic reactivity of prolinate **A1** relative to 2-methyl-pyrrolidine (**A3**) may be due to a hydrogen bond from the carboxylate group to the developing ammonium hydrogen during electrophilic attack (Scheme 6).

The imidazolidinones **A29**–**A32** can be regarded as intramolecular variants of 2-carboxamido-substituted pyrrolidines (Scheme 7). Two reasons may account for the fact that the endocyclic carboxamido group in the imidazolidinones **A29**–**A32** reduces basicity by 7–8 pK units and nucleophilic reactivity by 6–9 orders of magnitude more than the exocyclic

Scheme 5. Comparison of Brønsted Basicities and Relative Rate Constants for the Reactions of 2-Substituted Pyrrolidines with E11 (MeCN, 20 °C)





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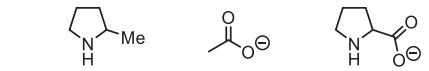
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 6. Comparison of the Brønsted Basicity and Nucleophilicity (k_{rel} vs E11) of the Prolinate Anion and Its Fragments (MeCN, 20 °C)[7g,23,24]



pK_{aH}	19.57	23.51	24.02
N (s_N)	16.78 (0.71)	16.90 (0.75) (at 25 °C)	19.95 (0.68)
k_{rel}	1.0	2.7	79

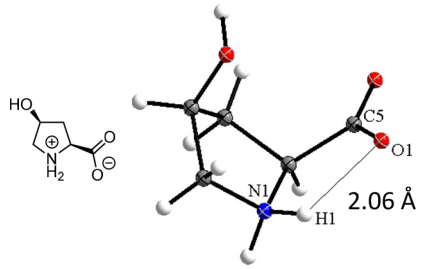
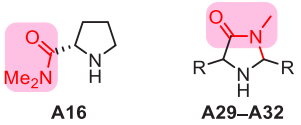


Figure 18. Single crystal structure of 4-hydroxyproline (CCDC 1101829).[22a] Crystal structures of the parent proline always include an additional HCl molecule (CCDC 775988).[22b]

Scheme 7. Comparison of Brønsted Basicities and Nucleophilic Reactivities of Proline Amide A16 and the Imidazolidinones A29–A32 (MeCN, 20 °C)



pK_{aH}	18.38	10.5 to 11.8
log k_2(with **E11**)	6.31	–3.10 to +0.48

carboxamido group in **A16**. The planar arrangement of the carboxamido group in the imidazolidinones leads to a stronger hyperconjugative interaction of the nitrogen lone pair of the NH group with the π^*-orbital of the carbonyl group. In addition, the two nitrogen atoms in **A29–A32** are in a geminal position, and the stabilizing anomeric interactions between these two nitrogen atoms[25] will be weakened by protonation.

CONCLUSION

In our efforts to pave the way to a rational design of organocatalytic reactions with secondary amines, we have now taken a further step. After quantifying the electrophilicities of common iminium intermediates[1l,o,3d,e,j,o,26] and the nucleophilicities of typical enamine intermediates,[2k,3k,27] we have now determined the basicities and nucleophilicities of a large variety of pyrrolidines and imidazolidinones in acetonitrile.

Their pK_{aH} values are significantly higher in acetonitrile than in aqueous solution, and we have found (Table 1, Figure 2) that the basicities of most pyrrolidines are in the range $16 < pK_{aH} < 20$, while the imidazolidinones are significantly less basic ($10 < pK_{aH} < 12$). Whereas the pK_{aH} values of 2-alkyl- and 2-aminoalkyl-substituted pyrrolidines differ by less than one pK unit from that of the parent pyrrolidine **A2**, ester groups as well as the trityl group reduce the basicity by 3 pK units. Since we had previously reported that iminium ions derived from 2-trityl-pyrrolidine are even more reactive than iminium ions derived from the unsubstituted pyrrolidine, we concluded that the trityl group reduces the basicity of pyrrolidine more through an electronic effect than through a steric effect.[2k]

Figure 13 shows that Brønsted basicities are not a useful guide for estimating nucleophilic reactivities. Since the steric demand of a proton is much smaller than that of the reference electrophiles **E1–E19**, one can rationalize why pyrrolidines with bulky substituents in 2-position are much less nucleophilic than pyrrolidines of similar basicity but smaller 2-substituents. Imidazolidinones are much weaker nucleophiles than the acceptor-substituted pyrrolidines with similar basicity (**A14**, **A21**). It is presently not clear whether this difference is entirely due to steric effects, because all investigated imidazolidinones have substituents on both carbons attached to the nucleophilic reaction center, or whether also electronic effects are involved which only affect the transition states, but not the products, which electronically resemble the protonated amines.

Using the newly determined nucleophilicities of pyrrolidines and imidazolidinones, we now can directly compare their reactivities with those of the corresponding enamines generated during the catalytic cycles. Figure 19 shows, for example, that the nucleophilicities of the enamines derived from 2-phenylacetaldehyde and pyrrolidines or imidazolidinones correlate linearly with the nucleophilicities of the corresponding amine precursors; i.e., substituent variation affects amine and enamine reactivities in the same way. From the slope of the correlation in Figure 19, one can see that 66% of the substituent effects on amine reactivities is reflected by the enamine reactivities. While pyrrolidines react approximately 2 orders of magnitude faster than the corresponding enamines derived from 2-phenylacetaldehyde, imidazolidinones have similar nucleophilic reactivities as the corresponding imidazolidinone-derived enamines (Figure 19).

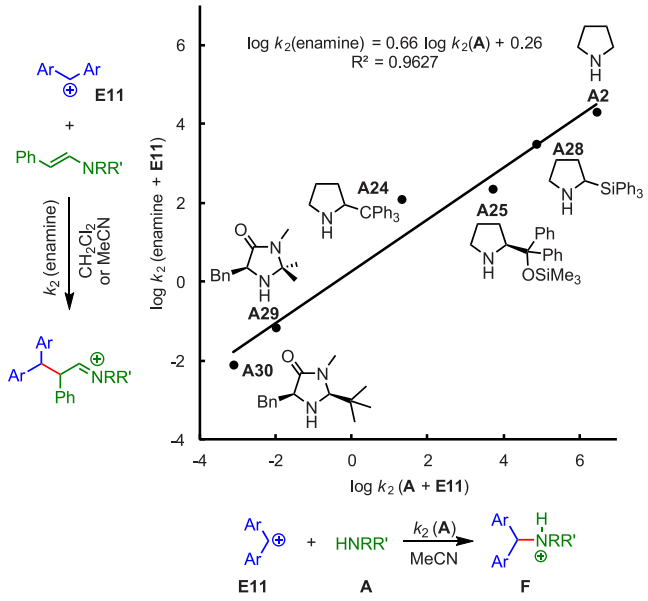


Figure 19. Correlation of the reactivities of enamines PhCH=CH—NR_2 toward **E11** (for **A2**, **A29**, and **A30** in MeCN and for **A24**, **A25**, and **A28** in CH_2Cl_2, 20 °C)[2k,3k,27a] vs the corresponding reactivities of the amines HNR_2 (in MeCN, 20 °C).

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J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

How was it then possible that MacMillan catalysts were successfully used for asymmetric alkylations of aldehydes by preformed carbocations and by S_N1-type reactions with alcohols?[28] The reversibility of the attack of imidazolidinones at carbocations with $E < -3$ observed in this work (cf. Figures 7 and 8) indicates the underlying reason: Even if the imidazolidinone catalyst is partially consumed by the addition to the S_N1 substrate, this reaction is reversible, and retroaddition takes the catalyst and the electrophile back to the productive organocatalytic cycle, in which the corresponding enamine undergoes an irreversible reaction with the electrophilic substrate.

The kinetic and thermodynamic data determined in this investigation can now be used for optimizing the conditions for reactions catalyzed by secondary amines. Fine-tuning requires consideration of the nucleophilicities of the secondary amines and the electrophilicities of the carbonyl substrates as well as adjusting the pK_a values of the cocatalyzing Brønsted acids to the pK_{aH} values of the corresponding amines. The low nucleophilicities of the imidazolidinones (Figure 12) explain, for example, why they generally do not react with non-activated carbonyl groups and require the presence of Brønsted acids, most commonly trifluoroacetic acid, which is slightly less acidic (pK_a 12.7)[29] than the protonated imidazolidinones and, therefore, does not deactivate the imidazolidinones. On the other hand, most pyrrolidines are much more nucleophilic than the imidazolidinones and may react with carbonyl compounds without Brønsted acid activation.[2m,4ay,5h,m,ag,ao] In some cases, strong Brønsted acids[30] may even be detrimental because they can deactivate pyrrolidines by protonation. We did not observe any reaction when cinnamaldehyde was combined with equimolar amounts of pyrrolidine and trifluoroacetic acid in acetonitrile at ambient temperature, for example. The exact role of Brønsted acid additives depends on the particular combination of substrates and catalyst, however, because organocatalytic enamine- or iminium-activated reactions involve several protonation/deprotonation steps in the catalytic cycle, which can be rate determining also at later stages of the cycle.[2n] For example, so-called "parasitic equilibria", that is, cyclobutane or oxazolidine formation in reactions catalyzed by prolinols, prolinol ethers, or other pyrrolidines, are more easily overcome or avoided in the presence of appropriate Brønsted acids.[2e,4n] As the performance of organocatalytic reactions also depends on the absolute concentrations of reactants and additives, NMR spectroscopic methods have recently been developed to link the rate of amine-catalyzed reactions with the distribution of the relevant catalytic species. This analytical approach helps to identify whether acidic or basic additives lead to maximum catalytic efficiency for a given combination of reactants and solvents.[2r]

In addition to using the pK_{aH} values and nucleophilicities reported in this work for optimizing the reaction conditions for known organocatalysts, the described relationships between structure, basicity, and nucleophilicity can be considered as guidelines for the design of novel organocatalysts with so far unexploited structural motifs. The observation that the acceptor-substituted pyrrolidines **A14** and **A21** are much stronger nucleophiles than imidazolidinones of comparable basicity (Figure 13) is of particular interest. Preliminary work in our laboratory has already shown that iminium ions are generated 10^2 times faster in the reaction of cinnamaldehyde with an equimolar mixture of 2-(trifluoromethyl)pyrrolidine (**A14**) and trifluoroacetic acid than in the analogous reaction with the MacMillan catalyst **A29**. A systematic investigation of the catalytic activities of 2-acceptor-substituted pyrrolidines, therefore, appears promising.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b11877.

Procedures for the preparation of **A1**−**A32** and **C1**H−**C6**H, details of the product studies, NMR and IR spectra of characterized compounds, details of kinetic experiments, and determinations of equilibrium constants (PDF)

Crystal structure for 4,4′-((2-tritylpyrrolidin-1-yl)-methylene)bis(*N*,*N*-dimethylaniline) (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) General reviews: (a) Dalko, P. I.; Moisan, L. Enantioselective Organocatalysis. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748. (b) List, B. Proline-catalyzed Asymmetric Reactions. *Tetrahedron* **2002**, *58*, 5573−5590. (c) Notz, W.; Tanaka, F.; Barbas, C. F., III Enamine-Based Organocatalysis with Proline and Diamines: The Development of Direct Catalytic Asymmetric Aldol, Mannich, Michael, and Diels−Alder Reactions. *Acc. Chem. Res.* **2004**, *37*, 580−591. (d) Dalko, P. I.; Moisan, L. In the Golden Age of Organocatalysis. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.* **2007**, *107*, 5471−5569. (f) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium Catalysis. *Chem. Rev.* **2007**, *107*, 5416−5470. (g) Enders, D.; Grondal, C.; Hüttl, M. R. M. Asymmetric Organocatalytic Domino Reactions. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570−1581. (h) Tsogoeva, S. B. Recent Advances in Asymmetric Organocatalytic 1,4-Conjugate Additions. *Eur. J. Org. Chem.* **2007**, 1701−1716. (i) Dondoni, A.; Massi, A. Asymmetric Organocatalysis: from Infancy to Adolescence. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638−4660. (j) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. Asymmetric Aminocatalysis—Gold Rush in Organic Chemistry. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138−6171. (k) *Topics*

DOI: 10.1021/jacs.9b11877
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

in current chemistry: Asymmetric Organocatalysis; List, B., Ed.; Springer-Verlag: Berlin, Heidelberg, 2009. (l) Lakhdar, S.; Ofial, A. R.; Mayr, H. Reactivity parameters for rationalizing iminium-catalyzed reactions. *J. Phys. Org. Chem.* **2010**, *23*, 886−892. (m) MacMillan, D. W. C. α-Functionalization of carbonyl compounds. In *Science of Synthesis: Stereoselective Synthesis 3*; Evans, P. A., Ed.; Thieme: Stuttgart, Germany, 2011. (n) *Science of Synthesis: Asymmetric Organocatalysis 1, Lewis Base and Acid Catalysts*; List, B., Ed.; Thieme: Stuttgart, Germany, 2012. (o) Mayr, H.; Lakhdar, S.; Maji, B.; Ofial, A. R. A quantitative approach to nucleophilic organocatalysis. *Beilstein J. Org. Chem.* **2012**, *8*, 1458−1478. (p) *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2013. (q) *Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes*; Torres, R. R., Ed.; Wiley: Hoboken, NJ, 2013. (r) Volla, C. M. R.; Atodiresei, I.; Rueping, M. Catalytic C−C Bond-Forming Multi-Component Cascade or Domino Reactions: Pushing the Boundaries of Complexity in Asymmetric Organocatalysis. *Chem. Rev.* **2014**, *114*, 2390−2431. (s) Davis, R. L.; Stiller, J.; Naicker, T.; Jiang, H.; Jørgensen, K. A. Asymmetric Organocatalytic Epoxidations: Reactions, Scope, Mechanisms, and Applications. *Angew. Chem., Int. Ed.* **2014**, *53*, 7406−7426. (t) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. The Diarylprolinol Silyl Ethers: Ten Years After. *Angew. Chem., Int. Ed.* **2015**, *54*, 13860−13874. (u) Matos Paz, B.; Jiang, H.; Jørgensen, K. A. Aminocatalysis: Beyond Steric Shielding and Hydrogen-Bonding. *Chem. - Eur. J.* **2015**, *21*, 1846−1853. (v) Ishikawa, H.; Shiomi, S. Alkaloid synthesis using chiral secondary amine organocatalysts. *Org. Biomol. Chem.* **2016**, *14*, 409−424. (w) *Lewis Base Catalysis in Organic Synthesis*; Vedejs, E., Denmark, S. E., Eds.; Wiley-VCH: Weinheim, Germany, 2016. (x) Klier, L.; Tur, F.; Poulsen, P. H.; Jørgensen, K. A. Asymmetric cycloaddition reactions catalyzed by diarylprolinol silyl ethers. *Chem. Soc. Rev.* **2017**, *46*, 1080−1120. (y) Liu, J.; Wang, L. Recent Advances in Asymmetric Reactions Catalyzed by Proline and Its Derivatives. *Synthesis* **2017**, *49*, 960−972. (z) Chauhan, P.; Mahajan, S.; Enders, D. Achieving Molecular Complexity via Stereoselective Multiple Domino Reactions Promoted by a Secondary Amine Organocatalyst. *Acc. Chem. Res.* **2017**, *50*, 2809−2821. (aa) Zhu, L.; Wang, D.; Jia, Z.; Lin, Q.; Huang, M.; Luo, S. Z. Catalytic Asymmetric Oxidative Enamine Transformations. *ACS Catal.* **2018**, *8*, 5466−5484. (ab) Reyes-Rodríguez, G. J.; Rezayee, N. M.; Vidal-Albalat, A.; Jørgensen, K. Prevalence of Diarylprolinol Silyl Ethers as Catalysts in Total Synthesis and Patents. *Chem. Rev.* **2019**, *119*, 4221−4260.

(2) Pyrrolidines as organocatalysts: (a) List, B. Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents. *Acc. Chem. Res.* **2004**, *37*, 548−557. (b) Limbach, M. 'Five at One Stroké: Proline and Small Peptides in the Stereoselectve *de novo* Synthesis and Enantiotopic Functionalization of Carbohydrates. *Chem. Biodiversity* **2005**, *2*, 825−836. (c) Grošelj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. Structures of the Reactive Intermediates in Organocatalysis with Diarylprolinol Ethers. *Helv. Chim. Acta* **2009**, *92*, 1225−1259. (d) Xu, L.-W.; Li, L.; Shi, Z.-H. Asymmetric Synthesis with Silicon-Based Bulky Amino Organocatalysts. *Adv. Synth. Catal.* **2010**, *352*, 243−279. (e) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. Formation and Stability of Prolinol and Prolinol Ether Enamines by NMR: Delicate Selectivity and Reactivity Balances and Parasitic Equilibria. *J. Am. Chem. Soc.* **2011**, *133*, 7065−7074. (f) Ren, Q.; Wang, J. Recent Developments in Amine-catalyzed Non-asymmetric Transformations. *Asian J. Org. Chem.* **2013**, *2*, 542−557. (g) Kano, T.; Maruoka, K. Unique properties of chiral biaryl-based secondary amine catalysts for asymmetric enamine catalysis. *Chem. Sci.* **2013**, *4*, 907−915. (h) Meninno, S.; Lattanzi, A. Asymmetric organocatalysis mediated by α,α-L-diaryl prolinols: recent advances. *Chem. Commun.* **2013**, *49*, 3821−3832. (i) Martín-Santos, C.; Jarava-Barrera, C.; del Pozo, S.; Parra, A.; Díaz-Tendero, S.; Mas-Ballesté, R.; Cabrera, S.; Alemán, J. Highly Enantioselective Construction of Tricyclic Derivatives by the Desymmetrization of Cyclohexadienones. *Angew. Chem., Int. Ed.* **2014**, *53*, 8184−8189. (j) McNulty, J.; Zepeda-Velázquez, C. Enantioselective Organocatalytic Michael/Aldol Sequence: Anticancer Natural Product (+)-*trans*-Dihydrolycoricidine. *Angew. Chem., Int. Ed.* **2014**, *53*, 8450−8454. (k) Erdmann, H.; An, F.; Mayer, P.; Ofial, A. R.; Lakhdar, S.; Mayr, H. Structures and Reactivities of 2-Trityl- and 2-(Triphenylsilyl)pyrrolidine-Derived Enamines: Evidence for Negative Hyperconjugation with the Trityl Group. *J. Am. Chem. Soc.* **2014**, *136*, 14263−14269. (l) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. Asymmetric organocatalytic functionalization of α,α-disubstituted aldehydes through enamine activation. *Tetrahedron* **2014**, *70*, 2491−2513. (m) Wang, S.; Li, X.; Liu, H.; Li, X.; Zhuang, J.; Li, J.; Li, H.; Wang, W. Organocatalytic Enantioselective Direct Additions of Aldehydes to 4-Vinylpyridines and Electron-Deficient Vinylarenes and Their Synthetic Applications. *J. Am. Chem. Soc.* **2015**, *137*, 2303−2310. (n) Burés, J.; Armstrong, A.; Blackmond, D. G. Explaining Anomalies in Enamine Catalysis: "Downstream Species" as a New Paradigm for Stereocontrol. *Acc. Chem. Res.* **2016**, *49*, 214−222. (o) Li, Y.; Tur, F.; Nielsen, R. P.; Jiang, H.; Jensen, F.; Jørgensen, K. Enantioselective Formal [4 + 2] Cycloadditions to 3-Nitroindoles by Trienamine Catalysis: Synthesis of Chiral Dihydrocarbazoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 1020−1024. (p) Monleón, A.; Glaus, F.; Vergura, S.; Jørgensen, K. A. Organocatalytic Strategy for the Enantioselective Cycloaddition to Trisubstituted Nitroolefins to Create Spirocyclohexene-Oxetane Scaffolds. *Angew. Chem., Int. Ed.* **2016**, *55*, 2478−2482. (q) Zheng, S.-C.; Wu, S.; Zhou, Q.; Chung, L. W.; Ye, L.; Tan, B. Organocatalytic atroposelective synthesis of axially chiral styrenes. *Nat. Commun.* **2017**, *8*, 15238. (r) Companyó, X.; Burés, J. Distribution of Catalytic Species as an Indicator to Overcome Reproducibility Problems. *J. Am. Chem. Soc.* **2017**, *139*, 8432−8435. (s) Husch, T.; Seebach, D.; Beck, A. K.; Reiher, M. Rigorous Conformational Analysis of Pyrrolidine Enamines with Relevance to Organocatalysis. *Helv. Chim. Acta* **2017**, *100*, No. e1700182. (t) Girvin, Z. C.; Gellman, S. H. Exploration of Diverse Reactive Diad Geometries for Bifunctional Catalysis via Foldamer Backbone Variation. *J. Am. Chem. Soc.* **2018**, *140*, 12476−12483. (u) de Gracia Retamosa, M.; Ruiz-Olalla, A.; Bello, T.; de Cozar, A.; Cossio, F. P. A Three-Component Enantioselective Cyclization Reaction Catalyzed by an Unnatural Amino Acid Derivative. *Angew. Chem., Int. Ed.* **2018**, *57*, 668−672. (v) Hayashi, Y.; Umekubo, N. Direct Asymmetric Michael Reaction of α,β-Unsaturated Aldehydes and Ketones Catalyzed by Two Secondary Amine Catalysts. *Angew. Chem., Int. Ed.* **2018**, *57*, 1958−1962. (w) Poulsen, P. H.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. B.; Palazzo, T. A.; Meazza, M.; Jørgensen, K. A. Organocatalytic Formation of Chiral Trisubstituted Allenes and Chiral Furan Derivatives. *Angew. Chem., Int. Ed.* **2018**, *57*, 10661−10665. (x) Przydacz, A.; Skrzyńska, A.; Albrecht, Ł. Breaking Aromaticity with Aminocatalysis: A Convenient Strategy for Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2019**, *58*, 63−73. (y) Vega-Peñaloza, A.; Paria, S.; Bonchio, M.; Dell'Amico, L.; Companyó, X. Profiling the Privileges of Pyrrolidine-Based Catalysts in Asymmetric Synthesis: From Polar to Light-Driven Radical Chemistry. *ACS Catal.* **2019**, *9*, 6058−6072.

(3) Imidazolidinones as organocatalysts: (a) Lelais, G.; MacMillan, D. W. C. Modern Strategies in Organic Catalysis: The Advent and Development of Iminium Activation. *Aldrichimica Acta* **2006**, *39*, 79−87. (b) Burley, J. C.; Gilmour, R.; Prior, T. J.; Day, G. M. Structural Diversity in Imidazolidinone Organocatalysts: a Synchrotron and Computational Study. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2008**, *C64*, o10−o14. (c) Seebach, D.; Grošelj, U.; Badine, D. M.; Schweizer, W. B.; Beck, A. K. Isolation and X-Ray Structures of Reactive Intermediates of Organocatalysis with Diphenylprolinol Ethers and with Imidazolidinones − A Survey and Comparison with Computed Structures and with 1-Acyl-imidazolidinones: The 1,5-Repulsion and the Geminal-Diaryl Effect at Work. *Helv. Chim. Acta* **2008**, *91*, 1999−2034. (d) Lakhdar, S.; Tokuyasu, T.; Mayr, H. Electrophilic Reactivities of α,β-Unsaturated Iminium Ions. *Angew. Chem., Int. Ed.* **2008**, *47*, 8723−8726. (e) Lakhdar, S.; Appel, R.;

DOI: 10.1021/jacs.9b11877
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Mayr, H. How Does Electrostatic Activation Control Iminium-Catalyzed Cyclopropanations? *Angew. Chem., Int. Ed.* **2009**, *48*, 5034−5037. (f) Grošelj, U.; Schweizer, W. B.; Ebert, M.-O.; Seebach, D. 5-Benzyl-3-methylimidazolidin-4-one-derived Reactive Intermediates of Organocatalysis − A Comforting Resemblance of X-Ray, NMR, and DFT Solid-Phase, Liquid-Phase, and Gas-Phase Structures. *Helv. Chim. Acta* **2009**, *92*, 1−13. (g) Brazier, J. B.; Evans, G.; Gibbs, T. J. K.; Coles, S. J.; Hursthouse, M. B.; Platts, J. A.; Tomkinson, N. C. O. Solution Phase, Solid State, and Theoretical Investigations on the MacMillan Imidazolidinone. *Org. Lett.* **2009**, *11*, 133−136. (h) Devery, J. J., III; Conrad, J. C.; MacMillan, D. W. C.; Flowers, R. A., II Mechanistic Complexity in Organo−SOMO Activation. *Angew. Chem., Int. Ed.* **2010**, *49*, 6106−6110. (i) Beel, R.; Kobialka, S.; Schmidt, M. L.; Engeser, M. Direct Experimental Evidence for an Enamine Radicalcation in SOMO Catalysis. *Chem. Commun.* **2011**, *47*, 3293−3295. (j) Lakhdar, S.; Ammer, J.; Mayr, H. Generation of α,β-Unsaturated Iminium Ions by Laser Flash Photolysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 9953−9956. (k) Lakhdar, S.; Maji, B.; Mayr, H. Imidazolidinone-Derived Enamines: Nucleophiles with Low Reactivity. *Angew. Chem., Int. Ed.* **2012**, *51*, 5739−5742. (l) Holland, M. C.; Paul, S.; Schweizer, W. B.; Bergander, K.; Mück-Lichtenfeld, C.; Lakhdar, S.; Mayr, H.; Gilmour, R. Noncovalent interactions in organocatalysis: modulating conformational diversity and reactivity in the MacMillan catalyst. *Angew. Chem., Int. Ed.* **2013**, *52*, 7967−7971. (m) Grošelj, U.; Beck, A.; Schweizer, W. B.; Seebach, D. Preparation and Structures of 2-Substituted 5-Benzyl-3-methylimidazolidin-4-one-Derived Iminium Salts, Reactive Intermediates in Organocatalytic Transformations Involving α,β-Unsaturated Aldehydes. *Helv. Chim. Acta* **2014**, *97*, 751−796. (n) Abeykoon, G. A.; Chatterjee, S.; Chen, J. S. anti-Diols from α-Oxyaldehydes: Synthesis and Stereochemical Assignment of Oxylipins from Dracontium loretense. *Org. Lett.* **2014**, *16*, 3248−3251. (o) An, F.; Paul, S.; Ammer, J.; Ofial, A. R.; Mayer, P.; Lakhdar, S.; Mayr, H. Structures and Reactivities of Iminium Ions Derived from Substituted Cinnamaldehydes and Various Chiral Imidazolidin-4-ones. *Asian J. Org. Chem.* **2014**, *3*, 550−555. (p) Chen, J. S.; Abeykoon, G. A. Catalytic Enantioselective α,β,γ-Trioxygenation. *Org. Lett.* **2015**, *17*, 6050−6053. (q) Hooper, J. F.; James, N. C.; Bozkurt, E.; Aviyente, V.; White, J. M.; Holland, M. C.; Gilmour, R.; Holmes, A. B.; Houk, K. N. Medium-Ring Effects on the Endo/Exo Selectivity of the Organocatalytic Intramolecular Diels-Alder Reaction. *J. Org. Chem.* **2015**, *80*, 12058−12075. (r) Welin, E. R.; Warkentin, A. A.; Conrad, J. C.; MacMillan, D. W. C. Enantioselective α-Alkylation of Aldehydes by Photoredox Organocatalysis: Rapid Access to Pharmacophore Fragments from β-Cyanoaldehydes. *Angew. Chem., Int. Ed.* **2015**, *54*, 9668−9672. (s) Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. Ring-Opening Regio-, Diastereo-, and Enantioselective 1,3-Chlorochalcogenation of Cyclopropyl Carbaldehydes. *Chem. - Eur. J.* **2016**, *22*, 18756−18759. (t) Kinghorn, M. J.; Valdivia-Berroeta, G. A.; Chantry, D. R.; Smith, M. S.; Ence, C. C.; Draper, S. R. E.; Duval, J. S.; Masino, B. M.; Cahoon, S. B.; Flansburg, R. R.; Conder, C. J.; Price, J. L.; Michaelis, D. J. Proximity-Induced Reactivity and Product Selectivity with a Rationally Designed Bifunctional Peptide Catalyst. *ACS Catal.* **2017**, *7*, 7704−7708. (u) Ben Ayed, K.; Laurent, M. Y.; Martel, A.; Selim, K. B.; Abid, S.; Dujardin, G. Enantioselective 1,3-Dipolar Cycloaddition Reactions of C-Carboxy Ketonitrones and Enals with MacMillan Catalysts: Evidence of a Nonconcerted Mechanism. *Eur. J. Org. Chem.* **2017**, 6763−6774. (v) Patil, M. Stereocontrol through Synergistic Catalysis in the Enantioselective α-Alkenylation of Aldehyde: A Computational Study. *J. Org. Chem.* **2018**, *83*, 1304−1311. (w) Nacsa, E. D.; MacMillan, D. W. C. Spin-Center Shift-Enabled Direct Enantioselective α-Benzylation of Aldehydes with Alcohols. *J. Am. Chem. Soc.* **2018**, *140*, 3322−3330. (x) Morack, T.; Mück-Lichtenfeld, C.; Gilmour, R. Bioinspired Radical Stetter Reaction: Radical Umpolung Enabled by Ion-Pair Photocatalysis. *Angew. Chem., Int. Ed.* **2019**, *58*, 1208−1212.

(4) Transformations via intermediate enamines: (a) Hajos, Z. G.; Parrish, D. R. Asymmetrische Synthese Polycyclischer Organischer Verbindungen. German Patent DE 2102623, 1971. (b) Eder, U.; Sauer, G.; Wiechert, R. New Type of Asymmetric Cyclization to Optically Active Steroid CD Partial Structures. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. (c) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. A New Class of Chiral Pyrrolidine−Pyridine Conjugate Base Catalysts for Use in Asymmetric Michael Addition Reactions. *J. Am. Chem. Soc.* **2004**, *126*, 9558−9559. (d) Peelen, T. J.; Chi, Y.; Gellman, S. H. Enantioselective organocatalytic Michael additions of aldehydes to enones with imidazolidinones: Cocatalyst effects and evidence for an enamine intermediate. *J. Am. Chem. Soc.* **2005**, *127*, 11598−11599. (e) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. Enantioselective Organocatalyzed α Sulfenylation of Aldehydes. *Angew. Chem., Int. Ed.* **2005**, *44*, 794−797. (f) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. Diphenylprolinol Silyl Ethers as Efficient Organocatalysts for the Asymmetric Michael reaction of Aldehydes and Nitroalkenes. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212−4215. (g) Ibrahem, I.; Córdova, A. Direct Catalytic Asymmetric anti-Selective Mannich-type Reactions. *Chem. Commun.* **2006**, 1760−1762. (h) Luo, S.; Xu, H.; Mi, X.; Li, J.; Zheng, X.; Cheng, J. P. Evolution of Pyrrolidine-Type Asymmetric Organocatalysts by "Click" Chemistry. *J. Org. Chem.* **2006**, *71*, 9244−9247. (i) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J. P. Functionalized Chiral Ionic Liquids as Highly Efficient Asymmetric Organocatalysts for Michael Addition to Nitroolefins. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093−3097. (j) Cao, Y. J.; Lai, Y. Y.; Wang, X.; Li, Y. J.; Xiao, W. Michael Additions in Water of Ketones to Nitroolefins Catalyzed by Readily Tunable and Bifunctional Pyrrolidine−Thiourea Organocatalysts. *Tetrahedron Lett.* **2007**, *48*, 21−24. (k) Kobayashi, S.; Kinoshita, T.; Uehara, H.; Sudo, T.; Ryu, L. Organocatalytic Enantioselective Synthesis of Nitrogen-Substituted Dihydropyran-2-ones, a Key Synthetic Intermediate of 1β-Methylcarbapenems. *Org. Lett.* **2009**, *11*, 3934−3937. (l) Kano, T.; Mii, H.; Maruoka, K. Direct Asymmetric Benzoyloxylation of Aldehydes Catalyzed by 2-Tritylpyrrolidine. *J. Am. Chem. Soc.* **2009**, *131*, 3450−3451. (m) Husmann, R.; Jörres, M.; Raabe, G.; Bolm, C. Silylated Pyrrolidines as Catalysts for Asymmetric Michael Additions of Aldehydes to Nitroolefins. *Chem. - Eur. J.* **2010**, *16*, 12549−12552. (n) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. Organocatalyzed *Michael* Addition of Aldehydes to Nitro Alkenes − Generally Accepted Mechanism Revisited and Revised. *Helv. Chim. Acta* **2011**, *94*, 719−745. (o) Alachraf, M. W.; Handayani, P. P.; Hüttl, M. R. M.; Grondal, C.; Enders, D.; Schrader, W. Electrospray Mass Spectrometry for Detailed Mechanistic Studies of a Complex Organocatalyzed Triple Cascade Reaction. *Org. Biomol. Chem.* **2011**, *9*, 1047−1053. (p) Jia, Z. J.; Jiang, H.; Li, J. L.; Gschwend, B.; Li, Q. Z.; Yin, X.; Grouleff, J.; Chen, Y. C.; Jørgensen, K. A. Trienamines in Asymmetric Organocatalysis: Diels−Alder and Tandem Reactions. *J. Am. Chem. Soc.* **2011**, *133*, 5053−5061. (q) Burés, J.; Armstrong, A.; Blackmond, D. G. Mechanistic Rationalization of Organocatalyzed Conjugate Addition of Linear Aldehydes to Nitroolefins. *J. Am. Chem. Soc.* **2011**, *133*, 8822−8825. (r) Sahoo, G.; Rahaman, H.; Madarász, Á.; Pápai, I.; Melarto, M.; Valkonen, A.; Pihko, P. M. Dihydrooxazine Qxides as Key Intermediates in Organocatalytic Michael Additions of Aldehydes to Nitroalkenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 13144−13148. (s) Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. Enantio- and Diastereoselective Synthesis of Substituted Tetrahydro-1H-isochromanes through a Dynamic Kinetic Resolution Proceeding under Dienamine Catalysis. *Org. Lett.* **2012**, *14*, 3740−3743. (t) Parra, A.; Reboredo, S.; Alemán, J. Asymmetric Synthesis of Cyclobutanes by a Formal [2 + 2] Cycloaddition Controlled by Dienamine Catalysis. *Angew. Chem., Int. Ed.* **2012**, *51*, 9734−9736. (u) Chia, P. W.; Brennan, S. C.; Slawin, A. M. Z.; Riccardi, D.; O'Hagan, D. Allosteric Agonists of the Calcium Receptor (CaR): Fluorine and SF_5 Analogues of Cinacalcet. *Org. Biomol. Chem.* **2012**, *10*, 7922−7927. (v) Albrecht, Ł.; Dickmeiss, G.; Acosta, C. A.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. Asymmetric

DOI: 10.1021/jacs.9b11877
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Organocatalytic Formal [2 + 2]-Cycloadditions via Bifunctional H-Bond Directing Dienamine Catalysis. *J. Am. Chem. Soc.* **2012**, *134*, 2543−2546. (w) Ansari, S.; Raabe, G.; Enders, D. Asymmetric Michael Addition of 1,3-Bis(phenylthio)propan-2-one to Nitroalkenes Employing Takemoto's Thiourea Catalyst. *Monatsh. Chem.* **2013**, *144*, 641−646. (x) Khumsubdee, S.; Zhou, H.; Burgess, K. Homo-Roche Ester Derivatives by Asymmetric Hydrogenation and Organocatalysis. *J. Org. Chem.* **2013**, *78*, 11948−11955. (y) Zhu, K.; Huang, H.; Wu, W.; Wei, Y.; Ye, J. Aminocatalyzed Asymmetric Diels−Alder Reaction of 2,4-Denals and Rhodanine/Hydantoin Derivatives. *Chem. Commun.* **2013**, *49*, 2157−2159. (z) Zhang, S. J.; Zhang, J.; Zhou, Q. Q.; Dong, L.; Chen, Y. C. Aminocatalytic Asymmetric *exo*-Diels−Alder Reaction with Methiodide Salts of Mannich Bases and 2,4-Dienals to Construct Chiral Spirocycles. *Org. Lett.* **2013**, *15*, 968−971. (aa) Jiang, H.; Cruz, D. C.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. Asymmetric Organocatalytic Thio-Diels−Alder Reactions via Trienamine Catalysis. *J. Am. Chem. Soc.* **2013**, *135*, 5200−5207. (ab) Seebach, D.; Sun, X.; Ebert, M.-O.; Schweizer, W. B.; Purkayastha, N.; Beck, A. K.; Duschmalé, J.; Wennemers, H.; Mukaiyama, T.; Benohoud, M.; Hayashi, Y.; Reiher, M. Stoichiometric Reactions of Enamines Derived from Diphenylprolinol Silyl Ethers with Nitro Olefins and Lessons for the Corresponding Organocatalytic Conversions − a Survey. *Helv. Chim. Acta* **2013**, *96*, 799−852. (ac) Meng, Z.; Sun, S.; Yuan, H.; Lou, H.; Liu, L. Catalytic Enantioselective Oxidative Cross-Coupling of Benzylic Ethers with Aldehydes. *Angew. Chem., Int. Ed.* **2014**, *53*, 543−547. (ad) Halskov, K.; Donslund, B. S.; Barfüsser, S.; Jørgensen, K. A. Organocatalytic Asymmetric Formation of Steroids. *Angew. Chem., Int. Ed.* **2014**, *53*, 4137−4141. (ae) Link, A.; Sparr, C. Organocatalytic Atroposelective Aldol Condensation: Synthesis of Axially Chiral Biaryls by Arene Formation. *Angew. Chem., Int. Ed.* **2014**, *53*, 5458−5461. (af) Burés, J.; Dingwall, P.; Armstrong, A.; Blackmond, D. G. Rationalization of an Unusual Solvent-Induced Inversion of Enantiomeric Excess in Organocatalytic Selenylation of Aldehydes. *Angew. Chem., Int. Ed.* **2014**, *53*, 8700−8704. (ag) Koley, D.; Krishna, Y.; Srinivas, K.; Khan, A. A.; Kant, R. Organocatalytic Asymmetric Mannich Cyclization of Hydroxylactams with Acetals: Total Syntheses of (−)-Epilupinine, (−)-Tashiromine, and (−)-Trachelanthamidine. *Angew. Chem., Int. Ed.* **2014**, *53*, 13196−13200. (ah) Kano, T.; Shirozu, F.; Maruoka, K. Practical Approach for Asymmetric Hydroxyamination of Aldehydes with in Situ Generated Nitrosocarbonyl Compounds: Application to One-Pot Synthesis of Chiral Allylamines. *Org. Lett.* **2014**, *16*, 1530−1532. (ai) Caruana, L.; Kniep, F.; Johansen, T.; Poulsen, P. H.; Jørgensen, K. A. A New Organocatalytic Concept for Asymmetric α-Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2014**, *136*, 15929−15932. (aj) Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. Organocatalytic Enamine-Activation of Cyclopropanes for Highly Stereoselective Formation of Cyclobutanes. *J. Am. Chem. Soc.* **2015**, *137*, 1685−1691. (ak) Haindl, M. H.; Hioe, J.; Gschwind, R. M. The Proline Enamine Formation Pathway Revisited in Dimethyl Sulfoxide: Rate Constants Determined via NMR. *J. Am. Chem. Soc.* **2015**, *137*, 12835−12842. (al) Berti, F.; Malossi, F.; Marchetti, F.; Pineschi, M. A highly Enantioselective Mannich Reaction of Aldehydes with Cyclic N-Acyliminium Ions by Synergistic Catalysis. *Chem. Commun.* **2015**, *51*, 13694−13697. (am) Buckingham, F.; Kirjavainen, A. K.; Forsback, S.; Krzyczmonik, A.; Keller, T.; Newington, I. M.; Glaser, M.; Luthra, S. K.; Solin, O.; Gouverneur, V. Organomediated Enantioselective ^{18}F Fluorination for PET Applications. *Angew. Chem., Int. Ed.* **2015**, *54*, 13366−13369. (an) Fjelbye, K.; Marigo, M.; Clausen, R. P.; Juhl, K. Diastereodivergent Access to *Syn* and *Anti* 3,4-Substituted β-Fluoropyrrolidines: Enhancing or Reversing Substrate Preference. *Org. Lett.* **2016**, *18*, 1170−1173. (ao) Xie, Z.; Zan, X.; Sun, S.; Pan, X.; Liu, L. Organocatalytic Enantioselective Cross-Dehydrogenative Coupling of N-Carbamoyl Cyclic Amines with Aldehydes. *Org. Lett.* **2016**, *18*, 3944−3947. (ap) Poulsen, P. H.; Vergura, S.; Monleón, A.; Jørgensen, D.; Jørgensen, K. A. Controlling Asymmetric Remote and Cascade 1,3-Dipolar Cycloaddition Reactions by Organocatalysis. *J. Am. Chem. Soc.* **2016**, *138*, 6412−6415. (aq) Seegerer, A.; Hioe, J.; Hammer, M. M.; Morana, F.; Fuchs, P. J. W.; Gschwind, R. M. Remote-Stereocontrol in Dienamine Catalysis: Z-Dienamine Preferences and Electrophile−Catalyst Interaction Revealed by NMR and Computational Studies. *J. Am. Chem. Soc.* **2016**, *138*, 9864−9873. (ar) Fäseke, V. C.; Sparr, C. Stereoselective Arene-Forming Aldol Condensation: Synthesis of Axially Chiral Aromatic Amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 7261−7264. (as) Donslund, B. S.; Nielsen, R.; Mønsted, S. M. N.; Jørgensen, K. A. Benzofulvenes in Trienamine Catalysis: Stereoselective Spiroindene Synthesis. *Angew. Chem., Int. Ed.* **2016**, *55*, 11124−11128. (at) Srinivas, K.; Singh, N.; Das, D.; Koley, D. Organocatalytic, Asymmetric Synthesis of Aza-Quaternary Center of Izidine Alkaloids: Synthesis of (−)-Tricyclic Skeleton of Cylindricine. *Org. Lett.* **2017**, *19*, 274−277. (au) Lang, J. H.; Jones, P. G.; Lindel, T. Total Synthesis of the Marine Natural Product Hemiasterlin by Organocatalyzed α-Hydrazination. *Chem. - Eur. J.* **2017**, *23*, 12714−12717. (av) Donslund, B. S.; Monleón, A.; Palazzo, T. A.; Christensen, M. L.; Dahlgaard, A.; Erickson, J. D.; Jørgensen, K. A. Organocatalytic Enantioselective Higher-Order Cycloadditions of In Situ Generated Amino Isobenzofulvenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 1246−1250. (aw) Macharia, J.; Wambua, V.; Hong, Y.; Harris, L.; Hirschi, J. S.; Evans, G. B.; Vetticatt, M. A Designed Approach to Enantiodivergent Enamine Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 8756−8760. (ax) Donslund, B. S.; Jessen, N. I.; Bertuzzi, G.; Giardinetti, M.; Palazzo, T. A.; Christensen, M. L.; Jørgensen, K. A. Catalytic Enantioselective [10 + 4] Cycloadditions. *Angew. Chem., Int. Ed.* **2018**, *57*, 13182−13186. (ay) Apel, C.; Hartmann, S. S.; Lentz, D.; Christmann, M. Dienamine-Induced Divinylcyclopropane−Cycloheptadiene Rearrangements. *Angew. Chem., Int. Ed.* **2019**, *58*, 5075−5079.

(5) Transformations via iminium ions: (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. Asymmetric Michael Addition of Malonate Anions to Prochiral Acceptors Catalyzed by L-Proline Rubidium Salt. *J. Org. Chem.* **1996**, *61*, 3520−3530. (b) Yamaguchi, M.; Yokota, N.; Minami, T. The Michael Addition of Dimethyl Malonate to α,β-Unsaturated Aldehydes Catalysed by Proline Lithium Salt. *J. Chem. Soc., Chem. Commun.* **1991**, 1088−1089. (c) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: the First Highly Enantioselective Organocatalytic Diels−Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244. (d) Jen, W. S.; Wiener, J. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: the First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition. *J. Am. Chem. Soc.* **2000**, *122*, 9874−9875. (e) Paras, N. A.; MacMillan, D. W. C. The Enantioselective Organocatalytic 1,4-Addition of Electron-rich Benzenes to α, β-Unsaturated Aldehydes. *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895. (f) Northrup, A. B.; MacMillan, D. W. C. The First General Enantioselective Catalytic Diels-Alder Reaction with Simple α, β-Unsaturated Ketones. *J. Am. Chem. Soc.* **2002**, *124*, 2458−2460. (g) Sundén, H.; Ibrahem, I.; Córdova, A. Direct Organocatalytic Asymmetric Epoxidation of α,β-Unsaturated Aldehydes. *Tetrahedron Lett.* **2006**, *47*, 99−103. (h) Zhao, G. L.; Ibrahem, I.; Sundén, H.; Córdova, A. Amine-Catalyzed Asymmetric Epoxidation of α,β-Unsaturated Aldehydes. *Adv. Synth. Catal.* **2007**, *349*, 1210−1224. (i) Chow, S. S.; Nevalainen, M.; Evans, C. A.; Johannes, C. W. A New Organocatalyst for 1,3-Dipolar Cycloadditions of Nitrones to α,β-Unsaturated Aldehydes. *Tetrahedron Lett.* **2007**, *48*, 277−280. (j) Zu, L.; Zhang, S.; Xie, H.; Wang, W. Catalytic Asymmetric Oxa-Michael−Michael Cascade for Facile Construction of Chiral Chromans via an Aminal Intermediate. *Org. Lett.* **2009**, *11*, 1627−1630. (k) Luo, S. P.; Li, Z. Bo.; Wang, L. P.; Guo, Y.; Xia, A. B.; Xu, D. Q. Chiral Amine/Chiral Acid as an Excellent Organocatalytic System for the Enantioselective Tandem Oxa-Michael-aldol Reaction. *Org. Biomol. Chem.* **2009**, *7*, 4539−4546. (l) Borths, C. J.; Carrera, D. E.; MacMillan, D. W. C. Development of a General, Enantioselective Organocatalytic Mukaiyama−Michael Reaction with α,β-Unsaturated Aldehydes. *Tetrahedron* **2009**, *65*, 6746−6753. (m) Fleischer, I.; Pfaltz, A. Enantioselective Michael Addition to α,β-Unsaturated Aldehydes: Combinatorial Catalyst Preparation and Screening, Reaction Optimization, and Mechanistic Studies. *Chem. -*

DOI: 10.1021/jacs.9b11877
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Eur. J. **2010**, *16*, 95−99. (n) Tang, J.; Xu, D. D.; Xia, A. B.; Wang, Y. F.; Jiang, J. R.; Luo, S. P.; Xu, Z. Y. An Organocatalytic Domino Thia-Michael/Aldol Condensation Reaction: Highly Enantioselective Synthesis of Functionalized Dihydrothiophenes. *Adv. Synth. Catal.* **2010**, *352*, 2121−2126. (o) Zhang, F.; Wei, M.; Dong, J.; Zhou, Y.; Lu, D.; Gong, Y.; Yang, X. A Recyclable Organocascade Reaction System: Stereoselective Precipitation of Optically Active cis-*δ*-Lactols with Quaternary Stereocenters during the Michael-Hemiacetalization Reaction. *Adv. Synth. Catal.* **2010**, *352*, 2875−2880. (p) Xu, F.; Zacuto, M.; Yoshikawa, N.; Desmond, R.; Hoerrner, S.; Itoh, T.; Journet, M.; Humphrey, G. R.; Cowden, C.; Strotman, N.; Devine, P. Asymmetric Synthesis of Telcagepant, a CGRP Receptor Antagonist for the Treatment of Migraine. *J. Org. Chem.* **2010**, *75*, 7829−7841. (q) Brazier, J. B.; Jones, K. M.; Platts, J. A.; Tomkinson, N. C. O. On the Roles of Protic Solvents in Imidazolidinone-Catalyzed Transformations. *Angew. Chem., Int. Ed.* **2011**, *50*, 1613−1616. (r) Shi, Z. H.; Sheng, H.; Yang, K. F.; Jiang, J. X.; Lai, G. Q.; Lu, Y.; Xu, L. W. Diarylprolinol Silyl Ether Catalyzed Asymmetric Friedel−Crafts Alkylation of Indoles with *α,β*-Unsaturated Aldehydes: Enhanced Enantioselectivity and Mechanistic Investigations. *Eur. J. Org. Chem.* **2011**, 66−70. (s) Lin, S.; Deiana, L.; Zhao, G. L.; Sun, J.; Córdova, A. Dynamic One-Pot Three-Component Catalytic Asymmetric Transformation by Combination of Hydrogen-Bond-Donating and Amine Catalysts. *Angew. Chem., Int. Ed.* **2011**, *50*, 7624−7630. (t) Shen, H.; Yang, K. F.; Shi, Z. H.; Jiang, J. X.; lai, G. Q.; Xu, L. W. Recyclable Tertiary Amine Modified Diarylprolinol Ether as Aminocatalyst for the Sequential Asymmetric Synthesis of Functionalized Cyclohexanes and Chromenes. *Eur. J. Org. Chem.* **2011**, 5031−5038. (u) Zhu, H. L.; Ling, J. B.; Xu, P. F. *α*-Oxo-*γ*-Butyrolactam, N-Containing Pronucleophile in Organocatalytic One-Pot Assembly of Butyrolactam-Fused Indoloquinolizidines. *J. Org. Chem.* **2012**, *77*, 7737−7743. (v) Gupta, V.; Sudhir, V. S.; Mandal, T.; Schneider, C. Organocatalytic, Highly Enantioselective Vinylogous Mukaiyama−Michael Reaction of Acyclic Dienol Silyl Ethers. *Angew. Chem., Int. Ed.* **2012**, *51*, 12609−12612. (w) Duan, G. J.; Ling, J. B.; Wang, W. P.; Luo, Y. C.; Xu, P. F. Organocatalytic Formal [2 + 2] Cycloaddition Initiated by Vinylogous Friedel-Crafts Alkylation: Enantioselective Synthesis of Substituted Cyclobutane Derivatives. *Chem. Commun.* **2013**, *49*, 4625−4627. (x) Jiang, X.; Tan, B.; Barbas, C. F., III Core-Structure-Motivated Design of Iminium−Enolate Organocascade Reactions: Enantioselective Syntheses of 5,6-Dihydroindolizines. *Angew. Chem., Int. Ed.* **2013**, *52*, 9261−9265. (y) Dell'Amico, L.; Albrecht, Ł.; Naicker, T.; Poulsen, P. H.; Jørgensen, K. A. Beyond Classical Reactivity Patterns: Shifting from 1,4- to 1,6-Additions in Regio- and Enantioselective Organocatalyzed Vinylogous Reactions of Olefinic Lactones with Enals and 2,4-Dienals. *J. Am. Chem. Soc.* **2013**, *135*, 8063−8070. (z) Khalaf, A.; Grée, D.; Abdallah, H.; Jaber, N.; Hachem, A.; Grée, R. Asymmetric Organocatalytic 1,4-Addition Reactions Starting from Enals with gem-Difluoroalkyl Side Chains. *Eur. J. Org. Chem.* **2013**, 653−657. Veerasamy, N.; Carlson, E. C.; Collett, N. D.; Saha, M.; Carter, R. G. Enantioselective Approach to Quinolizidines: Total Synthesis of Cermizine D and Formal Syntheses of Senepodine G and Cermizine C. *J. Org. Chem.* **2013**, *78*, 4779−4800. (ac) Lear, M. J.; Hayashi, Y. Remote 1,6-Stereocontrol by Iminium-mediated Organocatalytic Events. *ChemCatChem* **2013**, *5*, 3499−3501. (ad) Caruana, L.; Fochi, M.; Franchini, M. C.; Ranieri, S.; Mazzanti, A.; Bernardi, L. Asymmetric Synthesis of 3,4-Annulated Indoles through an Organocatalytic Cascade Approach. *Chem. Commun.* **2014**, *50*, 445−447. (ae) Du, H.; Rodriguez, J.; Bugaut, X.; Constantieux, T. Organocatalytic Enantioselective Multicomponent Synthesis of Pyrrolopiperazines. *Adv. Synth. Catal.* **2014**, *356*, 851−856. (af) Gu, Y.; Wang, Y.; Yu, T. Y.; Liang, Y. M.; Xu, P. F. Rationally Designed Multifunctional Supramolecular Iminium Catalysis: Direct Vinylogous Michael Addition of Unmodified Linear Dienol Substrates. *Angew. Chem., Int. Ed.* **2014**, *53*, 14128−14131. (ag) Morales, S.; Guijarro, F. G.; Ruano, J.; Cid, M. B. A General Aminocatalytic Method for the Synthesis of Aldimines. *J. Am. Chem. Soc.* **2014**, *136*, 1082−1089. (ah) Brindani, N.; Rassu, G.; Dell'Amico, L.; Zambrano, V.; Pinna, L.; Curti, C.; Sartori, A.; Battistini, L.; Casiraghi, G.; Pelosi, G.; Greco, D.; Zanardi, F. Organocatalytic, Asymmetric Eliminative [4 + 2] Cycloaddition of Allylidene Malononitriles with Enals: Rapid Entry to Cyclohexadiene-Embedding Linear and Angular Polycycles. *Angew. Chem., Int. Ed.* **2015**, *54*, 7386−7390. (ai) Poulsen, P. H.; Feu, K.; Paz, B.; Jensen, F.; Jørgensen, K. A. Organocatalytic Asymmetric 1,6-Addition/1,4-Addition Sequence to 2,4-Dienals for the Synthesis of Chiral Chromans. *Angew. Chem., Int. Ed.* **2015**, *54*, 8203−8207. (aj) Claraz, A.; Sahoo, G.; Berta, D.; Madarász, Á.; Pápai, I.; Pihko, P. M. A Catalyst Designed for the Enantioselective Construction of Methyl- and Alkyl-Substituted Tertiary Stereocenters. *Angew. Chem., Int. Ed.* **2016**, *55*, 669−673. (ak) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. Visible-light excitation of iminium ions enables the enantioselective catalytic *β*-alkylation of enals. *Nat. Chem.* **2017**, *9*, 868−873. (al) Liu, Q.; Zu, L. Organocatalytic Enantioselective Cross-Vinylogous Rauhut−Currier Reaction of Methyl Coumalate with Enals. *Angew. Chem., Int. Ed.* **2018**, *57*, 9505−9509. (am) Jia, S.; Chen, Z.; Zhang, N.; Tan, Y.; Liu, Y.; Deng, J.; Yan, H. Organocatalytic Enantioselective Construction of Axially Chiral Sulfone-Containing Styrenes. *J. Am. Chem. Soc.* **2018**, *140*, 7056−7060. (an) Izzo, J. A.; Poulsen, P. H.; Intrator, J. A.; Jørgensen, K. A. Isotope Effects Reveal an Alternative Mechanism for "Iminium-Ion" Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 8396−8400. (ao) Sofiadis, M.; Kalaitzakis, D.; Sarris, J.; Montagnon, T.; Vassilikogiannakis, G. Vinylogous Reactivity of Cyclic 2-Enones: Organocatalysed Asymmetric Addition to 2-Enals to Synthesize Fused Carbocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 6742−6746.

(6) Brønsted basicities (pK_{aH}) in aqueous solution: For **A6**: (a) Starr, D. F.; Bulbrook, H.; Hixon, R. M. Electron Sharing Ability of Organic Radicals. vi. Alpha-Substituted Pyrrolines and Pyrrolidines. *J. Am. Chem. Soc.* **1932**, *54*, 3971−3976. For **A1**: (b) Ratner, S.; Clarke, H. T. The Action of Formaldehyde upon Cysteine. *J. Am. Chem. Soc.* **1937**, *59*, 200−206. For **A2**: (c) Searles, S.; Tamres, M.; Block, F.; Quarterman, L. A. Hydrogen Bonding and Basicity of Cyclic Imines. *J. Am. Chem. Soc.* **1956**, *78*, 4917−4920. For **A1** and **A2**: (d) Christensen, J. J.; Izatt, R. M.; Wrathall, D. P.; Hansen, L. D. Thermodynamics of Proton Ionization in Dilute Aqueous Solution. Part XI. p*K*, ΔH°, and ΔS° Values for Proton Ionization from Protonated Amines at 25°. *J. Chem. Soc. A* **1969**, 1212−1223. For **A9**: (e) Hine, J.; Evangelista, R. A. Rates of Formation of Iminium Ions from Acetone and Monoprotonated 2-[(Dimethylamino)-methyl] pyrrolidine. *J. Org. Chem.* **1980**, *45*, 3890−3892. For **A2**: (f) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D. Amine basicities in benzene and in water. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1865−1868. For **A2** and **A12**: (g) Yang, D.; Zuccarello, G.; Mattes, B. R. Physical Stabilization or Chemical Degradation of Concentrated Solutions of Polyaniline Emeraldine Base Containing Secondary Amine Additives. *Macromolecules* **2002**, *35*, 5304−5313.

(7) Brønsted basicities (pK_{aH}) in aprotic solvents: For **A2** in ACN, 18.92: (a) Brzeziński, B.; Schroeder, G.; Grech, E.; Malarski, Z.; Sobczyk, L. Basicity, IR spectra and protonation of some proton sponges in acetonitrile. *J. Mol. Struct.* **1992**, *274*, 75−82. For **A2** in DMSO, 11.06: (b) Crampton, M. R.; Robotham, I. A. Acidities of Some Substituted Ammonium Ions in Dimethyl Sulfoxide. *J. Chem. Res., Synop.* **1997**, 22−23. For **A2** in ACN, 19.62: (c) Tshepelevitsh, S.; Kütt, A.; Lõkov, M.; Kaljurand, I.; Saame, J.; Heering, A.; Pliger, P. G.; Vianello, R.; Leito, I. On the Basicity of Organic Bases in Different Media. *Eur. J. Org. Chem.* **2019**, 6735−6748. For **A2** in ACN, 19.8: (d) Spillane, W. J.; O'Byrne, A.; McCaw, C. J. A. Elimination Mechanisms in the Aminolysis of Sulfamate Esters of the Type $NH_2SO_2OC_6H_4X$ − Models of Enzyme Inhibitors. *Eur. J. Org. Chem.* **2008**, 4200−4205. For **A22**−H^+ in DMSO, 13.38: (e) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. (Thio)urea Organocatalyst Equilibrium Acidities in DMSO. *Org. Lett.* **2012**, *14*, 1724−1727. For **A1** in DMSO, 13.35: (f) Li, Z.; Li, X.; Ni, X.; Cheng, J. P. Equilibrium Acidities of Proline Derived Organocatalysts in DMSO. *Org. Lett.* **2015**, *17*, 1196−1199. (g) For a general overview: Internet Bond-energy Databank (pK_a and BDE)−*i*BonD Home Page. http://ibond.nankai.edu.cn.

DOI: 10.1021/jacs.9b11877
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

(8) (a) Kütt, A.; Leito, I.; Kaljurand, I.; Sooväli, L.; Vlasov, V. M.; Yagupolskii, L. M.; Koppel, I. A. A. Comprehensive Self-Consistent Spectrophotometric Acidity Scale of Neutral Brønsted Acids in Acetonitrile. *J. Org. Chem.* **2006**, *71*, 2829−2838. (b) Eckert, F.; Leito, I.; Kaljurand, I.; Kütt, A.; Klamt, A.; Diedenhofen, M. Prediction of Acidity in Acetonitrile Solution with COSMO-RS. *J. Comput. Chem.* **2009**, *30*, 799−810.

(9) Electrophilicity parameters *E* for the reference electrophiles in Chart 3 were taken from our database for reactivity parameters, which provides links to the original references. This database is freely accessible via http://www.cup.lmu.de/oc/mayr/DBintro.html.

(10) Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1959909). These supplementary crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(11) (a) Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr, H. Nucleophilic Reactivities of Primary and Secondary Amines in Acetonitrile. *Eur. J. Org. Chem.* **2009**, 6379−6385. (b) Nigst, T. A.; Antipova, A.; Mayr, H. Nucleophilic Reactivities of Hydrazines and Amines: The Futile Search for the α-Effect in Hydrazine Reactivities. *J. Org. Chem.* **2012**, *77*, 8142−8155.

(12) Um, I.-H.; Kang, J.-S.; Park, J.-Y. Kinetic Study on Michael-Type Reactions of β-Nitrostyrenes with Cyclic Secondary Amines in Acetonitrile: Transition-State Structures and Reaction Mechanism Deduced from Negative Enthalpy of Activation and Analyses of LFERs. *J. Org. Chem.* **2013**, *78*, 5604−5610.

(13) Volz, H.; Kiltz, H.-H. Methylenimmoniumsalze durch Hydrid-Abstraktion aus tertiären Aminen. *Liebigs Ann. Chem.* **1971**, *752*, 86−101.

(14) Anne, A.; Moiroux, J.; Savéant, J. M. Formal Hydride Transfer from NADH Analogues. 1-Benzyl-4-tert-butyl-1,4-dihydronicotinamide as a Mechanistic Probe. *J. Am. Chem. Soc.* **1993**, *115*, 10224−10230.

(15) (a) Mayr, H.; Patz, M. Scales of Nucleophilicity and Electrophilicity: A System for Ordering Polar Organic and Organometallic Reactions. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957. (b) Mayr, H.; Kempf, B.; Ofial, A. R. π-Nucleophilicity in Carbon-Carbon Bond-Forming Reactions. *Acc. Chem. Res.* **2003**, *36*, 66−77. (c) Horn, M.; Schappele, L. H.; Lang-Wittkowski, G.; Mayr, H.; Ofial, A. R. Towards a Comprehensive Hydride Donor Ability Scale. *Chem. - Eur. J.* **2013**, *19*, 249−263. (d) Mayr, H. Reactivity Scales for Quantifying Polar Organic Reactivity: The Benzhydrylium Methodology. *Tetrahedron* **2015**, *71*, 5095−5111. (e) Mayr, H.; Ofial, A. R. A Quantitative Approach to Polar Organic Reactivity. *SAR QSAR Environm. Res.* **2015**, *26*, 619−646.

(16) Bordwell, F. G.; Cripe, T. A.; Hughes, D. L. Nucleophilicity, Basicity, and the Brønsted Equation. In *Nucleophilicity*; Harris, J. M., McManus, S. P., Eds.; American Chemical Society: Washington, DC, 1987; pp 137−153.

(17) (a) Brotzel, F.; Chu, Y. C.; Mayr, H. Nucleophilicities of Primary and Secondary Amines in Water. *J. Org. Chem.* **2007**, *72*, 3679−3688. (b) Brotzel, F.; Mayr, H. Nucleophilicities of Amino Acids and Peptides. *Org. Biomol. Chem.* **2007**, *5*, 3814−3820. (c) Ammer, J.; Baidya, M.; Kobayashi, S.; Mayr, H. Nucleophilic Reactivities of Tertiary Alkylamines. *J. Phys. Org. Chem.* **2010**, *23*, 1029−1035. (d) Breugst, M.; Tokuyasu, T.; Mayr, H. Nucleophilic Reactivities of Imide and Amide Anions. *J. Org. Chem.* **2010**, *75*, 5250−5258.

(18) (a) Hansch, C.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165−195. (b) Hansch, C.; Leo, A.; Hoekman, D. *Exploring QSAR: Hydrophobic, Electronic, and Steric Constants*; American Chemical Society: Washington, DC, 1995; pp 219−304.

(19) For Brønsted basicities (pK_a) of acetic acid in DMSO, see: (a) Kozak, A.; Czaja, M.; Chmurzynski, L. Investigations of (Acid + Base) Equilibria in Systems Modelling Interactions Occurring in Biomolecules. *J. Chem. Thermodyn.* **2006**, *38*, 599−605 (12.05). (b) Bartnicka, H.; Bojanowska, I.; Kalinowski, M. K. Solvent Effect on the Dissociation Constants of Aliphatic Carboxylic Acids. *Aust. J. Chem.* **1991**, *44*, 1077−1084 (12.48). (c) Bordwell, F. G. Equilibrium Acidities in Dimethyl Sulfoxide Solution. *Acc. Chem. Res.* **1988**, *21*, 456−463 (12.3). (d) Kolthoff, I. M.; Chantooni, M. K., Jr; Bhowmik, S. Dissociation constants of uncharged and monovalent cation acids in dimethyl sulfoxide. *J. Am. Chem. Soc.* **1968**, *90*, 23−28 (12.6). (e) Courtot-Coupez, J.; Le Demezet, M. Electrochemistry in Dimethyl Sulfoxide. II. Use of Hydrogen Electrode. *Bull. Soc. Chim. Fr.* **1969**, 1033−1040 (12.6). (f) Ritchie, C. D.; Uschold, R. E. Acidity in Nonaqueous Solvents. IV. Hydrocarbon Acids in Dimethyl Sulfoxide. *J. Am. Chem. Soc.* **1967**, *89*, 1721−1725 (11.6).

(20) Höck, S.; Marti, R.; Riedl, R.; Simeunovic, M. Thermal Cleavage of the Fmoc Protection Group. *Chimia* **2010**, *64*, 200−202.

(21) Hughes, D. L.; Bergan, J. J.; Grabowski, E. J. J. Amino Acid Chemistry in Dipolar Aprotic Solvents: Dissociation Constants and Ambident Reactivity. *J. Org. Chem.* **1986**, *51*, 2579−2588.

(22) (a) Shamala, N.; Guru Row, T. N.; Venkatesan, K. Crystal and Molecular Structure of allo-4-Hydroxy-L-proline Dihydrate. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *32*, 3267−3270. (b) Gharzaryan, V. V.; Fleck, M.; Petrosyan, A. M. New Salts of Amino Acids with Dimeric Cations. *Proc. SPIE* **2011**, *7998*, 79980F-1−79980F-9.

(23) Brønsted acidity (pK_a) of acetic acid in ACN: (a) See ref 8a (23.51). (b) Czaja, M.; Makowski, M.; Chmurzyński, L. A Potentiometric Study of Molecular Heteroconjugation Equilibria in (*n*-Butylamine + Acetic Acid) Systems in Binary (Acetonitrile + 1,4-Dioxane) Solvent Mixtures. *J. Chem. Thermodyn.* **2006**, *38*, 606−610 (22.13). (c) See ref 19b (21.57). (d) See ref 19d (22.3).

(24) Schaller, H. F.; Tishkov, A. A.; Feng, X. L.; Mayr, H. Direct Observation of the Ionization Step in Solvolysis Reactions: Electrophilicity versus Electrofugality of Carbocations. *J. Am. Chem. Soc.* **2008**, *130*, 3012−3022.

(25) Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. Do anomeric effects involving the second-row substituents, chlorine, mercapto, and phosphino exist? Stabilization energies and structural preferences. *J. Am. Chem. Soc.* **1985**, *107*, 6393−6394.

(26) Appel, R.; Chelli, S.; Tokuyasu, T.; Troshin, K.; Mayr, H. Electrophilicities of Benzaldehyde-Derived Iminium Ions: Quantification of the Electrophilic Activation of Aldehydes by Iminium Formation. *J. Am. Chem. Soc.* **2013**, *135*, 6579−6587.

(27) (a) Timofeeva, D.; Mayer, R. J.; Mayer, P.; Ofial, A. R.; Mayr, H. Which Factors Control the Nucleophilic Reactivities of Enamines? *Chem. - Eur. J.* **2018**, *24*, 5901−5910. (b) Leonov, A. I.; Timofeeva, D. S.; Ofial, A. R.; Mayr, H. Metal Enolates - Enamines - Enol Ethers: How Do Enolate Equivalents Differ in Nucleophilic Reactivity? *Synthesis* **2019**, *51*, 1157−1170.

(28) (a) Cozzi, P. G.; Benfatti, F.; Zoli, L. Organocatalytic Asymmetric Alkylation of Aldehydes by S_N1-Type Reaction of Alcohols. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313−1316. (b) Benfatti, F.; Benedetto, E.; Cozzi, P. G. Organocatalytic Stereoselective α-Alkylation of Aldehydes with Stable Carbocations. *Chem. - Asian J.* **2010**, *5*, 2047−2052. (c) Capdevila, M. G.; Benfatti, F.; Zoli, L.; Stenta, M.; Cozzi, P. G. Merging Organocatalysis with an Indium(III)-Mediated Process: A Stereoselective α-Alkylation of Aldehydes with Allylic Alcohols. *Chem. - Eur. J.* **2010**, *16*, 11237−11241. (d) Gualandi, A.; Emer, E.; Capdevila, M. G.; Cozzi, P. G. Highly Enantioselective α-Alkylation of Aldehydes with 1,3-Benzodithiolylium Tetrafluoroborate: A Formal Organocatalytic α-Alkylation of Aldehydes by the Carbenium Ion. *Angew. Chem., Int. Ed.* **2011**, *50*, 7842−7846. (e) Sinisi, R.; Vita, M. V.; Gualandi, A.; Emer, E.; Cozzi, P. G. S_N1-Type Reactions in the Presence of Water: Indium(III)-Promoted Highly Enantioselective Organocatalytic Propargylation of Aldehydes. *Chem. - Eur. J.* **2011**, *17*, 7404−7408. (f) Chiarucci, M.; di Lillo, M.; Romaniello, A.; Cozzi, P. G.; Cera, G.; Bandini, M. Gold meets enamine catalysis in the enantioselective α-allylic alkylation of aldehydes with alcohols. *Chem. Sci.* **2012**, *3*, 2859−2863. (g) Gualandi, A.; Cozzi, P. G. Stereoselective Organocatalytic Alkylations with Carbenium Ions. *Synlett* **2013**, *24*, 281−

DOI: 10.1021/jacs.9b11877
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

296. (h) Porta, R.; Benaglia, M.; Puglisi, A.; Mandoli, A.; Gualandi, A.; Cozzi, P. G. A Catalytic Reactor for the Organocatalyzed Enantioselective Continuous Flow Alkylation of Aldehydes. *ChemSusChem* **2014**, *7*, 3534−3540. (i) Gualandi, A.; Mengozzi, L.; Giacoboni, J.; Saulnier, S.; Ciardi, M.; Cozzi, P. G. A Practical and Stereoselective Organocatalytic Alkylation of Aldehydes with Benzodithiolylium Tetrafluoroborate. *Chirality* **2014**, *26*, 607−613. (j) Gualandi, A.; Mengozzi, L.; Manoni, E.; Cozzi, P. G. From QCA (Quantum Cellular Automata) to Organocatalytic Reactions with Stabilized Carbenium Ions. *Chem. Rec.* **2016**, *16*, 1228−1243.

(29) Hayakawa, Y.; Iwase, T.; Nurminen, E. J.; Tsukamoto, M.; Kataoka, M. Carboxylic acids as promoters for internucleotide-bond formation via condensation of a nucleoside phosphoramidite and a nucleoside: relationship between the acidity and the activity of the promoter. *Tetrahedron* **2005**, *61*, 2203−2209.

(30) Li, Z.; Li, X.; Cheng, J.-P. Recent Progress in Equilibrium Acidity Studies of Organocatalysts. *Synlett* **2019**, *30*, 1940−1949.

DOI: 10.1021/jacs.9b11877
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX