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Nucleophilicities and Lewis Basicities of Isothiourea Derivatives

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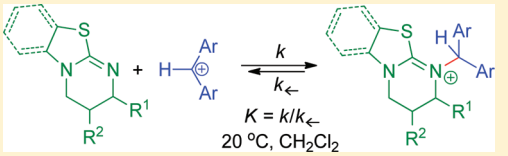
Supporting Information

ABSTRACT: Rate and equilibrium constants for the reactions of a series of isothioureas with benzhydrylium ions have been measured photometrically. The data were employed to determine the nucleophilicities and nucleofugalities of isothioureas and compare them with those of other organocatalysts.



INTRODUCTION

Lewis bases (e.g., **1**−**17**, Figure 1) have the ability to promote the acylation of alcohols and amines.[1] 4-(Dimethylamino)pyridine[2] (DMAP, **1**) and *N*-methylimidazole[3] (NMI, **2**) as well as the amidines 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **3**)[4] or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, **4**)[4] are among the most common achiral catalysts used for these reactions. Birman has shown that chiral amidines act as enantioselective catalysts for the kinetic resolution of alcohols.[5] Recent independent work by the Okamoto and Birman groups has demonstrated that isothioureas are highly active O-acylation catalysts.[6,7] Okamoto found 3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole (DHPB, **10**) to be remarkably active for catalyzing the acylation of 1-phenylethanol, even more active than the "benchmark" catalyst DMAP (**1**).[6] Birman's concurrent investigations of the acylations of primary and secondary alcohols with a series of amidines and isothioureas revealed a significant variation in catalytic activity with ring size. Notably, tetrahydropyrimidine-based isothioureas THTP (**9**) and DHPB (**10**) showed catalytic activity in chloroform similar to or slightly higher than that of DMAP, depending on their concentrations.[7] Subsequent related studies probed the ability of a variety of amidines and isothioureas to catalyze the *O*- to *C*-carboxyl transfer rearrangement of oxazolyl and related heterocyclic carbonates and the C-acylation of silyl ketene acetals and showed that tetrahydropyrimidine-based DHPB (**10**) was also the optimal achiral catalyst in Figure 1.[8]

Given their promising reactivity profiles, a series of chiral isothioureas have been prepared and utilized in asymmetric catalysis. Pioneering studies by Birman and Li showed that tetramisole **11** and its benzannulated analogue BTM **12** can catalyze the kinetic resolution of alcohols with exquisite selectivity.[9] Since the demonstration of this methodology, a range of chiral isothioureas (of which **12**−**17** are representative) have been successfully utilized in a variety of asymmetric processes including kinetic resolutions,[10] desymmetrizations,[11,12] dynamic kinetic resolutions,[13] and the generation of ammonium enolates from carboxylic acids,[14] as well as enantioselective carboxy and acyl group transfer reactions.[15] The commercial availability of tetramisole **11** and the ease of synthesis of chiral isothioureas such as **12**−**17** from enantiopure amino alcohols arguably make these derivatives more readily accessible than many common

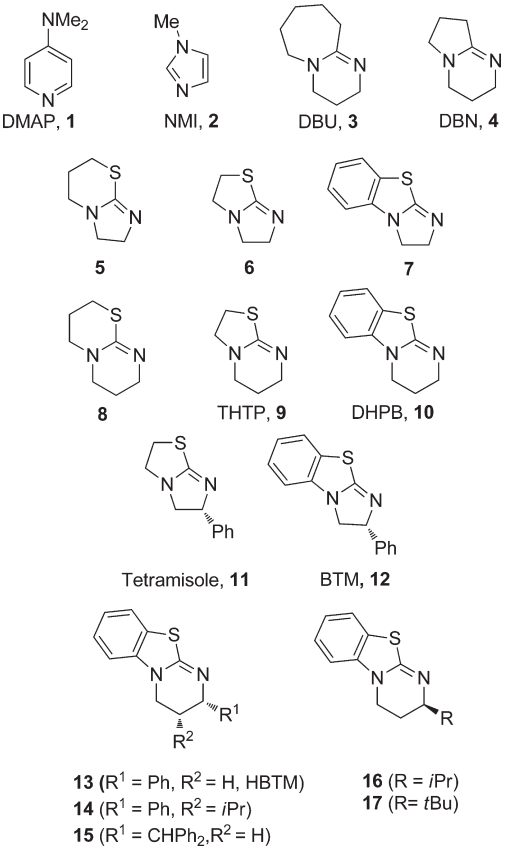


Figure 1. Selected nitrogen-containing heterocycles commonly used as acyl transfer catalysts.

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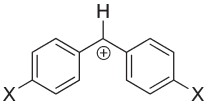
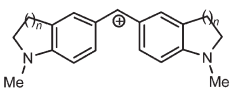
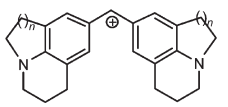
Table 1. Abbreviations and Electrophilicity Parameters for the Benzhydrylium Ions Used for this Work



X	Abbreviations	E [a]
$N(CH_3)CH_2CF_3$	$(mfa)_2CH^+$	–3.85
NPh_2	$(dpa)_2CH^+$	–4.72
$N(CH_2CH_2)_2O$	$(mor)_2CH^+$	–5.53
$N(Ph)CH_3$	$(mpa)_2CH^+$	–5.89
$N(CH_3)_2$	$(dma)_2CH^+$	–7.02
$N(CH_2)_4$	$(pyr)_2CH^+$	–7.69
	$n = 2$ $(thq)_2CH^+$	–8.22
	$n = 1$ $(ind)_2CH^+$	–8.76
	$n = 2$ $(jul)_2CH^+$	–9.45
	$n = 1$ $(lil)_2CH^+$	–10.04

[a] Electrophilicity parameters E for benzhydrylium ions from ref 19a.

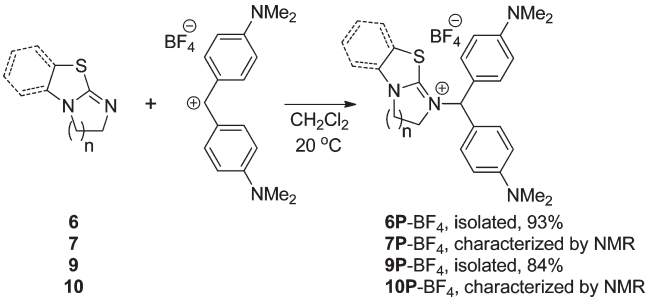
chiral DMAP derivatives.[16] Notably, in many of these processes the catalytic activity and enantioselectivity vary significantly with ring size and stereodirecting unit. For example, Birman has shown that the incorporation of an additional *syn*-C(3)-methyl group within the HBTM-skeleton (**14**, Me instead of *i*Pr) has a dramatic effect upon both catalytic activity and stereoselectivity in kinetic resolutions of aryl-cycloalkanols,[17] and a similar effect has been noted on the kinetic resolution of aryl alkyl alcohols when introducing a *syn*-C(3)-isopropyl unit (**14**).[18]

While it may be expected that the organocatalytic activities of these heterocycles will depend on their relative nucleophilicities and Lewis basicities, to date a quantitative comparison of these properties has not been reported. To gain insight into some of the factors that may affect their catalytic activities, we have determined rate and equilibrium constants of the reactions of the isothiourea derivatives **5**−**10** and **13**−**17** with stabilized benzhydrylium ions (Table 1) and compared these data with those of other nucleophilic organocatalysts such as DMAP (**1**), NMI (**2**), DBU (**3**) and DBN (**4**).[19,20]

RESULTS AND DISCUSSIONS

Product Studies. When CH_2Cl_2 solutions of the isothioureas **6** or **9** were added to CH_2Cl_2 solutions of $(dma)_2CH^+BF_4^-$ at room temperature, the thiouronium tetrafluoroborates **6P**-BF_4 and **9P**-BF_4 formed, which were isolated and characterized (Scheme 1). The ^{13}C NMR spectra show that the benzhydryl carbon, which absorbs at $\delta \approx 160$ ppm in $(dma)_2CH^+$, is shifted to $\delta \approx 70$ ppm due to the change in hybridization from sp^2 to sp^3. Since the reactions of the benzannulated isothioureas **7** and **10** with $(dma)_2CH^+BF_4^-$ are highly reversible, the corresponding

Scheme 1. Products from Reactions of Isothioureas with $(dma)_2CH^+BF_4^-$



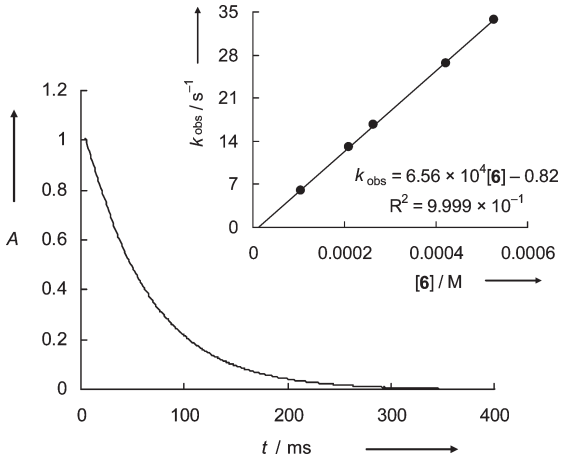


Figure 2. Exponential decay of the absorbance at 613 nm during the reaction of **6** (2.11×10^{-4} M) with $(dma)_2CH^+BF_4^-$ (1.41×10^{-3} M) at 20 °C in CH_2Cl_2 (k_{obs} = 13.0 s^{-1}). Insert: Determination of the second-order rate constant $k = 6.56 \times 10^4$ M^{-1} s^{-1} from the dependence of k_{obs} on the concentration of **6**.

adducts **7P**-BF_4 and **10P**-BF_4 were not isolated but identified by NMR after mixing the isothioureas **7** and **10** with equimolar amounts of $(dma)_2CH^+BF_4^-$ in deuterated dimethyl sulfoxide; details are specified in the Supporting Information.

Kinetics. Using this information, the rates of the reactions of the isothioureas **5**−**10** and **13**−**17** with the benzhydrylium ions shown in Table 1 were measured photometrically by monitoring the decay of the absorbances of the benzhydrylium ions; conventional or stopped-flow techniques were used as previously described.[19] By employing the isothioureas in high excess over the benzhydrylium ions, first-order conditions were achieved. The first-order rate constants k_{obs} (s^{-1}), obtained by fitting the decay of the absorbances of the benzhydrylium ions to the monoexponential function $A = A_0\, e^{-k_{obs}t} + C$ correlated linearly with the nucleophile concentrations (Figure 2). The slopes of these correlation lines yielded the second-order rate constants k (M^{-1} s^{-1}), which are collected in Table 2. The kinetic profiles of the reactions of $(ind)_2CH^+$ with **7**, **9** and **10** were also studied at variable temperature to determine the Eyring activation parameters, which are collected in the footnotes of Table 2. The negative activation entropies (−57 to −68 J mol^{-1} K^{-1}) are similar to those reported for the reactions of other *n*-nucleophiles with benzhydrylium ions in CH_2Cl_2.[20]

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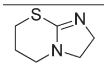
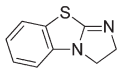
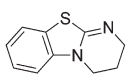
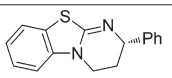
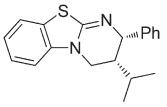
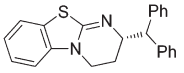
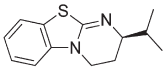
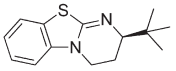
Table 2. Second-Order Rate Constants k for the Reactions of the Isothiourea Derivatives 5−10 and 13−17 with Benzhydrylium Ions (Ar_2CH^+, Table 1) in CH_2Cl_2 at 20 °C

Isothiourea	N, s_N [a]	Ar_2CH^+	k ($M^{-1}s^{-1}$)
	13.00, 0.83	$(dma)_2CH^+$	9.16×10^4
		$(pyr)_2CH^+$	2.55×10^4
5		$(thq)_2CH^+$	7.72×10^3
		$(ind)_2CH^+$	3.54×10^3
	12.98, 0.81	$(dma)_2CH^+$	6.56×10^4
		$(pyr)_2CH^+$	1.93×10^4
6		$(thq)_2CH^+$	5.86×10^3
		$(ind)_2CH^+$	2.79×10^3
	13.42, 0.73	$(dma)_2CH^+$	4.76×10^4
		$(pyr)_2CH^+$	1.46×10^4
7		$(thq)_2CH^+$	5.83×10^3
		$(ind)_2CH^+$	2.60×10^3 [b]
	14.10, 0.82	$(thq)_2CH^+$	5.88×10^4
		$(ind)_2CH^+$	2.76×10^4
8		$(jul)_2CH^+$	4.85×10^3
		$(lil)_2CH^+$	2.27×10^3
	14.45, 0.78	$(thq)_2CH^+$	7.09×10^4
		$(ind)_2CH^+$	3.68×10^4 [c]
THTP, **9**		$(jul)_2CH^+$	6.69×10^3
		$(lil)_2CH^+$	3.15×10^3
	13.86, 0.78	$(dma)_2CH^+$	2.29×10^5
		$(pyr)_2CH^+$	7.49×10^4
DHPB, **10**		$(thq)_2CH^+$	2.07×10^4
		$(ind)_2CH^+$	1.11×10^4 [d]

Isothiourea	N, s_N [a]	Ar_2CH^+	k ($M^{-1}s^{-1}$)
	13.45, 0.72	$(mor)_2CH^+$	3.80×10^5
		$(mpa)_2CH^+$	2.91×10^5
13		$(dma)_2CH^+$	5.15×10^4
		$(pyr)_2CH^+$	1.40×10^4
		$(thq)_2CH^+$	4.60×10^3
	14.96, 0.64	$(mpa)_2CH^+$	5.28×10^5
		$(dma)_2CH^+$	1.26×10^5
		$(pyr)_2CH^+$	4.06×10^4
14		$(thq)_2CH^+$	1.76×10^4
		$(ind)_2CH^+$	8.59×10^3
	15.30, 0.55	$(dpa)_2CH^+$	6.09×10^5
		$(mor)_2CH^+$	2.22×10^5
15		$(mpa)_2CH^+$	1.37×10^5
		$(dma)_2CH^+$	3.38×10^4
	16.50, 0.48	$(dpa)_2CH^+$	4.48×10^5
		$(mor)_2CH^+$	1.57×10^5
16		$(mpa)_2CH^+$	1.05×10^5
		$(dma)_2CH^+$	3.73×10^4
		$(pyr)_2CH^+$	1.53×10^4
	12.95, 0.58	$(mfa)_2CH^+$	2.51×10^5
		$(dpa)_2CH^+$	4.57×10^4
17		$(mor)_2CH^+$	2.06×10^4
		$(mpa)_2CH^+$	1.58×10^4

[a] Parameters as defined by eq 1. [b] Eyring activation parameters: $\Delta H^{\ddagger} = 32.6 \pm 1.3$ kJ mol^{-1}, $\Delta S^{\ddagger} = -68.0 \pm 4.7$ J mol^{-1} K^{-1}. [c] Eyring activation parameters: $\Delta H^{\ddagger} = 29.3 \pm 0.7$ kJ mol^{-1}, $\Delta S^{\ddagger} = -57.3 \pm 2.5$ J mol^{-1} K^{-1}. [d] Eyring activation parameters: $\Delta H^{\ddagger} = 30.6 \pm 1.8$ kJ mol^{-1}, $\Delta S^{\ddagger} = -63.0 \pm 6.3$ J mol^{-1} K^{-1}.

Correlation Analysis. In previous publications, we have shown that the rates of the reactions of carbocations and Michael acceptors with n-, π-, and σ-nucleophiles can be described by the linear-free-energy relationship (eq 1), where electrophiles are characterized by the electrophilicity parameter E, nucleophiles are characterized by the nucleophilicity parameter N and the nucleophile-dependent sensitivity parameter s_N (previously termed s). On the basis of eq 1 it was possible to develop the most comprehensive nucleophilicity scale presently available.[19]

$$\log k_{20\ ^\circ C} = s_N(N + E) \qquad (1)$$

Figure 3 shows linear correlations between the second-order rate constants k and the previously published electrophilicity parameters E, as required by eq 1. The slopes of the correlation lines yield the nucleophile-specific sensitivity parameters s_N, and the intercepts on the abscissa give the nucleophilicity parameters N, which are tabulated in Table 2.

The almost equal slopes ($0.73 < s_N < 0.83$) of the correlation lines for the isothioureas **5**−**10** (unsubstituted at C-2) indicate that their relative nucleophilicities are almost independent of the reactivity of the electrophilic reaction partner. In contrast, the chiral derivatives **13**−**17** have somewhat lower, variable, s_N parameters reflecting the dependence of their relative nucleophilicities on the reaction partner.

Lewis Basicities and Intrinsic Reactivities of Isothioureas. Brønsted basicities, which have often been used for a first screening of potential nucleophilic organocatalysts, have been reported for only a few isothioureas.[21] As Lewis basicities are more relevant for their reactions with carbon electrophiles, we have now studied the equilibrium constants of the reactions of several isothioureas with benzhydrylium ions.

The reactions of **7**, **9**, and **10** and of the C(2)-substituted chiral isothioureas **13**−**17** with several colored amino-substituted benzhydrylium ions proceed incompletely, allowing the measurement of the equilibrium constants for these reactions by UV−vis spectroscopy. Assuming proportionality between the absorbances and the concentrations of the benzhydrylium ions (as for the evaluation of the kinetic experiments), the equilibrium constants for the reactions (eq 2) can be determined from the initial absorbances (A_0) of the benzhydrylium ions and the

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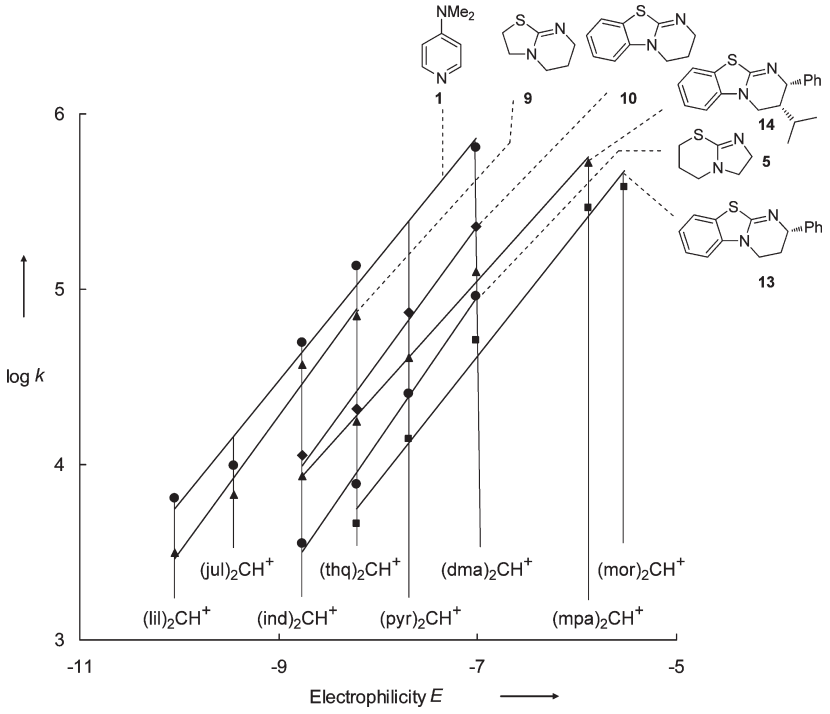

Figure 3. Plots of log k for the reactions of some isothioureas with benzhydrylium ions versus their electrophilicity parameters E in CH_2Cl_2 at 20 °C. Rate constants for DMAP were taken from ref 20a.

absorbances at equilibrium (A) according to eq 3, and results are listed in Table 3.

$$Ar_2CH^+ + Nu \underset{CH_2Cl_2}{\overset{K}{\rightleftharpoons}} Ar_2CH\text{-}Nu^+ \qquad (2)$$

$$K = \frac{[Ar_2CH\text{-}Nu^+]}{[Ar_2CH^+][Nu]} = \frac{A_0 - A}{A[Nu]} \qquad (3)$$

Substitution of the activation free energies $\Delta G^{\ddagger}$ and Gibbs free energies ΔG^0 into the Marcus equation (eq 4)[22] yields the intrinsic barriers $\Delta G_0^{\ddagger}$ (i.e., the barriers of the corresponding reactions with $\Delta G^0 = 0$), which are also listed in Table 3.

$$\Delta G^{\ddagger} = \Delta G_0^{\ddagger} + 0.5\Delta G^{\circ} + ((\Delta G^{\circ})^2/16\Delta G_0^{\ddagger}) \qquad (4)$$

With $\Delta G_0^{\ddagger}$ between 54 and 65 kJ mol^{-1}, the intrinsic barriers are of similar magnitude as previously reported for the reactions of benzhydrylium ions with pyridines[20a,b] and azoles.[20c] Table 3 shows also that the dependence of the intrinsic barriers $\Delta G_0^{\ddagger}$ on the structures of the benzhydrylium ions mirrors previously observed patterns. In particular, the intrinsic barriers for the reactions of the five-membered ring compounds $(ind)_2CH^+$ and $(lil)_2CH^+$ are always 1−2 kJ mol^{-1} higher than those of the corresponding six-membered ring analogues $(thq)_2CH^+$ and $(jul)_2CH^+$, respectively, resulting in a breakdown of rate-equilibrium relationships.[23,24]

Structure Reactivity Relationships. From the observation that the isothioureas **5**, **6**, and **8** (like the amidines DBU **3** and DBN **4**) react quantitatively with all benzhydrylium tetrafluoroborates investigated, it can be derived that they have Lewis basicities higher than those of the isothioureas listed in Table 3.

As Figure 3 shows that the relative reactivities of isothioureas are somewhat dependent on the reactivity of the benzhydrylium ion used as the reaction partner, we will first consider the rate and equilibrium constants for the reactions with $(ind)_2CH^+$, for which directly measured rate and equilibrium constants are available for most isothioureas (Figure 4).

Comparison of the imidazoline derivatives **5**−**7** shows that their nucleophilic reactivities are only slightly affected by the nature of the annelated sulfur-containing heterocycle. The benzannulation in compound **7** accelerates the reverse reaction k_{-1}, however, with the consequence that the equilibrium constant for adduct formation becomes measurable for the reaction of $(ind)_2CH^+$ with **7**.

A comparable trend was observed for the tetrahydropyrimidine series **8**−**10** (line 2 of Figure 4), which are approximately 1 order of magnitude more nucleophilic than their lower homologues **5**−**7** ($k(\mathbf{8})/k(\mathbf{5}) \approx 8$; $k(\mathbf{9})/k(\mathbf{6}) \approx 13$; $k(\mathbf{10})/k(\mathbf{7}) \approx 4$). Also in this series, variation of the annelated sulfur heterocycle had a relatively small effect ($k(\mathbf{9})/k(\mathbf{10}) \approx 3$) on the nucleophilic reactivity but a large effect on Lewis basicity ($K(\mathbf{9})/K(\mathbf{10}) \approx 10^2$). Thus lines 1 and 2 of Figure 4 show the same trend that benzannulation has a much larger effect on Lewis basicity than on nucleophilicity.

Introduction of the phenyl group in the 2-position of **10** (→ **13**) reduces the nucleophilic reactivity by a factor of 4.5 but the Lewis basicity by a factor of 100. Remarkably, an additional *syn*-C(3)-isopropyl group in **14** (relative to HBTM **13**) increases its Lewis basicity (by a factor of 6) and nucleophilicity (by a factor of 3.6). Though there is no direct correlation between these data, it is notable that this trend corresponds with the experimentally observed beneficial effect of an additional *syn*-3-substituent to **13** (→ **14**) in kinetic resolution reactions in terms of catalytic activity and enantioselectivity.[17,18] The last entry of Figure 4 shows that both nucleophilicities and Lewis basicities of the tetrahydropyrimidine derivatives **9** and **10** are comparable to those of DMAP (**1**).

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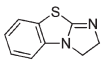
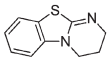
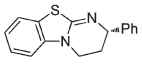
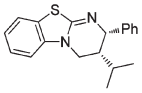
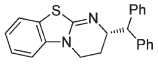
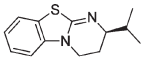
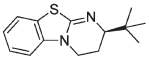
Table 3. Equilibrium Constants K, Activation Free Energies $\Delta G^{\ddagger}$, Reaction Free Energies ΔG^{0}, Intrinsic Barriers $\Delta G_0^{\ddagger}$, and the Reverse Rate Constants ($k_{\leftarrow}$) for the Reactions of Isothioureas with Benzhydrylium Ions (Ar_2CH^+) in CH_2Cl_2 at 20 °C

Isothioureas	Ar_2CH^+	K [M^{-1}]	$\Delta G^{\neq}$ [a] [kJ mol^{-1}]	ΔG^{0} [b] [kJ mol^{-1}]	$\Delta G_0^{\neq}$ [c] [kJ mol^{-1}]	$k_{\leftarrow}$ [d] [s^{-1}]	N_f [e]
 **7**	$(thq)_2CH^+$	2.56×10^4	50.6	–24.7	62.3	2.28×10^{-1}	–5.79
	$(ind)_2CH^+$	2.00×10^4 [f]	52.6	–24.1 [f]	64.1	1.30×10^{-1}	
 THTP **9**	$(ind)_2CH^+$	1.90×10^6 [g]	46.1	–35.2 [g]	62.5	1.94×10^{-2}	–6.49
	$(jul)_2CH^+$	6.16×10^4	50.3	–26.9	63.0	1.09×10^{-1}	
	$(lil)_2CH^+$	6.27×10^4	52.1	–26.9	64.9	5.02×10^{-2}	
 DHPB **10**	$(pyr)_2CH^+$	7.73×10^4	44.4	–27.4	57.3	9.69×10^{-1}	–5.26
	$(thq)_2CH^+$	2.75×10^4	47.5	–24.9	59.3	7.53×10^{-1}	
	$(ind)_2CH^+$	2.02×10^4 [h]	49.0	–24.2 [h]	60.5	5.50×10^{-1}	
 HBTM **13**	$(mpa)_2CH^+$	5.95×10^5	41.1	–32.4	56.1	4.89×10^{-1}	–3.98
	$(dma)_2CH^+$	1.07×10^4	45.3	–22.6	56.0	4.81×10^{0}	
	$(pyr)_2CH^+$	8.96×10^2	48.5	–16.6	56.5	1.56×10^{1}	
	$(thq)_2CH^+$	3.32×10^2	51.2	–14.1	58.0	1.39×10^{1}	
	$(ind)_2CH^+$	1.98×10^2 [i]	52.8 [j]	–12.9 [i]	59.1	1.20×10^{1}	
 **14**	$(dma)_2CH^+$	5.54×10^4	43.1	–26.6	55.6	2.27×10^{0}	–4.24
	$(pyr)_2CH^+$	3.88×10^3	45.9	–20.1	55.5	1.05×10^{1}	
	$(thq)_2CH^+$	1.67×10^3	47.9	–18.1	56.6	1.05×10^{1}	
	$(ind)_2CH^+$	1.17×10^3	49.7	–17.2	58.0	7.34×10^{0}	
 **15**	$(mpa)_2CH^+$	4.66×10^4	42.9	–26.2	55.2	2.94×10^{0}	–3.15
	$(dma)_2CH^+$	9.95×10^2	46.3	–16.8	54.4	3.40×10^{1}	
 **16**	$(mpa)_2CH^+$	1.01×10^5	43.6	–28.1	56.8	1.04×10^{0}	–3.57
	$(dma)_2CH^+$	2.70×10^3	46.1	–19.3	55.3	1.38×10^{1}	
 **17**	$(mor)_2CH^+$	1.36×10^4	47.5	–23.2	58.5	1.51×10^{0}	–2.75
	$(mpa)_2CH^+$	2.45×10^3	48.2	–19.0	57.3	6.45×10^{0}	
DMAP, **1** [k]	$(thq)_2CH^+$	2.81×10^5	42.9	–30.6	57.2	4.80×10^{-1}	–5.32 [l]
	$(ind)_2CH^+$	1.71×10^5	45.4	–29.4	59.2	2.90×10^{-1}	

[a] From rate constants in Table 2 using the Eyring equation. [b] From equilibrium constants K in this table ($-RT \ln K$). [c] From eq 4. [d] $k_{\leftarrow} = k/K$. [e] From eq 5 assuming $s_f = 1$. [f] $\Delta H^{\circ} = -49.8$ kJ mol^{-1}, $\Delta S^{\circ} = -87.7$ J mol^{-1} K^{-1}. [g] $\Delta H^{\circ} = -63.9$ kJ mol^{-1}, $\Delta S^{\circ} = -97.9$ J mol^{-1} K^{-1}. [h] $\Delta H^{\circ} = -50.2$ kJ mol^{-1}, $\Delta S^{\circ} = -88.7$ J mol^{-1} K^{-1}. [i] Equilibrium constant extrapolated from a van't Hoff plot from measurements at lower temperatures (see the Supporting Information). $\Delta H^{\circ} = -44.2$ kJ mol^{-1}, $\Delta S^{\circ} = -106.9$ J mol^{-1} K^{-1}. [j] Calculated using eq 1 and reactivity parameters from Table 1 and Table 3. [k] Data for DMAP was taken from ref 20a. [l] From ref 24.

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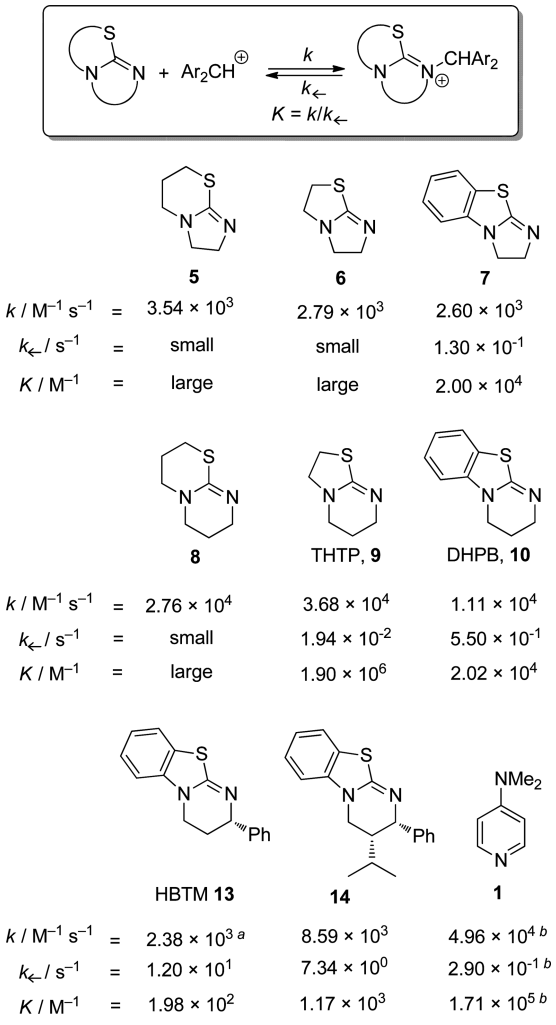


Figure 4. Second-order rate constants k, reverse rate constants $k_{←}$, and equilibrium constants K for the reactions of the isothiourea derivatives **5**−**10** with $(ind)_2CH^+BF_4^-$ in CH_2Cl_2 at 20 °C. [a] Rate constant calculated by using eq 1, the E value of $(ind)_2CH^+$ (Table 1) and the N and s_N values of **13** from Table 2. [b] Data for **1** was taken from ref 20a.

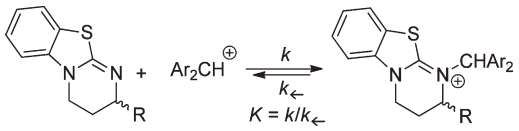
The influence of the substituent at C-2 can be derived from the rate and equilibrium constants of its reactions with $(dma)_2CH^+$ (Table 4). As in the comparisons of Figure 4, variation of the substituents affects the equilibrium constants much more than the rate constants. While the change from phenyl to *tert*-butyl reduces nucleophilicity by approximately 1 order of magnitude, the equilibrium constant decreases by more than 2 orders of magnitude.

Nucleofugalities of Isothioureas. In analogy to eq 1,[19] which has been used to construct a comprehensive nucleophilicity scale, eq 5[24] has recently been suggested as the basis for a comprehensive nucleofugality scale. Benzhydrylium ions of variable electrofugality (characterized by E_f) have been employed as reference electrofuges for characterizing the nucleofugalities of leaving groups in different solvents.

$$\log k_{←}(25\ °C) = s_f(E_f + N_f) \qquad (5)$$

In general, the nucleofugality parameters N_f and the nucleofuge-specific sensitivity parameters s_f are obtained from the linear plots of log $k_{←}$ (25 °C) vs the previously reported[24] electrofugality parameters E_f of the benzhydrylium ions, analogously to the procedure used in Figure 3 for determining the nucleophile-specific parameters N and s_N. It has been suggested, however, to assume $s_f = 1.0$ if only heterolysis rate constants of low precision and/or referring to benzhydrylium ions of similar electrofugality are known. This is the case for the $k_{←}$ values given in Table 3, which are obtained indirectly as the ratios of k/K and furthermore refer to 20 °C. Neglecting the small difference in temperature, we have therefore calculated the N_f parameters of isothioureas (listed in Table 3) from eq 5 setting the s_f parameter to 1.0 (see also Tables S39 in the Supporting Information).

Table 4. Second-Order Rate Constants k, Reverse Rate Constants $k_{←}$, and Equilibrium Constants K for the Reactions of the Isothiourea Derivatives 13 and 15−17 with $(dma)_2CH^+BF_4^-$ in CH_2Cl_2



R	k (M^{-1} s^{-1})	$k_{←}$ (s^{-1})	K (M^{-1})
Ph (**13**)	5.15×10^4	4.81	1.07×10^4
$CHPh_2$ (**15**)	3.38×10^4	3.40×10^1	9.95×10^2
*i*Pr (**16**)	3.73×10^4	1.38×10^1	2.70×10^3
*t*Bu (**17**)	2.8×10^{3a}	$\approx 5 \times 10^1$	$\approx 6 \times 10^{1b}$

[a] Rate constant calculated by using eq 1, the E value of $(dma)_2CH^+$, (Table 1), and the N/s_N values of **17**(Table 2). [b] Estimated by dividing $K[(mpa)_2CH^+]$ by 40, the ratio derived from equilibrium constants of **15** and **16** with $(mpa)_2CH^+$ and $(dma)_2CH^+$.

Due to the high Lewis basicities of DBU **3**, DBN **4**, and the isothioureas **5**, **6**, and **8** equilibrium constants could not be measured, indicating that they are poor nucleofuges. The trends in N_f shown in Table 3 are equivalent to the trends in $k_{←}$ discussed for Figure 4 and Table 4.

It is the benefit of the N_f values in Table 3 that they allow a comparison of the leaving group abilities in CH_2Cl_2 of isothioureas with those of other nucleofuges. Thus, comparison with N_f values listed in ref 24 shows that the nucleofugalities of **7**, **9**, and **10** are comparable to those of DMAP (**1**) ($N_f = -5.32$), *N*-methyl-imidazole (**2**) ($N_f = -6.29$ in CH_3CN) and *N*-phenyl-imidazole ($N_f = -5.59$ in CH_3CN), or tris(*p*-tolyl)phosphane ($N_f = -5.20$) and tris(*p*-anisyl)phosphane ($N_f = -5.91$). The nucleofugalities of **13** and **14** are comparable to that of triphenylphosphane ($N_f = -4.44$), and N_f of the *tert*-butyl substituted compound **17** is similar to that of 4-methoxypyridine ($N_f = -2.80$) and isoquinoline ($N_f = -3.04$ in CH_3CN).

CONCLUSION

In a systematic study Birman et at. observed that the relative catalytic activities of DMAP (**1**) and THTP (**9**) in the acylation of alcohols with Ac_2O/iPr_2NEt in chloroform vary dramatically and can be reversed when the concentration of the catalyst and/or the nature of the alcohols are altered.[7] One must, therefore, conclude that there is not a single, best acylation catalyst. Thus the nucleophilicities and Lewis basicities of isothioureas reported in this work are two important but not the only factors controlling catalytic activities.

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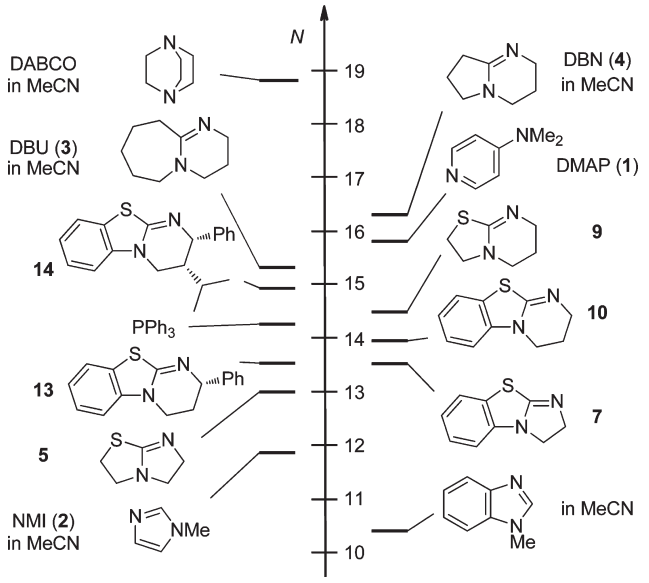

Figure 5. Comparison of the nucleophilicities *N* of isothioureas with other nucleophilic organocatalysts (solvent is CH_2Cl_2 unless otherwise stated, *N* from ref 20).

As the reactions of isothioureas with benzhydrylium ions have been found to follow the linear-free energy relationship (eq 1), it was possible to determine the nucleophilicity parameters for the isothioureas **5**−**10** and **13**−**17** and to include these compounds into our comprehensive nucleophilicity scale. Figure 5 shows that the nucleophilicities *N* of the investigated isothioureas are in between those of the classical organocatalysts DMAP (**1**) and NMI (**2**).

The availability of rate and equilibrium constants for the reactions of these nucleophiles with the benzhydrylium ion $(ind)_2CH^+$ furthermore allows us to construct the quantitative energy profile diagrams as depicted for some reactions in Figure 6. It is thus found that imidazoles are less nucleophilic as well as less Lewis basic than isothioureas. Although the kinetic and thermodynamic properties of most isothioureas investigated are comparable to those of DMAP, DABCO is a stronger nucleophile than all isothioureas investigated, while its Lewis basicity is comparable to those of the least basic isothioureas.

In future work we will examine the relevance of these kinetic and thermodynamic data for various organocatalytic transformations.

EXPERIMENTAL SECTION

General. CH_2Cl_2 was freshly distilled over CaH_2. Isothioureas were synthesized according to literature procedures.[7,15,18] Benzhydrylium tetrafluoroborates were prepared as described before.[19a] All other chemicals were purchased from commercial sources and (if necessary) purified by recrystallization or distillation prior to use. ^1H and ^{13}C NMR spectra were recorded on NMR-systems (400 MHz) in d_6-DMSO or CD_3CN, and the chemical shifts in ppm refer to the solvent residual signal as internal standard ($\delta_H(CD_3CN)$ = 1.94, $\delta_C(CD_3CN)$ = 1.4 ppm; $\delta_H(d_6\text{-DMSO})$ = 2.50, $\delta_C(d_6\text{-DMSO})$ = 39.5 ppm).

Kinetics. The reactions of isothioureas with the colored benzhydrylium ions (Ar_2CH^+) were followed photometrically at or close to the absorption maxima of (Ar_2CH^+) by UV−vis spectroscopy as described previously.[19] Slow reactions ($\tau_{1/2}$ > 10 s) were determined by using conventional UV−vis spectrophotometers. Stopped-flow techniques were used for the investigation of rapid reactions ($\tau_{1/2}$ < 10 s). The temperature

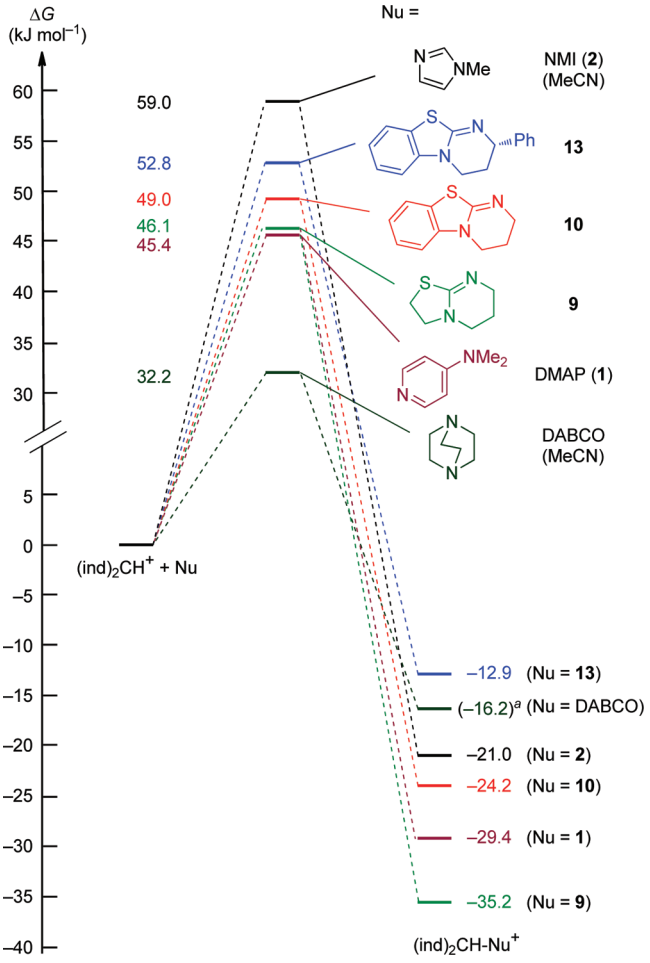

Figure 6. Gibbs energy profiles for the reactions of various nucleophilic organocatalysts with the benzhydrylium ion $(ind)_2CH^+$ in CH_2Cl_2 at 20 °C ($\Delta G^{\ddagger}$ and $\Delta G°$ values from Table 3 or from ref 20). [a]$\Delta G°$ was estimated in ref 20e.

of the solutions was kept constant at 20.0 ± 0.1 °C during all kinetic studies by using a circulating bath thermostat. The pseudo-first-order rate constants k_{obs} (s^{-1}) were obtained by least-squares fitting of the absorbances to the monoexponential function $A_t = A_0 \exp(-k_{obs}t) + C$. The second-order rate constants k (M^{-1} s^{-1}) were obtained from the slopes of the linear plots of k_{obs} against the nucleophile concentrations. Tables with concentrations of reactants and individual rate constants are collected in the Supporting Information.

Determination of Equilibrium Constants. Equilibrium constants were determined by UV−vis spectroscopy as follows. To solutions of benzhydrylium tetrafluoroborates in CH_2Cl_2 were added small amounts of stock solutions of isothioureas, and the absorbances of the benzhydrylium tetrafluoroborates were monitored at their corresponding λ_{max} before (A_0) and immediately after (A) the addition of isothioureas. This procedure was carried out with different concentrations of the isothioureas. The temperature was kept constant at 20.0 ± 0.1 °C using a circulating bath thermostat. For details see the Supporting Information.

Product Studies. Formation of 6P-BF_4. To a blue solution of $(dma)_2CH^+BF_4^-$ (21 mg, 0.062 mmol) in CH_2Cl_2 (1 mL) was added drop by drop a solution of **6** (7.9 mg, 0.062 mmol) in dry CH_2Cl_2 (1 mL) under nitrogen at room temperature. After the disappearance of the blue color of the solution the solvent was evaporated, and the residue was washed with *i*-hexane to afford **6P**-BF_4: 27 mg (0.058 mmol, 93%, viscous liquid). **6P**-BF_4: ^1H NMR (CD_3CN, 400 MHz): δ 2.93

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(s, 12 H), 3.59−3.66 (m, 4 H), 3.72−3.77 (m, 2 H), 4.03−4.08 (m, 2 H), 5.67 (s, 1 H), 6.74 (d, J = 8.9 Hz, 4 H), 7.11 ppm (d, J = 8.9 Hz, 4 H). ^{13}C NMR (CD_3CN, 100 MHz): δ 38.0 (t), 40.6 (q), 47.4 (t), 48.1 (t), 56.6 (t), 66.9 (d), 113.2 (d), 124.0 (s), 130.7 (d), 152.1 (s), 177.5 ppm (s). HRMS (ESI) calculated for $C_{22}H_{29}N_4{}^{32}S$ [M^+] 381.2107, found 381.2112.

Formation of 7P-BF_4. Equimolar amounts of $(dma)_2CH^+BF_4^-$ (16 mg, 0.047 mmol) and **7** (8.3 mg, 0.047 mmol) were mixed in d_6-DMSO (0.6 mL) in an NMR tube under nitrogen and the NMR was taken after few minutes of shaking. **7P**-BF_4: ^{1}H NMR (d_6-DMSO, 400 MHz): δ 2.93 (s, 12 H), 4.27−4.32 (m, 2 H), 4.53−4.58 (m, 2 H), 5.91 (s, 1 H), 6.77 (d, J = 8.8 Hz, 4 H), 7.25 (d, J = 8.8 Hz, 4 H), 7.30−7.35 (m, 1 H), 7.55 (d, J = 3.9 Hz, 2 H), 7.93 ppm (d, J = 8.1 Hz, 1 H). ^{13}C NMR (d_6-DMSO, 100 MHz): δ 39.9 (q), 44.8 (t), 55.1 (t), 65.2 (d), 112.0 (d), 112.2 (d), 123.0 (s), 124.3 (d), 124.4 (d), 127.5 (s), 128.1 (d), 129.5 (d), 134.0 (s), 150.4 (s), 168.8 ppm (s).

Formation of 9P-BF_4. To a blue solution of $(dma)_2CH^+BF_4^-$ (22 mg, 0.065 mmol) in CH_2Cl_2 (1 mL) was added drop by drop a solution of **9** (9.2 mg, 0.062 mmol) in dry CH_2Cl_2 (1 mL) under nitrogen at room temperature. After the disappearance of the blue color of the solution the solvent was evaporated, and the residue was washed with *i*-hexane to get **9P**-BF_4: 27 mg (0.058 mmol, 89%, viscous liquid). **9P**-BF_4: ^{1}H NMR (CD_3CN, 400 MHz): δ 2.02−2.07 (m, 2 H), 2.94 (s, 12 H), 3.17−3.20 (m, 2 H), 3.41−3.47 (m, 4 H), 4.00 (t, J = 7.7 Hz, 2 H), 5.98 (s, 1 H), 6.75 (d, J = 8.9 Hz, 2 H), 7.03 ppm (d, J = 8.4 Hz, 4 H). ^{13}C NMR (CD_3CN, 100 MHz): δ 20.2 (t), 29.2 (t), 40.6 (q), 44.5 (t), 45.6 (t), 57.0 (t), 72.9 (d), 113.3 (d), 124.3 (s), 130.4 (d), 151.8 (s), 168.3 ppm (s). HRMS (ESI) calculated for $C_{23}H_{31}N_4{}^{32}S$ [M^+] 395.2264, found 395.2265.

Formation of 10P-BF_4. Equimolar amounts of $(dma)_2CH^+BF_4^-$ (13 mg, 0.038 mmol) and DHPB **10** (7.3 mg, 0.038 mmol) were mixed in d_6-DMSO (0.6 mL) in an NMR tube under nitrogen, and the NMR was taken after few minutes of shaking. **10P**-BF_4: ^{1}H NMR (d_6-DMSO, 400 MHz): δ 2.28−2.31 (m, 2 H), 2.92 (s, 12 H), 3.43−3.45 (m, 2 H), 4.23 (t, J = 5.9 Hz, 2 H), 6.12 (s, 1 H), 6.76 (d, J = 8.9 Hz, 4 H), 7.15 (d, J = 8.7 Hz, 4 H), 7.41−7.45 (m, 1 H), 7.59−7.63 (m, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 8.04 ppm (d, J = 8.0 Hz, 1 H). ^{13}C NMR (d_6-DMSO, 100 MHz): δ 18.4 (t), 39.9 (q), 43.0 (t), 45.0 (t), 70.9 (d), 112.2 (d), 112.9 (d), 121.9 (s), 122.4 (s), 123.3 (d), 125.0 (d), 128.0 (d), 129.4 (d), 138.8 (s), 150.3 (s), 164.3 ppm (s).

■ ASSOCIATED CONTENT

Supporting Information. Copies of NMR spectra of the products, details of the equilibrium and rate measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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