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# Enantioselective Catalytic α-Alkylation of Aldehydes via an $S_N1$ Pathway

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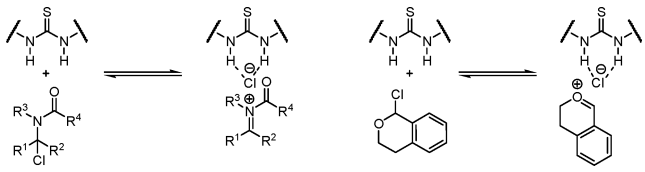
***Abstract:*** Primary aminothiourea derivatives are shown to catalyze enantioselective alkylation of α-arylpriopionaldehdyes with diarylbromomethane. Evidence for a stepwise, $S_N1$ mechanism in the substitution reaction induced by anion binding to the catalyst is provided by catalyst structure−activity studies, kinetic isotope effects, linear free-energy relationship studies, and competition experiments.

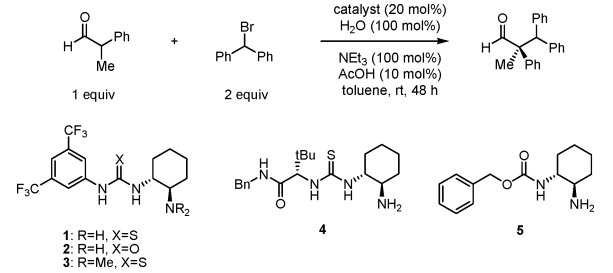
The anion-binding properties of urea and thiourea derivatives have been exploited recently in enantioselective catalytic reactions involving heteroatom-stabilized carbocations, such as *N*-acyliminium and oxocarbenium ions.[1,2] Experimental and computational data point to a consistent mechanistic framework wherein the H-bond donor catalysts promote these reactions by anion abstraction from a neutral organic precursor to generate the more reactive cationic electrophile (Scheme 1).[1b] We reasoned that, with the appropriate catalyst and nucleophilic partner, this mode of electrophile activation might also be applicable to catalysis of $S_N1$ pathways via formation and reaction of carbocations that are not heteroatom-stabilized.[3] Herein we report the successful application of this activation mode to formation of benzhydryl cations in the context of an asymmetric α-alkylation of α-branched aldehydes.

***Scheme 1.*** Hydrogen-Bond Catalysis by Anion Binding



The α-alkylation of 2-phenylpropionaldehyde (**6a**) with bromodiphenylmethane (benzhydryl bromide, **7a**) was chosen as a model reaction (Table 1). Classical studies with benzhydryl derivatives have helped to establish much of the conceptual foundations of carbocation reactivity,[4] and these compounds have been especially useful for characterizing the nature and stereochemical properties of ion pairs.[5] The α-alkylation of aldehydes was deemed particularly worthy of investigation because of the high value of chiral aldehydes bearing α-quaternary stereocenters as synthetic intermediates[6] and the inherent challenges associated with asymmetric catalysis of this type of transformation.[7] A broad screen of potential catalysts in the alkylation of 2-phenylpropionaldehyde with bromodiphenylmethane led to the discovery that primary aminothiourea derivatives were unique in inducing good reactivity and enantioselectivity (Table 1).[8] This class of catalysts has been applied previously in additions of aldehydes and ketones to nitroalkenes,[9] through the proposed intermediacy of covalent catalyst-enamine derivatives. The presence of a primary amino group was shown to be necessary for catalysis in the present case, as well (Table 1, entries 1 vs 4). The thiourea also plays an essential role in promoting reactivity and enantioinduction (entries 1−5 vs entries 6−7), suggesting that the dual H-bond donor component may be involved directly in electrophile activation (*vide infra*).[10] It is noteworthy that the relatively simple thiourea **1**[11] proved to be optimal, as more elaborate primary aminothiourea catalysts bearing additional stereochemical elements afforded no advantage (e.g., **4**, entry 5).[8]

***Table 1.*** Catalyst Structure−Activity Relationship Study

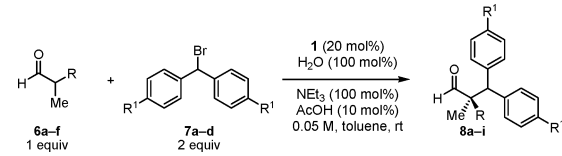



| entry | catalyst | concentration (M) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **1** | 0.05 | 71 | 91 |
| 2 | **1** | 0.1 | 54 | 90 |
| 3 | **2** | 0.05 | 44 | 89 |
| 4 | **3** | 0.05 | 0 | − |
| 5 | **4** | 0.05 | 26 | 89 |
| 6 | **5** | 0.05 | trace | n.d. |
| 7 | **5** | 0.1 | 2 | 20 |

[a] Determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b] Determined by HPLC analysis of alcohol following reduction with $NaBH_4$.

Alkylation of a variety of 2-arylpropionaldehydes proceeded in moderate-to-good yield and high enantioselectivity in the presence of catalyst **1** (Table 2).[12] The scope of the reaction also included halo-substituted benzhydryl electrophiles, which underwent alkylation to afford products **8g**−**8i** in high ee.[13,14]

***Table 2.*** Reaction Scope




| entry | R | $R^1$ | product | time (d) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | $C_6H_5$ | H | **8a** | 3 | 70 | 91 |
| 2 | 2-naphthyl | H | **8b** | 2 | 68 | 92 |
| 3 | *p*-Br $C_6H_4$ | H | **8c** | 4 | 56 | 94 |
| 4 | *p*-F $C_6H_4$ | H | **8d** | 4 | 57 | 92 |
| 5 | *p*-(Me)$C_6H_4$ | H | **8e** | 2 | 59 | 85 |
| 6 | *p*-(OMe)$C_6H_4$ | H | **8f** | 3 | 52 | 85 |
| 7 | $C_6H_5$ | F | **8g** | 3 | 60 | 90 |
| 8 | $C_6H_5$ | Cl | **8h** | 3 | 61 | 91 |
| 9 | $C_6H_5$ | Br | **8i** | 3 | 61 | 91 |

[a] Yield of isolated alcohol after reduction with $NaBH_4$ (entries 1−6, 8); Yield of isolated aldehyde (entries 7 and 9). [b] Determined by HPLC analysis of alcohol following reduction with $NaBH_4$.

The essential role of the catalyst (thio)urea moiety in promoting these enantioselective alkylation reactions may be ascribed to elec-



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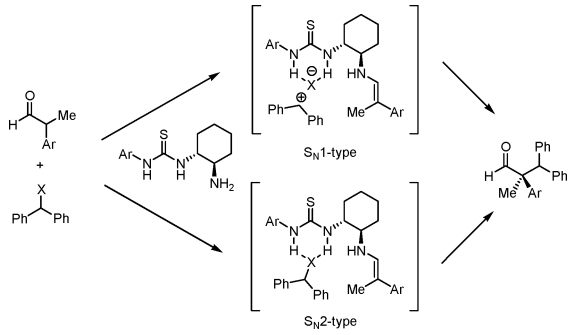
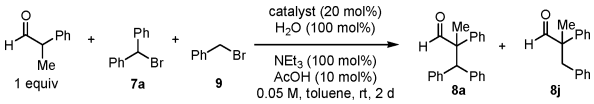
trophile activation by H-bonding to the leaving group in either of two limiting mechanisms: (1) general acid catalysis to induce a concerted, $S_N2$-like substitution or (2) formation of an ion-pair intermediate and promotion of an $S_N1$-like pathway (Scheme 2). In an effort to distinguish between these possibilities, we analyzed the effects of isotopic and electronic substitution of the electrophile on the reaction rate. A normal secondary kinetic isotope effect ($k_H/k_D$) of 1.12 was observed upon deuterium-substitution of the benzhydryl proton, indicating a change in hybridization of the electrophilic carbon from $sp^3$ to $sp^2$ in the transition state.[15,16] A Hammett study revealed a strong dependence on the electronic properties of the electrophile, with benzhydryl derivatives bearing electron-donating substituents reacting more rapidly ($\rho = -1.95$).[17,18] The results of both experiments provide strong evidence that this transformation proceeds through a discrete, catalyst-associated carbocation in an $S_N1$-like substitution mechanism.

***Scheme 2.*** Possible Electrophile Activation Modes




Additional evidence for a catalyst-induced $S_N1$ pathway was provided through the evaluation of benzyl bromide as a potential electrophile in the alkylation reaction. In competition experiments, alkylation of 1-cyclohexenylpyrrolidine was found to proceed exclusively with benzyl bromide in the presence of equimolar amounts of bromodiphenylmethane, a degree of selectivity attributable to the relative reactivity of these electrophiles in $S_N2$ pathways. In contrast, under the catalytic conditions using either **1** or **2**, no alkylation of 2-phenylpropionaldehyde was obtained with benzyl bromide (Table 3, entries 1−2). This absence of reactivity was not ascribable to catalyst deactivation, as experiments with mixtures of benzyl bromide and bromodiphenylmethane (**7a**) demonstrated that the catalyst maintained activity (Table 3, entries 3−4).

***Table 3.*** Electrophile Competition Experiments




| entry | catalyst | **7a** (equiv) | **9** (equiv) | yield **8a** (%) | ee **8a** (%) | yield **8j** (%) |
|---|---|---|---|---|---|---|
| 1 | **1** | 0 | 2 | − | n.a. | 0 |
| 2 | **2** | 0 | 2 | − | n.a. | 0 |
| 3 | **1** | 2 | 2 | 49 | 90 | 0 |
| 4 | **2** | 2 | 2 | 42 | 85 | 0 |

Alkylations using enantioenriched *p*-chlorobenzhydryl chloride were found to proceed with nearly complete (95%) stereospecificity,[19] which requires that addition of the catalyst-associated enamine to the ion-pair intermediate is rapid relative to ion-pair reorganization.[20] This observation is in line with the known reactivity of benzhydryl cations and enamines as analyzed by Mayr,[21] which would predict that these partners should undergo intermolecular reaction at a rate near the diffusion limit.[22] This stands in sharp contrast to solvolyses of benzhydryl electrophiles, wherein substitution has been shown to be slow relative to racemization.[5]

This work demonstrates that urea and thiourea derivatives effectively induce alkylation pathways through simple carbocations via anion abstraction and can control the reactivity of such cationic intermediates in asymmetric bond-forming reactions. The possibility of extending this activation mode to enantioselective additions to prochiral carbocations is under investigation.

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**Supporting Information Available:** Complete experimental procedures and characterization data for products and all isolated intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Details of catalyst and reaction optimization studies are provided in the Supporting Information. Solvent, concentration, and the presence of additives are also important factors that influence both enantioselectivity and reactivity. The presence of water and acetic acid accelerates the reaction, presumably by influencing the imine and enamine formation and imine hydrolysis steps, while $NEt_3$ serves to trap the HBr byproduct. Water and weak acid have been shown to be beneficial in other primary amine thiourea catalyzed reactions (see ref 9b−c).

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(10) The fact that both urea **2** and thiourea **1** display catalytic activity and similar enantioselectivity in this transformation (Table 1, entries 1 and 3) would appear to rule out any direct role of the thiocarbonyl moiety in the alkylation mechanism.

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(12) Moderate yields are a result of starting material aldehyde decomposition via α-oxidation and incomplete conversion.

(13) Benzhydryl electrophiles bearing strongly electron-withdrawing groups were unreactive under the catalytic conditions. In contrast, analogs bearing electron-donating groups such as $(p\text{-MeOC}_6H_4)_2CH(Br)$ effected alkylation

to give racemic products without (thio)urea activation (i.e., similar results were obtained with **1**, **2**, and with catalytic cyclohexylamine).
(14) No reactions with α,α-dialkyl aldehydes or α-alkoxy aldehydes were observed under the optimal catalytic conditions.
(15) A KIE of 1.11 was observed for the reaction mediated by urea catalyst **2**.
(16) This KIE is consistent with what is observed in solvolysis reactions of benzhydryl chlorides: Streitwieser, A.; Klein, H. S. *J. Am. Chem. Soc.* **1964**, *86*, 5170.
(17) Plots of log $k_{rel}$ vs Hammett's substituent constants ($\sigma^+$) are provided in the Supporting Information.
(18) The rates of $S_N1$ reactions of benhydryl bromides (solvolysis in DMSO) depend strongly on the electronic properties of the electrophile ($\rho = -2.9$), while the rates of $S_N2$ reactions of benzhydryl bromides are only marginally affected and display poor Hammett correlations: Phan, T. B.; Nolte, C.; Kobayashi, S.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2009**, *131*, 11392.
(19) See Supporting Information for experimental details and analysis.
(20) Benzhydryl chlorides and bromides underwent reaction with very similar enantioselectivities (91% ee in the reaction of **6a** with both benzhydryl chloride and benzhydryl bromide). The mechanistic experiments were performed using the chlorobenzhydryl derivative because it was not possible to synthesize the bromide in highly enantioenriched form.
(21) For quantitative data describing the reactivity of these reacting partners, see ref 4c and: Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2003**, *9*, 2209.
(22) Reaction of 1-*N*-morpholino-1-phenylethene with benzhydryl cation, $s = 0.79$, $N = 9.96$ (ref 21), and $E = 5.9$ (ref 4c), so log $k(20\ °C) = s(N + E) = 12.5$.

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