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Highly Enantioselective Aza-Baylis–Hillman Reactions Catalyzed by Chiral Thiourea Derivatives

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Abstract: We report the discovery of asymmetric aza-Baylis–Hillman (ABH) reactions of *N*-*p*-nitrobenzenesulfonylimines with methyl acrylate catalyzed by chiral thiourea derivatives. A series of aromatic imines was found to undergo coupling with methyl acrylate with unprecedented levels of enantioselectivity (87–99% ee), albeit only in modest (25–49%) yields. A DABCO-acrylate-imine adduct was isolated as a key intermediate in the ABH reaction. We provide a mechanistic analysis based on the identity of this intermediate as well as kinetic investigations and isotope studies, and propose a rationale for the observed limitations in yield. Synthetic applications of the ABH products are also described.

Keywords: asymmetric catalysis; aza-Baylis–Hillman reaction; kinetic isotope effect; organocatalysis; thiourea catalyst

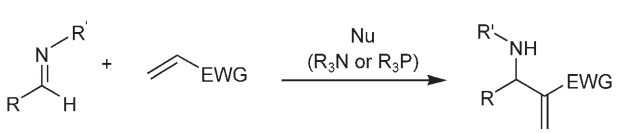
Introduction

The nucleophile-catalyzed coupling of imines with electron-deficient olefins, known as the aza-Baylis–Hillman (ABH) reaction, provides direct access to highly functionalized chiral amines from readily available achiral starting materials (Scheme 1).[1] While important advances have been made recently in asymmetric catalysis of the ABH reaction with enone substrates (EWG = COR),[2a–e] no general and highly enantioselective variants employing simple acrylate derivatives (EWG = CO_2R) have been identified,[2f–i] despite the clear utility that such processes might hold. In this paper we report ABH reactions of methyl acrylate and *p*-nitrobenzenesulfonyl (nosyl) imines catalyzed by chiral thiourea derivatives, in a method that provides highly enantioenriched nosyl-protected amines[3] albeit in low-to-moderate yield. Our investigations into the mechanism of this reaction have led to the isolation of a late-stage intermediate, and provided insight into the basis for the observed trade-off between enantioselectivity and yield.

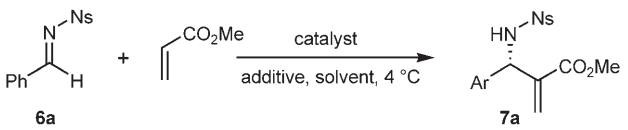
Results and Discussion

Methodology Development and Reaction Optimization

Over the past several years, our group[4] and others[5] have developed chiral thiourea derivatives (e.g., **1**–**5**, Figure 1) as an important new class of asymmetric catalysts. Given the demonstrated ability of these compounds to activate imines and imine derivatives toward a variety of enantioselective additions,[4a–g] and the established utility of weak acids in catalyzing asymmetric Baylis–Hillman (BH) reactions,[6,7] we considered their possible application to the ABH reaction. In an early screening study, ABH adduct **7a** was generated from methyl acrylate and *N*-nosylbenzaldimine (**6a**) in 30% ee and 60% conversion using the known Strecker thiourea catalyst **1a**[4c] in THF, with Ph_2PMe as a nucleophilic additive [Eq. (1)]. This promising lead result prompted us to undertake systematic optimization studies.



Scheme 1. The aza-Baylis–Hillman reaction.



(1)

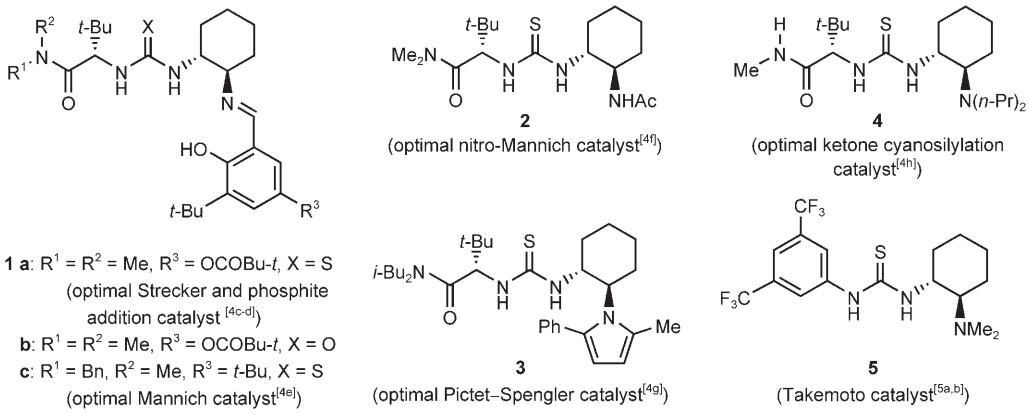


Figure 1. Representative thiourea catalysts.

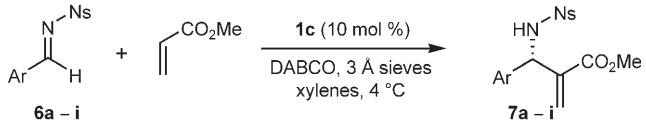
Among the various imine *N*-protecting groups examined, the nosyl group was found to be optimal, as Boc-, Moc-, phosphonyl-, *p*-toluenesulfonyl-, and alkyl-protected imines underwent the ABH reaction with methyl acrylate with only marginal enantioselectivities. Catalyst design strategies involving covalent tethering of tertiary amine or phosphine units to the chiral thiourea framework were all unsuccessful, with greatly diminished catalytic activity observed. However, markedly higher reactivity and enantioselectivities were obtained by careful selection of reaction solvent and nucleophilic additive. Improved enantioselectivities were obtained by replacing Ph_2PMe with 1,4-diazabicyclo[2.2.2]octane (DABCO) as the nucleophilic additive. Whereas an inverse correlation between enantiomeric excess and nucleophile loading was seen with Ph_2PMe (Table 1, entries 6–8), reactions employing DABCO exhibited the opposite trend (Table 1, entries 9–11), and addition of exactly one equivalent of DABCO relative to methyl acrylate led to highest enantioselectivity (Table 1, entries 11–13). An extensive screen of thiourea catalysts led to the identification of **1a** and **1c** as optimal (entries 11 and 12), with **1c** selected for further study due to its greater synthetic accessibility.[8] Pronounced solvent and concentration effects were observed, with reactions carried out in non-polar solvents (toluene, Et_2O, xylenes) affording highest ees, but producing highly heterogeneous mixtures and generally low yields of **7a**.

Table 1. Effect of solvent and nucleophilic additive in the thiourea-catalyzed ABH reaction [Eq. (1)].

Entry[a]	Catalyst	Solvent	Additive (equivs.)[b]	Conv. [%][c]	ee [%][d]
1	**1a**	THF	PPh_3 (0.2)	0	–
2	**1a**	THF	PMe_3 (0.2)	Decomp.	–
3	**1a**	THF	Ph_2PMe (0.2)	80	28
4	**1a**	EtOAc	Ph_2PMe (0.2)	86	17
5	**1a**	Toluene	Ph_2PMe (0.2)	90	41
6	**1a**	Et_2O	Ph_2PMe (0.2)	41	60
7	**1a**	Et_2O	Ph_2PMe (0.5)	62	52
8	**1a**	Et_2O	Ph_2PMe (1.0)	79	40
9	**1a**	Et_2O	DABCO (0.2)	16	76
10	**1a**	Et_2O	DABCO (0.5)	30	87
11	**1a**	Et_2O	DABCO (1.0)	61	93
12	**1c**	Et_2O	DABCO (1.0)	53	94
13	**1c**[e]	Xylenes (0.15 M)	DABCO (1.0)	55	97
14	**1c**	Xylenes (0.03 M)	DABCO (1.0)	90	53
15	**1c**	Toluene	DABCO (1.0)	57	90
16	**1c**	EtOAc	DABCO (1.0)	65	84
17	**1c**	CH_2Cl_2	DABCO (1.0)	95	12

[a] Unless noted otherwise, reactions were carried out on 0.05 mmol scale with nucleophile, imine (1 equiv.), acrylate (4 equivs.), and catalyst (20 mol %) in freshly distilled solvent for 24–36 h.
[b] See Supporting Information for a listing of other additives examined.
[c] Determined by GC analysis.
[d] Determined by HPLC analysis using commercial chiral columns.
[e] 10 mol% catalyst.

Table 2. Thiourea-catalyzed aza-Baylis–Hillman reaction.

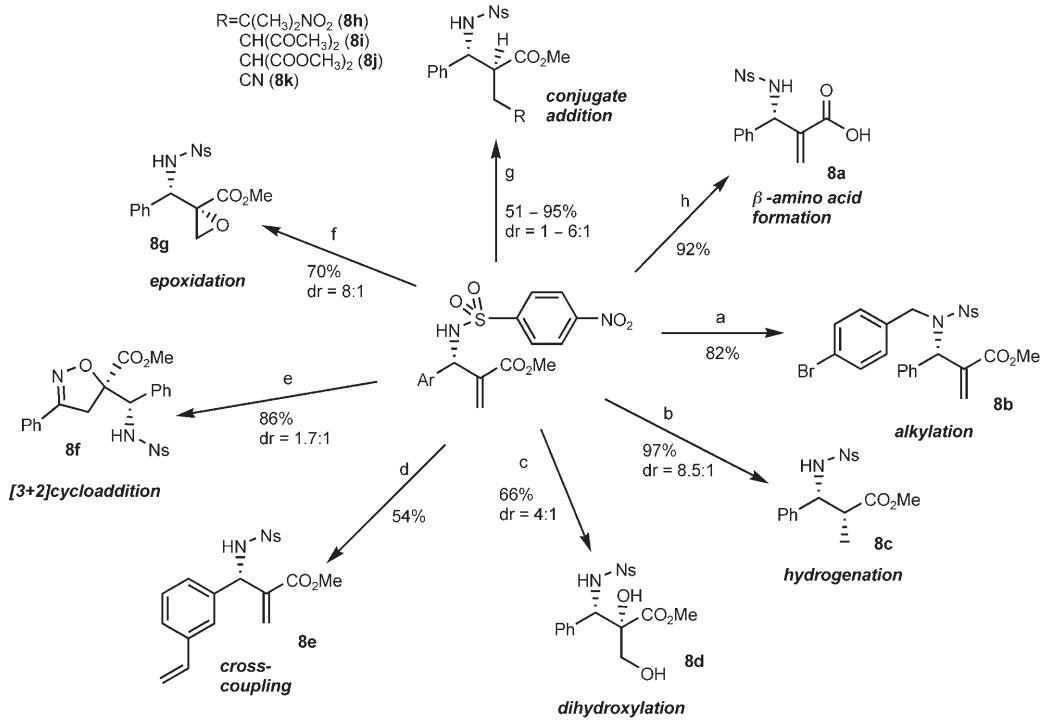


Entry	Ar	Time [h]	Product	Yield [%]	ee [%][a]
1	C_6H_5 (**6a**)	36	**7a**	49	95
2	3-$CH_3C_6H_4$ (**6b**)	24	**7b**	40	93
3	3-(OCH_3)C_6H_4 (**6c**)	24	**7c**	42	96
4	4-ClC_6H_4 (**6d**)	16	**7d**	36	87
5	3-ClC_6H_4 (**6e**)	16	**7e**	33	94
6	3-BrC_6H_4 (**6f**)	16	**7f**	39	92
7	1-Naphthyl (**6g**)	24	**7g**	27	91
8	2-Thiophenyl (**6h**)	36	**7h**	30	99
9	3-Furyl (**6i**)	36	**7i**	25	98

[a] Determined by HPLC analysis using commercial chiral columns (see Supporting Information).

More polar solvents (CH_2Cl_2, EtOAc) or more dilute conditions with xylenes led to a greater degree of solubilization and improved yields (entries 14, 16 and 17), but at the expense of enantioselectivity. The pronounced inverse relationship between ee and conversion indicated that a deeper mechanistic investigation was warranted (*vide infra*).

Under the optimized reaction conditions,[9] a variety of aromatic nosylimine derivatives were found to be suitable coupling partners with methyl acrylate (Table 2). Electron-donating, electron-withdrawing, and heteroaromatic substrates underwent reaction with high enantioselectivities in all cases, but with isolated yields ranging only from 25 to 49%. The synthetic utility

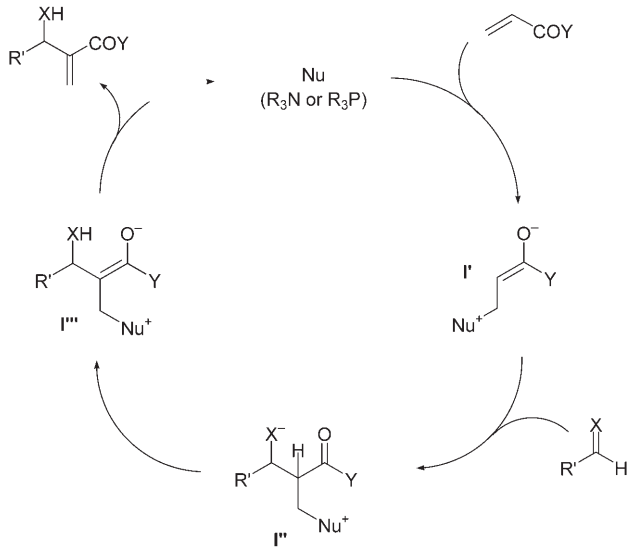


Scheme 2. Some representative synthetic transformations of aza-Baylis–Hillman adducts. *Conditions:* (a) Cs_2CO_3, $ArCH_2Br$, DMF; (b) Pfaltz catalyst,[10] H_2, CH_2Cl_2, 1 atm; (c) OsO_4 (5 mol %), NMO, H_2O/acetone; (d) tributylvinyltin, $Pd(OAc)_2$, S-Phos,[11] DMF; (e) chlorobenzaldoxime, Et_3N , CH_2Cl_2; (f) *t*-BuOOH, Triton B, THF; (g) See Supporting Information; (h) 20% aqueous HCl, reflux. See Supporting Information for full details.

of the densely functionalized ABH adducts is illustrated in the variety of transformations shown in Scheme 2.

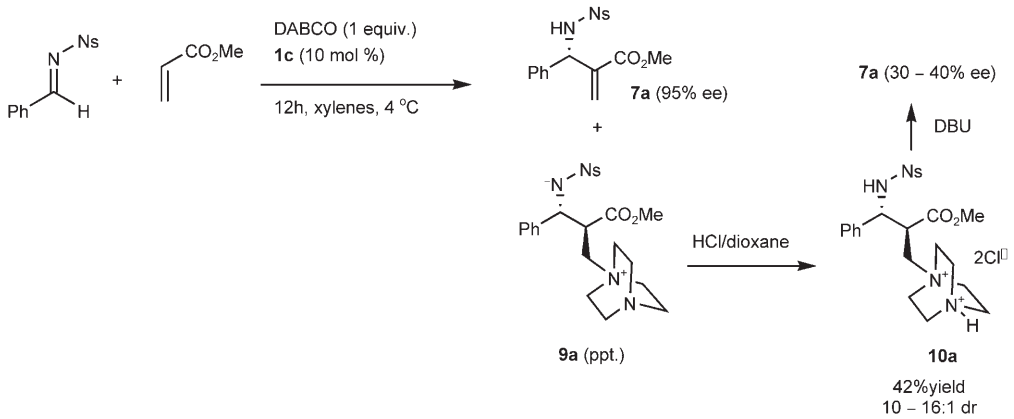
Isolation of Reaction Intermediate and Mechanistic Investigation

The Baylis–Hillman (BH) reaction and the analogous ABH reaction have been the focus of considerable mechanistic analysis over the past several years,[1,12] and compelling evidence has been gathered very recently indicating that the deprotonation step in BH reactions (**I**′ to **I**‴ in Scheme 3) can be rate-limiting.[13] With this framework in mind, we sought to glean insight into the mechanism of the thiourea-catalyzed ABH reaction, with the practical goal of elucidating the basis for the inverse relationship between ee and conversion. The reaction of **6a** and methyl acrylate catalyzed by **1c** and DABCO was chosen as a representative system. The physical properties of the reaction mixtures were observed to change within a few hours of initiation, with the system becoming more viscous and the appearance of a yellow precipitate. Initially, we suspected that the precipitate corresponded to undissolved imine and product, both of which display low solubility in xylenes. Instead, ESI mass spectral analysis of the precipitate isolated from reactions of **6a** revealed a prominent peak with an *m*/*z* value of 489.2, consistent with a structure corresponding to zwitterionic **9a** (Scheme 4), corresponding to intermediate **I**′ in Scheme 2. Further, addition of excess 4 N HCl to the crude reaction mixture, followed by aqueous extraction, afforded a glassy, off-white solid isolated from the aqueous layer that was characterized by ESI-MS, ^{1}H NMR, ^{13}C NMR, and IR as the dihydrochloride salt **10a**.[14] The analogous salts **10f** and **10i** were obtained in a similar manner from 3-bromobenzaldimine **6f** and furfuraldimine **6i**, respectively. In every case, **10** was isolated in high diastereomeric purity, with the relative stereochemistry of the major isomer assigned as *anti* by comparison of ^{1}H NMR spectral properties to those of closely related literature compounds.[15] This represents, to our knowledge, the first isolation and characterization of such intermediates in BH or ABH reactions.

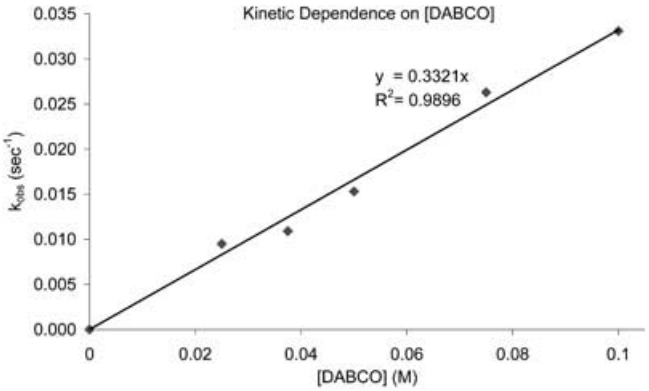


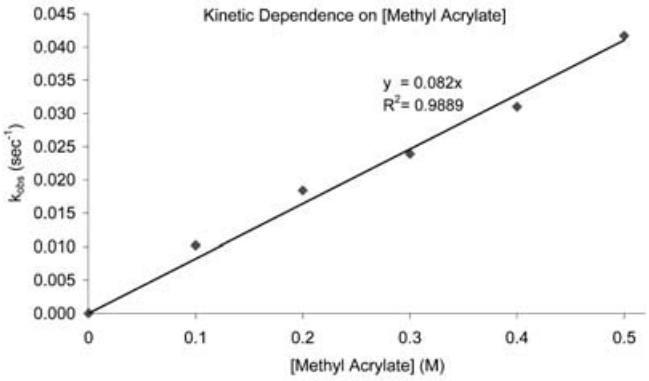
Scheme 3. Generally accepted mechanism of the Baylis–Hillman and aza-Baylis–Hillman reactions (Y = alkyl or alkoxy, X = O or NR′).

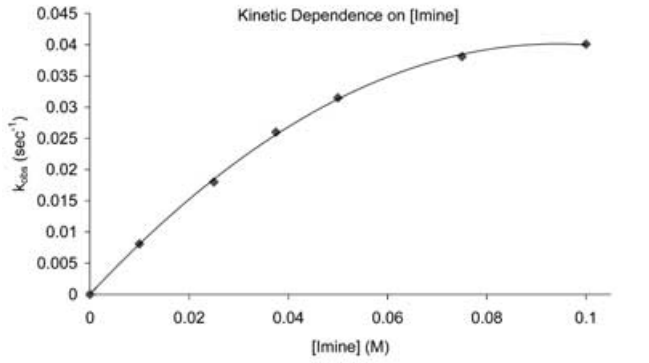
The dihydrochloride salt **10a** displayed a high level of stability, with no detectable decomposition after storage for over 5 months at room temperature. However, upon addition of two equivalents of DBU to a solution of **10a** in CD_3OD or DMSO-d_6, the resonance due to the sulfonamide N–H proton disappeared within 4 min and the benzylic C–H proton resonance α to the sulfonamide collapsed from a doublet of doublets to a simple doublet. Furthermore, the solution acquired the characteristic bright yellow color attributable to a sulfonamide anion. We therefore assign this species as the zwitterionic intermediate (**9a**). Spectra of **9a** generated in this manner were always accompanied by resonances due to methyl acrylate and imine in varying equilibrium concentra-



Scheme 4. Preparation of **10a**.







$$\text{rate} = \frac{a[\text{DABCO}][\text{Acrylate}][\text{Imine}]}{1 + b[\text{Imine}]}$$

Figure 2. Kinetic data and the derived rate law of the uncatalyzed ABH reaction obtained by measurement of initial rates.

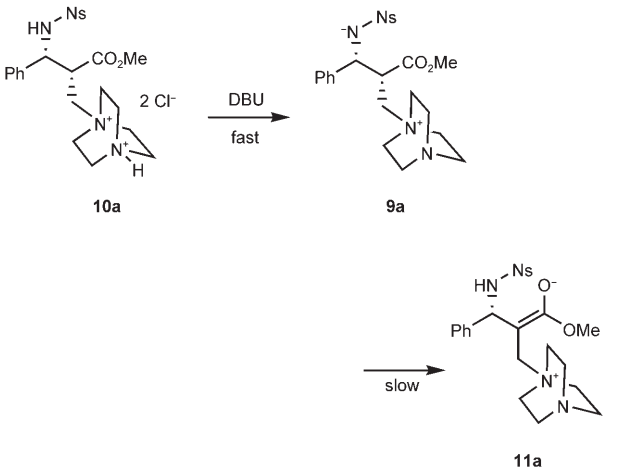
tions, indicating that **9a** undergoes reversion to its precursors. This constitutes a racemization pathway for **9a** in the absence of catalyst. This reversion pathway proved impossible to suppress despite extensive screens of solvent, base, and temperature in the elimination reaction. Compound **9a** generated in this manner underwent clean elimination to provide product **7a**, consistent with the notion that **9a** is indeed an intermediate in the catalytic cycle. However, **7a** obtained under these conditions was generated in lower ees than material produced *via* the direct ABH reaction.

The heterogeneous nature of the ABH reaction catalyzed by **1c** rendered kinetic studies difficult; however, the uncatalyzed reaction of methyl acrylate and **6a** promoted by DABCO proceeded homogeneously in $CHCl_3$ and proved amenable to kinetic analysis. The reaction was monitored by GC analysis, and was found to display a first-order kinetic dependence on both DABCO and methyl acrylate (Figure 2). In contrast to the BH reaction,[13a] rate saturation with respect to the imine electrophile was observed.

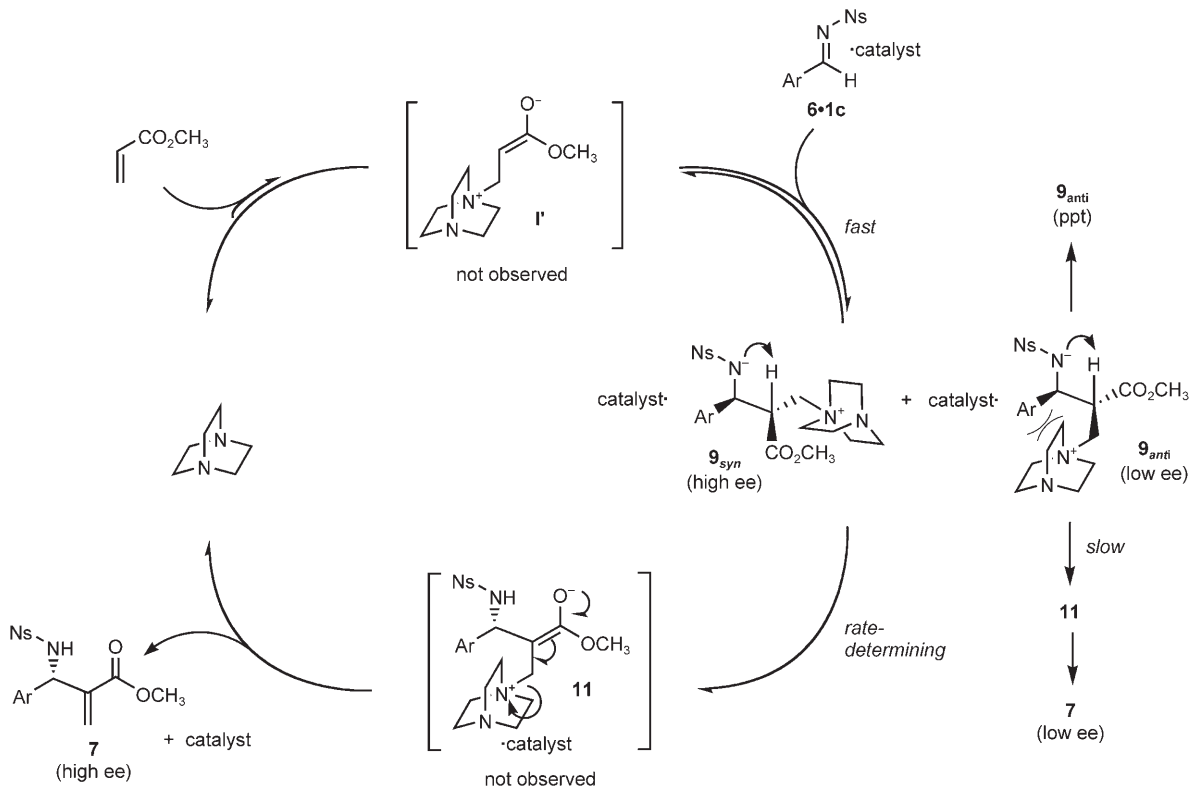
Kinetic isotope effect studies were also carried out based on initial rate measurements, by comparison of reactions of methyl acrylate with separate reactions of α-deuterio-methyl acrylate. A prominent primary kinetic isotope effect was observed ($k_H/k_D = 3.81$), strongly suggesting that deprotonation of the α-H(D) (**I**″ to **I**‴ in Scheme 2) is rate-limiting.

The DBU-mediated elimination of **10a** in MeOH was monitored by ReactIR® and was found to obey a first-order reaction rate profile over > 4 half lives. This is consistent with rapid and irreversible deprotonation of **10a** to **9a**, and intramolecular proton transfer of **9a** to the corresponding enolate **11a** (Scheme 5). Added imine had no effect on the rate of elimination, indicating that, in contrast to BH reactions,[13a] the electrophile does not play a role in mediating the deprotonation step.

The mechanism outlined in Scheme 6 is consistent with the experimental observations summarized above. Zwitterionic species **9** exists as both *syn* and *anti* diastereomers, but the *anti* diastereomer may undergo precipitation selectively. We propose that under the conditions of the ABH reaction both diastereomers of **9** are formed, but that $\mathbf{9}_{syn}$ is generated in high ee and decomposes relatively rapidly by intramolecular proton transfer/elimination to generate **7** in high ee. In contrast, $\mathbf{9}_{anti}$ may undergo relatively slow elimination to **7** due to less favorable steric interactions in the requisite eclipsed (or nearly eclipsed) conformation, and therefore its concentration builds up during the course of the reaction lead-



Scheme 5.



Scheme 6. Proposed pathway for the enantioselective aza-Baylis–Hillman reaction of nosylimines. The unfavorable steric interactions in $\mathbf{9}_{anti}$ presumably responsible for slow elimination of this intermediate to **7** are highlighted.

ing to precipitation. The fact that **7** is produced in low ee by base-induced elimination from **10a** suggests that $\mathbf{9}_{anti}$ may be generated in low ee. This would serve to explain why solvent systems that effectively solubilize both diastereomers of **9** lead to formation of **7** in depressed ee. Unfortunately, all efforts toward direct determination of the ee of **9a**, **10a** or any of their analogues were unsuccessful, so we have not secured definitive support for this hypothesis.

Conclusion

We have developed a highly enantioselective catalytic aza-Baylis–Hillman reaction of nosylimines with methyl acrylate. While product yields are very moderate ($<50\%$), the enantioselectivities for a variety of aromatic imines are high and unprecedented for ABH reactions with acrylate derivatives. Highest ees are obtained under conditions where a zwitterionic intermediate $\mathbf{9}_{anti}$ undergoes precipitation from the reaction mixture, presumably as a result of its slow rate of elimination to product. These studies suggest that both high enantio- and diastereoselectivity in the addition to the imine-catalyst complex may be crucial for obtaining high ees and yields in the overall reaction. Efforts directed toward this goal, and toward the further exploration of the utility of chiral thiourea derivatives in asymmetric catalysis are underway.

Experimental Section

General Procedure for Preparation of Nosylimines

N-*Benzylidene-4-nitro-benzenesulfonamide* (6a): To a flame-dried round-bottom flask containing activated 4 Å MS, Amberlyst 15 (cat.), and *p*-nitrobenzenesulfonamide (1 equiv.) were added freshly distilled toluene (0.25 M) and benzaldehyde (1.1 equivs.). A Dean–Stark trap equipped with reflux condenser was attached, all joints sealed with teflon tape, and the reaction mixture heated to a vigorous reflux for 20 h. The mixture was allowed to cool to room temperature, and was then filtered through a pad of Celite. The pad was washed with toluene, and the filtrate concentrated under vacuum to a solid. The solids were washed with $3\times$ hexanes, and the solid collected on a sintered glass funnel. This material was sufficiently pure to use in the ABH reactions, but could be further recrystallized in high yield from EtOAc/hexanes. The product was isolated as a light tan powder. FT-IR (CH_2Cl_2 thin film): $\nu = 1606$ (s), 1569 (s), 1528 (s), 1450 (w), 1350 (m), 1333 (w), 1310 (m), 1224 (w), 1161 (s), 1088 (m), 856 (m), 796 (s), 739 cm^{-1} (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.13$ (s, 1H), 8.39 (d, $J = 8.8$ Hz, 2H), 8.21 (d, $J = 8.8$ Hz, 2H), 7.96 (d, $J =$ 7.2 Hz, 2H), 7.67 (t, $J = 7.5$ Hz, 1H), 7.53 (t, $J = 7$ .6 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.62, 150.84, 144.43, 136.06, 131.96, 129.97, 129.62, 129.41, 124.59; LR-MS (ApCI): *m*/*z* = 291.0 (5%) $[M+H]^+$, 261.0 (100%) $[M-NO^+]^+$.

General Procedure for the Asymmetric Aza-Baylis–Hillman Reaction

***2-[(4-Nitrobenzenesulfonylamino)-(S)-phenylmethyl]-acrylic acid methyl ester* (7a):** An oven-dried vial was charged with *N*-benzylidene-4-nitro-benzenesulfonamide (**6a**, 1 equiv.), catalyst **1c** (10 mol %), DABCO (1 equiv.), and activated 3 Å MS. The vial was evacuated and purged with N_2. Pre-cooled, freshly distilled, anhydrous xylenes (0.15 M) and methyl acrylate (8 equivs.) were added via syringe at 4 °C, and the mixture stirred for 36 h. The mixture was diluted with anhydrous MeOH and then quenched *immediately* with 4 N HCl in dioxane. The crude adduct was purified by flash chromatography (100% CH_2Cl_2) to afford the pure aza-Baylis–Hillman adduct as a white solid. The ee of this material was determined to be 95% [ChiralPak AS, 1.0 mL/min, 280 nm, 40% IPA/hexanes, t_r(major) = 11.566 min, t_r(minor) = 17.618 min]; $[\alpha]_D^{23}$: +27.7° (*c* 2, EtOH); FT-IR (CH_2Cl_2 thin film): ν = 3293 (br), 3108 (w), 3068 (w), 1720 (s), 1632 (w), 1607 (w), 1531 (s), 1440 (m), 1350 (s), 1312 (m), 1166 (s), 1091 (m), 1062 (m), 855 (m), 738 cm^{-1} (s); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8, 3 Hz, 2H), 7.14–7.27 (m, 5H), 6.23 (s, 1H), 6.15 (d, *J* = 9.3 Hz, 1H), 5.82 (s, 1H), 5.40 (d, *J* = 9.3 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.96, 150.08, 146.74, 138.49, 138.01, 128.94, 128.50, 128.41, 128.32, 126.64, 124.30, 59.86, 52.50; LR-MS (ApCI): *m*/*z* = 377.0 (2%) $[M+H]^+$, 347.0 (30%) $[M-NO^+]^+$, 330.0 (32%) $[M-NO_2]^+$, 175.0 (100%) [M – sulfonamide]$^+$.

Isolation of Aza-Baylis–Hillman Intermediate as the Dihydrochloride Salt (10a)

A flame-dried, 10-mL round-bottom flask was charged with a stir bar, imine **6a** (75 mg, 0.259 mmol), thiourea catalyst **1c** (15.6 mg, 0.026 mmol), and DABCO (29 mg, 0.259 mmol). The flask was cooled to 4 °C, and charged with pre-cooled, freshly distilled xylenes (1.75 mL) and methyl acrylate (187 μL, 2.07 mmol). The mixture was allowed to stir for 12 h at 4 °C, over which time a bright yellow precipitate formed. Distilled H_2O (1.75 mL) was added, and the biphasic mixture was stirred vigorously for an additional 3–6 h at 4 °C. HCl (200 μL, 4 N in dioxane) was added. Additional 5 mL H_2O were added, and the reaction mixture was stirred vigorously for 5 min. The layers were allowed to separate, and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were back-extracted with 3 × 5 mL H_2O. The combined *aqueous* layers were concentrated directly under vacuum at 60 °C. The resulting clear oil was further subjected to high vacuum for 24 h to remove residual H_2O, affording the dihydrochloride salt of the aza-Baylis–Hillman intermediate (**10a**) as a glassy solid; yield: 61.2 mg (42%); FTIR (CH_2Cl_2 thin film): ν = 1734 (s), 1630 (w), 1530 (s), 1459 (w), 1438 (w), 1351 (s), 1313 (w), 1166 (s), 1089 (w), 853 (w), 739 cm^{-1} (m); ^{1}H NMR (500 MHz, DMSO-d_6, 10–16:1 mixture of diastereomers, with signals corresponding to major form indicated): δ = 9.72 (d, *J* = 10.3 Hz 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 4.9 Hz, 2H), 6.95–7.10 (m, 3H), 4.93 (dd, *J* = 6.0, 10.5 Hz, 1H), 4.16 (d, *J* = 13.2 Hz, 1H), 3.72–3.91 (m, 7H), 3.70 (s, 3H), 3.42–3.63 (m, 6H), 2.90 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.97, 149.69, 146.80, 136.04, 128.93, 128.80, 128.62, 127.95, 124.56, 61.69, 59.24, 53.62, 51.10, 46.24, 43.45; LR-MS (ESI): *m*/*z* = 489.2 (100%) [M – 2 HCl]$^+$.

Base-Mediated Elimination of 10a

***2-[(4-Nitrobenzenesulfonylamino)-(S)-phenylmethyl]-acrylic acid methyl ester* (7a, from 10a):** A flame-dried, 5-mL round-bottom flask was charged with dihydrochloride salt (**10a** from above, 150 mg, 0.267 mmol) which was dissolved in anhydrous DMSO (2 mL) or MeOH (2 mL) at room temperature. Freshly distilled DBU (84 μL, 0.560 mmol) was added *via* syringe, and the reaction mixture stirred for 16 h. The mixture was then diluted with 5 mL CH_2Cl_2, 1 N HCl (5 mL) was added with vigorous stirring, the layers were allowed to separate, and the organic layer removed. The aqueous layer was extracted with 3 × 10 mL CH_2Cl_2, dried over Na_2SO_4, and concentrated under vacuum to afford the crude aza-Baylis–Hillman adduct (**7a**), which matched the ^{1}H NMR and ^{13}C NMR spectra as previously reported (*vide supra*). As discussed, ees of this product were substantially depressed, and generally obtained in a range of 30–40%.

Acknowledgements

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References and Notes

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