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Nonenzymatic Acylative Kinetic Resolution of Baylis−Hillman Adducts

Ciarán Ó Dálaigh and Stephen J. Connon*

Centre for Synthesis and Chemical Biology, School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland

connons@tcd.ie

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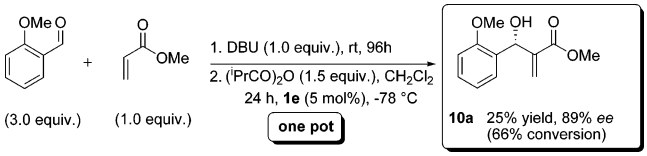

The first efficient nonenzymatic acylative kinetic resolution of Baylis−Hillman adducts is reported. Chiral pyridine catalyst **1a** and an optimized analogue **1e** are capable of promoting the synthetically useful enantioselective acylation (the efficiency of which is outstanding for sp^2-sp^2 carbinol substrates, $s = 3.5-13.1$, ee up to 97%) of Baylis−Hillman adducts derived from recalcitrant precursors which are currently difficult to synthesize utilizing benchmark asymmetric Baylis−Hillman reaction catalyst technology. A novel one-pot synthesis−kinetic resolution process involving a DBU-catalyzed Baylis−Hillman reaction and subsequent **1e**/DBU-mediated enantioselective acylation has also been developed.

The three-component nucleophile-catalyzed Baylis−Hillman reaction (BHR)[1] is a synthetically important carbon−carbon bond-forming process which can furnish chiral products of high utility from relatively simple achiral starting materials.[2] Two significant limitations associated with these transformations are slow reaction rates[3,4] and a general dearth of catalyst systems (relative to that of other Michael/aldol type processes) capable of promoting asymmetric BHRs *of wide substrate scope*. While a number of solutions have been found for the reactivity issues which have resulted in a significant expansion of reaction scope, the pace of progress toward the development of the corresponding catalytic asymmetric methodologies has been relatively slow. The magnitude of this catalyst design challenge is amplified by a complex mechanistic picture in which the identity of the rate-limiting step has only been clarified in the last 2 years.[5] A number of chiral catalyst systems have been developed which can efficiently promote BHRs in which at least one reaction component (either aldehyde or Michael acceptor) is highly electrophilic with good enantioselectivity (>70% ee);[2,6] however, less activated aldehydes (e.g., anisaldehydes) and deactivated Michael acceptors (simple acrylates, acrylamides, etc.) are generally extremely poor partners from both efficiency and enantioselectivity standpoints.

For the synthesis of enantiopure/enantioenriched BH adducts not currently compatible with benchmark catalyst technology, kinetic resolution (KR) is a viable alternative. Several KR approaches have been reported including enantioselective hydrogenation,[7a−c] epoxidation,[7d,e] peroxidation,[7f] enzymatic acylation/hydrolysis of acylated BH adducts,[7g−i] and nucleophilic dynamic kinetic resolution of O-acylated BH adducts.[7j−l] In the past decade, several highly active nonenzymatic small molecule nucleophilic organocatalysts capable of the acylative KR of *sec*-alcohols with excellent selectivity have been developed;[8,9] however, their application in the resolution of BH adducts has not yet been reported. This is due (at least in part) to the fact that the stereogenic center of an aldehyde-derived BH adduct is flanked by two planar sp^2-hybridized substituents

(1) Baylis, A. B.; Hillman, M. E. D. *Offenlegungsschrift* 2155113, **1972**; U.S. Patent 3,743,669; *Chem. Abstr.* **1972**, *77*, 34174q.

(2) Reviews: (a) Masson, G.; Housseman, C.; Zhu, J.; *Angew. Chem., Int. Ed*. **2007**, *46*, early view article. (b) Methot, J. L.; Roush, J. R. *Adv. Synth. Catal*. **2004**, *346*, 1035. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.

(3) (a) Hill, J. S.; Isaacs, N. S. *Tetrahedron Lett.* **1986**, *27*, 5007. (b) Isaacs, N. S. *Tetrahedron* **1991**, *47*, 8463. (c) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun.* **1988**, *18*, 1565. (d) Markó, I. E.; Ollis, W. D.; Rasmussen, P. R. *Tetrahedron Lett.* **1990**, *31*, 4509. (e) Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965. (f) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311. (g) Leadbeater, N. E.; van der Pol, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2831. (h) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692. (i) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem*. **2000**, *65*, 3489. (j) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem*. **2001**, *66*, 5413. (k) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett*. **2002**, *4*, 4723. (l) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, A. *J. Org. Chem*. **2002**, *67*, 510. (m) Li, G.; Wei, H. X.; Gao, J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1. (n) Basavaiah, D.; Sreenivasulu, B.; Rao, A. J. *J. Org. Chem*. **2003**, *68*, 5983. (o) Aggarwal, V. K.; Tarver, G. J.; McCague, R. *Chem. Commun*. **1996**, 2713. (p) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem*. **1998**, *63*, 7183.

(4) (a) Pereira, S. I.; Adrio, J.; Silva, A. M. S.; Carretero, J. C. *J. Org. Chem*. **2005**, *70*, 10175. (b) Faltin, C.; Fleming, E. M.; Connon, S. J. *J. Org. Chem*. **2004**, *69*, 6496. (c) Maher, D. J.; Connon, S. J. *Tetrahedron Lett*. **2004**, *45*, 1301. (d) Luo, S.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem*. **2003**, *68*, 555. (e) Teng, W.-D.; Huang, R.; Kwong, C. K.-W.; Shi, M.; Toy, P. H. *J. Org. Chem*. **2006**, *71*, 368. (f) Mi, X.; Luo, S.; Xu, H.; Zhang, L.; Cheng, J.-P. *Tetrahedron* **2006**, *62*, 2537. (g) Lin, Y. S.; Lin, C. Y.; Liu, C.-W.; Tsai, T. Y. R. *Tetrahedron* **2006**, *62*, 872. (h) Shi, M.; Liu, Y.-H. *Org. Biomol. Chem.* **2006**, *4*, 1468. (i) He, Z.; Tang, X.; Chen, Y.; He, Z. *Adv. Synth. Catal*. **2006**, *348*, 413. (j) Kraft, M. E.; Seibert, K. A.; Haxell, T. F. N.; Hirosawa, C. *Chem. Commun*. **2005**, 5772. (k) Dadwal, M.; Mohan, R.; Panda, D.; Mobin, S. M.; Namboothiri, I. N. N. *Chem. Commun*. **2006**, 338. (l) You, J.; Xu, J.; Verkade, J. G. *Angew. Chem., Int. Ed*. **2003**, *42*, 5054.

(5) (a) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147. (b) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980. (c) Aggarwal, V. K.; Fulford, S. Y.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706. (d) For a related study on the aza-BHR, see: Buskens, P.; Klankermeyer, J.; Leitner, W. *J. Am. Chem. Soc*. **2005**, *127*, 16762.

(6) (a) Iwabuchi, Y.; Nakatami, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc*. **1999**, *121*, 10219. (b) Nakano, A.; Kawahara, S.; Akamatsu, S.; Morokuma, K.; Nakatani, M.; Iwabuchi, Y.; Yoshiharu, T.; Keisuke, I.; Ishihara, J.; Hatakeyama, S. *Tetrahedron* **2006**, *62*, 381. (c) McDougal, N. T.; Shaus, S. E. *J. Am. Chem. Soc*. **2003**, *125*, 12094. (d) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Shaus, S. E. *Adv. Synth. Catal*. **2004**, *346*, 1231. (e) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (f) Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett*. **2005**, *7*, 4293. (g) Berkessel, A.; Roland, K.; Neudörf, J. M. *Org. Lett.* **2006**, *8*, 4195. (h) Myers, E. L.; de Vries, J. G.; Aggarwal, V. K. *Angew. Chem., Int. Ed*. **2007**, *46*, 1893. (i) Hayashi, Y.; Tamura, T.; Shoji, M. *Adv. Synth. Catal*. **2004**, *346*, 1106. (j) Mocquet, C. M.; Warriner, S. L. *Synlett* **2004**, 356. (k) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741. (l) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem*. **2003**, *68*, 915. (m) Barrett, A. G. M.; Cook, A. S.; Kaminura, A. *Chem. Commun*. **1998**, 2533.

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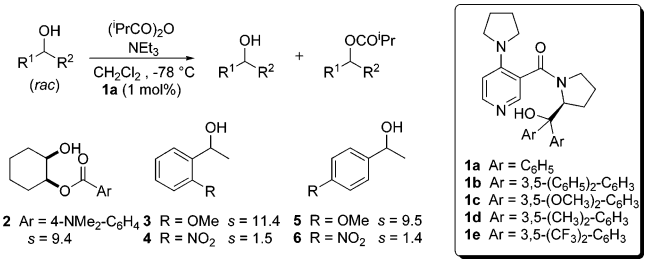
which are very difficult for the acylated catalyst to distinguish in the enantiodiscriminating acylation event; to the best of our knowledge, no examples of the effective enantioselective acylation of any such substrate promoted by a small molecule nucleophilic catalyst is known.[10] We have recently developed a highly active, chiral 4-*N*,*N*-dialkylaminopyridine catalyst **1a** for the acylative kinetic resolution (KR)[11] of *sec*-alcohols with moderate to excellent enantioselectivity (up to $s = 30$)[12] *which exhibited an unusually strong preference for substrates containing either electron-rich carbonyl or aromatic moieties* (Scheme 1).[12] Attracted to the twin catalytic challenges of asymmetric catalysis of BHRs involving electron-rich substrates (either Michael acceptor or aldehyde) and the nonenzymatic KR of sp^2-sp^2 *sec*-carbinols outlined above, we therefore decided to evaluate **1a** (and analogues) as a promoter of the KR of BH adducts difficult to synthesize in high enantiopurity using current benchmark catalytic methods.

SCHEME 1. Substrate Steric and Electronic Preferences of Previously Reported Catalyst 1a



In previous studies[12] investigating the mode of action of **1a**, we demonstrated that both the catalyst hydroxyl group and pendant aromatic moieties were required for high catalyst selectivity. A $\pi-\pi$ interaction between the phenyl and pyridine rings (which strengthens considerably on either N-alkylation or N-acylation of **1a**) was also detected;[12] however, its bearing on the stereochemical outcome of the acylation event was not fully explored. Given the inherent unsuitability of BHR adducts as substrates in acylative KR processes (vide supra), we decided to first investigate the influence of the steric/electronic properties of the aromatic substituents on catalyst performance so that an optimal catalyst structure could be identified for application in the KR of BHR adducts.

Catalysts **1b**−**e** were prepared[13] and evaluated as promoters of the KR of *sec*-alcohols **2**, **7**, and **8** (Table 1). It was expected that significant augmentation of the steric bulk of the aromatic substituents (i.e., catalyst **1b**) would lead to more enantioselective acylation (entries 1, 2, 6, and 7). However, in view of the proposed contribution of a π-pyridinium cation interaction to selectivity in reactions catalyzed by **1a**,[12] the clear, (reproducible) superiority of the catalyst equipped with electron-withdrawing trifluoromethyl substituents (**1e**, entries 5 and 10) over more electron-rich analogues (**1c** and **1d**, entries 3, 4, 8, and 9) was somewhat surprising.[14] Gratifyingly, the readily prepared catalyst **1e** proved capable of resolving substrates incorporating Lewis basic carbonyl moieties with synthetically useful selectivity ($s > 10$, entries 10−12) at either 0 or −78 °C, which allowed the recovery of either enantioenriched or enantiopure (87−99.9% ee) alcohols with reasonable efficiency (23−40%).

With a superior catalyst (to **1a**) in hand, attention now turned to the question of the KR of BHR adducts. To examine the potential utility of the proposed KR strategy, we decided to focus on the resolution of adducts currently difficult to synthesize in high enantiopurity using direct catalytic asymmetric BHRs. Bearing this in mind, we selected BH adducts **9**−**12** (Table 2) as candidates; these are derived from the coupling of Michael acceptor substrates which (to the best of our knowledge) do not readily participate in highly enantioselective organocatalytic asymmetric BHRs, such as methyl acrylate and acrylonitrile, with challenging, deactivated aromatic aldehydes (benzaldehyde and *o*-anisaldehyde). We were pleased to find that both **1a** and **1e** were compatible with these aryl vinyl carbinol substrates; treatment of acrylate **9** with substoichiometric loadings of isobutyric anhydride and amine base in the presence of **1a** or

(7) (a) Brown, J. M.; Cutting, I. *J. Chem. Soc., Chem. Commun*. **1985**, 578. (b) Yamamoto, K.; Takagi, M.; Tsuji, J. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 319. (c) Takaya, H.; Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R. *J. Org. Chem*. **1988**, *53*, 710. (d) Bailey, M.; Staton, I.; Ashton, P. R.; Markó, I. E.; Ollis, W. D. *Tetrahedron: Asymmetry* **1991**, *2*, 495. (e) Oishi, T.; Oguri, H.; Hirama, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1241. (f) Adam, W.; Hoch, U.; Saha-Möller, C. R.; Schreier, P. *Angew. Chem., Int. Ed.* **1993**, *32*, 1737. (g) Burgess, K.; Jennings, L. D. *J. Org. Chem*. **1990**, *55*, 1138. (h) Basavaiah, D.; Dharma Rao, P. *Synth. Commun.* **1994**, *24*, 917. (i) Hayashi, H.; Yanagihara, K.; Tsuboi, S. *Tetrahedron: Asymmetry* **1998**, *9*, 3825. (j) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc*. **2000**, *122*, 3534. (k) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett*. **2004**, *6*, 1337. (l) Du, Y.; Han, X.; Lu, X. *Tetrahedron Lett.* **2004**, *45*, 4967.

(8) Recent reviews: (a) Connon, S. J. *Lett. Org. Chem*. **2006**, *3*, 333. (b) Jarvo, E. R.; Miller, S. J. In *Comprehensive Asymmetric Catalysis*, Supplement 1; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2004; Chapter 43. (c) Miller, S. J. *Acc. Chem. Res*. **2004**, *37*, 601. (d) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.

(9) Selected leading references: (a) Vedejs, E.; Chen, X. *J. Am. Chem. Soc*. **1996**, *118*, 1809. (b) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem*. **1996**, *61*, 430. (c) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166. (d) Ruble, J. C.; Fu, G. C. *J. Org. Chem*. **1996**, *61*, 7230. (e) Garrett, C. E.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc*. **1998**, *120*, 7479. (f) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc*. **1999**, *121*, 5091. (g) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc*. **1997**, *119*, 3169. (h) Kawabata, T.; Yamamoto, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Commun*. **2001**, 2700. (i) Spivey, A. C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, *39*, 8919. (j) Spivey, A. C.; Leese, D. P.; Zhu, F.; Davey, S. G.; Jarvest, R. L. *Tetrahedron* **2004**, *60*, 4513. (k) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529. (l) Terakado, D.; Koutaka, H.; Oriyama, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1157. (m) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Horstmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc*. **1998**, *120*, 1629. (n) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc*. **2001**, *123*, 6496. (o) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem*. **2003**, *68*, 3844. (p) Ishihara, K.; Kosugi, Y.; Akahura, M. *J. Am. Chem. Soc*. **2004**, *126*, 12212. (q) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun*. **2004**, 2770. (r) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett*. **2005**, *7*, 1347. (s) Notte, G. T.; Sammakia, T.; Steel, P. J. *J. Am. Chem. Soc*. **2005**, *127*, 13502. (t) Setizberg, J. G.; Dissing, C.; Søtofte, I.; Norrby, P.-A.; Johannsen, M. *J. Org. Chem*. **2005**, *70*, 8332. (u) Díez, D.; Gil, M. J.; Moro, R. F.; Garrido, N. M.; Marcos, I. S.; Basabe, P.; Sanz, S.; Broughton, H. B.; Urones, J. G. *Tetrahedron: Asymmetry* **2005**, *16*, 2980. (v) Yamada, S.; Misono, T.; Iwai, Y. *Tetrahedron Lett.* **2005**, *46*, 2239. (w) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc*. **2004**, *126*, 12227. (x) Birman, V. B.; Jiang, H. *Org. Lett*. **2005**, *7*, 2445. (y) Poisson, T.; Penhoat, M.; Papamicaël, D. G.; Dalla, V.; Marsais, F. *Synlett* **2005**, 2285.

(10) For (a lone) example, Vedejs et al. (ref 9c) have reported a phosphine catalyst capable of promoting the enantioselective acylation of alkyl aryl carbinols with outstanding selectivity ($s = 15-390$). This catalyst promotes the acylation of methyl mandelate with $s = 3.0$ at rt.

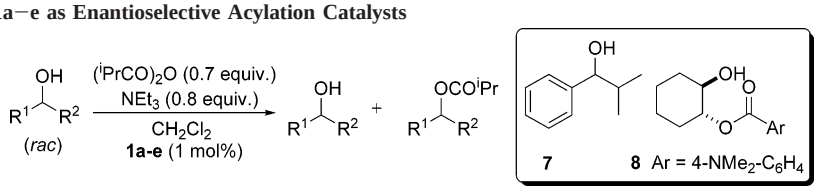
(11) Kagan H. B.; Fiaud, J. C. *Top. Stereochem*. **1988**, *18*, 249.

(12) (a) Ó Dálaigh, C.; Hynes, S. J.; Maher, D. J.; Connon, S. J. *Org. Biomol. Chem*. **2005**, *3*, 981. (b) (a) Ó Dálaigh, C.; Hynes, S. J.; O'Brien, J. E.; McCabe, T.; Maher, D. J.; Watson, G. W.; Connon, S. J. *Org. Biomol. Chem*. **2006**, *4*, 2785.

(13) See Supporting Information for details.

(14) The reasons for this are unclear at present; however, it should be noted that the electronic character of the aromatic substituents would also influence the hydrogen bond donating/accepting characteristics of the influential hydroxyl group.

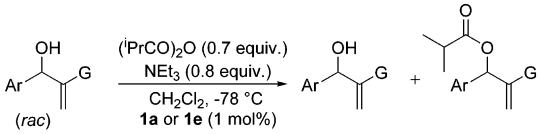
TABLE 1. Evaluation of 1a−e as Enantioselective Acylation Catalysts



entry	cat	substrate	T (°C)	C (%)[a]	ee_E (%)[b]	ee_A (%)[b]	s[c]	abs. config.[d]
1[e]	**1a**	7	0	35	50	27	3.9	(*R*)
2[e]	**1b**	7	0	63	43.5	74	5.3	(*R*)
3[e]	**1c**	7	0	62	40	65	4.4	(*R*)
4[e]	**1d**	7	0	56	31	40	2.7	(*R*)
5[e]	**1e**	7	0	61	44	69	5.1	(*R*)
6[e]	**1a**	2	0	57	54	71	6.9	(1*S*, 2*R*)
7[e]	**1b**	2	0	59	57	82	9.0	(1*S*, 2*R*)
8[e]	**1c**	2	0	60.5	50	76.5	6.6	(1*S*, 2*R*)
9[e]	**1d**	2	0	58	40	55	3.9	(1*S*, 2*R*)
10[e]	**1e**	2	0	60	58	87	10.1	(1*S*, 2*R*)
11[f]	**1e**	2	−78	66	50	96	10.8	(1*S*, 2*R*)
12[f]	**1e**	8	−78	77	30	>99	20.0	nd

[a] Conversion, which could be determined (with excellent agreement) either by ^{1}H NMR spectroscopy or chiral HPLC, where $C = 100 \times ee_{alcohol}/(ee_{alcohol} + ee_{ester})$. [b] Enantiomeric excess determined by chiral HPLC using a Chiralcel OD-H column (4.6 × 250 mm); ee_E = ee of the ester product, ee_A = ee of the recovered alcohol. [c] Enantioselectivity (k_{fast}/k_{slow}; see ref 11). [d] Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data (see Supporting Information). [e] 6 h reaction time. [f] 24 h reaction time.

TABLE 2. KR of Baylis−Hillman Adducts Catalyzed by 1a and 1e



9 Ar = C_6H_5, G = CO_2Me — **9a** — **9b** Ar = C_6H_5, G = CO_2Me
10 Ar = 2-OCH_3-C_6H_4, G = CO_2Me — **10a** — **10b** Ar = 2-OCH_3-C_6H_4, G = CO_2Me
11 Ar = C_6H_5, G = CN — **11a** — **11b** Ar = C_6H_5, G = CN
12 Ar = 2-OCH_3-C_6H_4, G = CN — **12a** — **12b** Ar = 2-OCH_3-C_6H_4, G = CN

entry	cat	substrate	C (%)[a]	s[b]	ee (%)[c]	yield (%)[d]	abs. config.[e]
1[f]	**1a**	**9**	70	3.1	62	29	(+)-(*S*)
2[g]	**1e**	**9**	72	3.7	74	27	(+)-(*S*)
3[h]	**1e**	**9**	83	3.8	95	16	(+)-(*S*)
4[f]	**1a**	**10**	61	10.9	90	36	(+)-(*S*)
5[f]	**1e**	**10**	56	11.0	82	40	(+)-(*S*)
6[h]	**1e**	**10**	64	13.1	97	35	(+)-(*S*)
7[g]	**1e**	**11**	51	3.5	41	45	nd
8[h]	**1e**	**11**	85	3.6	93	13	nd
9[g]	**1e**	**12**	32	4.0	25	64	(+)-(*R*)[i]
10[h]	**1e**	**12**	78	3.5	82	19	(+)-(*R*)[i]

[a] Conversion, determined by CSP-HPLC, where $C = 100 \times ee_{alcohol}/(ee_{alcohol} + ee_{ester})$. [b] Enantioselectivity (k_{fast}/k_{slow}; see ref 11). [c] Enantiomeric excess of the recovered alcohol determined by CSP-HPLC using either a Chiralcel OD-H or AS-H column (4.6 × 250 mm). [d] Refers to isolated yield of the recovered alcohol after chromatography. [e] Absolute configuration of the alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data (see Supporting Information). [f] 0.85 equiv of isobutyric anhydride, 0.95 equiv of NEt_3, 24 h. [g] 0.70 equiv of $(^iPrCO)_2O$, 0.80 equiv of NEt_3, 24 h. [h] 1.50 equiv of $(^iPrCO)_2O$, 0.80 equiv of NEt_3, 8 h. [i] Note that, due to a priority change, the label of the stereogenic center changes in (+)-**12a** from (*S*) to (*R*).

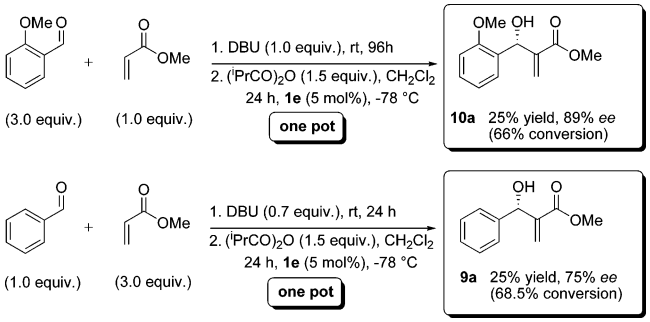
1e (1 mol %) at low temperature followed by column chromatography furnished resolved **9a** in moderate to good levels of enantioselectivity (entries 1 and 2, Table 2) and isolated yield (ca. 30%, max = 50%). While the selectivity of these acylation processes was unsurprisingly (given the planar nature of the substituents at the substrate's stereogenic center) moderate (s[11] = k_{fast}/k_{slow} = 3.7 using catalyst **1e**), it was of sufficient magnitude to allow **9a** to be isolated with excellent enantiomeric purity (95% ee) if the reaction was allowed to proceed to higher conversion (entry 3).[15]

In line with our earlier findings regarding the particular aptitude of **1a** for the resolution of *sec*-alcohols bearing electron-rich aromatic moieties,[12] the methoxy-substituted adduct **10**—*which is outside the scope of current asymmetric BHR nucleophilic catalyst technology*—proved an outstanding substrate which could be resolved with excellent selectivity (s >10) using either **1a** or **1e**. Thus **10a** could be isolated in respectable yields (for a KR process, 35−40%) and excellent enantioselectivity (up to 97% ee). It is noteworthy that the highly selective acylation observed in these reactions (entries 4−6) also allows the isolation of the acylated ester product **10b** in >50% ee.[13] While it was expected that the relatively unhindered acrylonitrile-derived adducts **11** and **12** would prove more difficult to resolve, their acylation catalyzed by **1e** was sufficiently selective to allow **11a** and **12a** to be prepared in high enantiopurity at high reaction conversion (entries 7−10).

Given the key roles that tertiary amines often play in both BHRs (as nucleophilic catalysts) and acylation reactions (as bases), we were intrigued by the possibility that a dual catalyst system could be developed whereby a single nucleophilic amine could first serve as a catalyst for a challenging BHR process and then as a base in a subsequent acylative resolution reaction, thereby providing a potentially useful, *one-pot* route to enantioenriched Baylis−Hillman products difficult to prepare using direct asymmetric catalysis. In 1999, Aggarwal et al. reported that DBU (somewhat unexpectedly) served as a highly active BHR catalyst compatible with a wide range of substrates including deactivated aldehydes and Michael acceptors.[3i] Interestingly (given its high nucleophilicity in the BHR), we recently reported that DBU does not compete to any great extent

(15) The Baylis−Hillman adduct derived from acrylamide and benzaldehyde proved an exceptionally difficult substrate which was insoluble under our optimal resolution conditions. At 0 °C, this substrate could be resolved (using **1e** as the catalyst) with poorer selectivity than that associated with **9**−**12** (90% conversion, recovered alcohol; 78% ee, ester product; 8% ee, s = 2.2).

SCHEME 2. One-Pot Synthesis and Acylative Resolution of BH Adducts



with **1a** as a catalyst in the acylation of alcohols by anhydrides,[12] and as such, it seemed possible that DBU and **1e** could act as orthogonal nucleophilic catalysts in a one-pot BHR−acylative KR operation. To test this hypothesis, *o*-anisaldehyde was reacted with methyl acrylate in the presence of DBU followed by cooling to −78 °C, addition of isobutyric anhydride, and finally catalyst **1e**. Using this novel tandem synthesis−kinetic resolution methodology, **10a** could be isolated in high enantioselectivity (89% ee) and 25% yield (Scheme 2). A similar one-pot process furnished enantioenriched **9a** from benzaldehyde and methyl acrylate.

In summary, catalyst **1a** and its optimized analogue **1e** promote the synthetically useful KR of Baylis−Hillman adducts **9**−**12** derived from deactivated precursors (difficult to synthesize using catalytic asymmetric BHRs)—allowing the convenient preparation of **9a**−**12a** in 82−97% ee. To the best of our knowledge, this study also represents the first examples of effective nonenzymatic acylative KR of *sec*-sp^2−sp^2 carbinols. A novel BHR−KR process which complements contemporary asymmetric BHR catalyst technology has also been developed in which DBU serves both as a nucleophilic promoter of the BHR and a base in the KR reaction without competing effectively with **1e** as an acylation catalyst. Using this strategy, **9a** and **10a** can be readily prepared in appreciable yield from their aldehyde and methyl acrylate precursors with high levels of enantiomeric excess in a convenient one-pot process.

Experimental Section

One-Pot Synthesis and Resolution of 10. A 1 mL reaction vessel charged with **1e** (4.3 mg, 6.14 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this were added *o*-anisaldehyde (50 mg, 0.368 mmol), DBU (18 μL, 0.123 mmol), and methyl acrylate (11 μL, 0.123 mmol) via syringe, and the resulting homogeneous solution was stirred at rt for 96 h. CH_2Cl_2 (500 μL) was then added via syringe, and the solution was cooled to −78 °C and left to stir for 30 min. Isobutyric anhydride (16 μL, 0.98 mmol) was subsequently added via syringe. After 24 h at −78 °C, the reaction was quenched by the addition of MeOH (200 μL) and allowed to warm to ambient temperature. Solvents were removed in vacuo. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude mixture (CH_2Cl_2) through a pad of silica gel. The selectivity of the kinetic resolution ($s = 7.6$) was then established by CSP-HPLC on a Chiralcel OD-H column (4.6 × 250 mm), hexanes/*i*-PrOH, 98/2, 1 mL min^{-1}, rt, UV detection at 220 nm. Retention times: **10a** (89% ee): 34.8 min, (*S*)-isomer (major) and 45.0 min, (*R*)-isomer (minor), **10b** (47% ee): 8.5 min, (*S*)-isomer (minor) and 22.3 min (*R*)-isomer (major). The alcohol was then isolated by column chromatography (CH_2Cl_2) to give (*S*)-**10a** (6.9 mg, 25%, 89% ee) as a colorless oil: $[\alpha]^{20}_D = +83$ (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 1H, $J = 7.5$ Hz), 7.28 (t, 1H, $J = 8.0$ Hz), 6.97 (app t, 1H, $J = 7.5$ Hz), 6.89 (d, 1H, $J = 8.0$ Hz), 6.31 (s, 1H), 5.88 (s, 1H), 5.73 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H). Absolute configuration is tentatively assigned based on a comparison of CSP-HPLC retention times and optical rotation data with that of (*S*)-**9a**.

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Supporting Information Available: General experimental procedures and details, characterization data for the synthesis of catalysts **1b**−**e** and adducts **9a**−**12a**, ^{1}H, ^{13}C NMR spectra, and CSP-HPLC data for **1b**−**e** and **9a**−**12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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