COMMUNICATION

ChemComm
www.rsc.org/chemcomm

'Double asymmetric induction' as a novel tool for high stereocontrol in Baylis–Hillman reaction†‡

Palakodety Radha Krishna,* Rachna Sachwani and V. Kannan

D-206/B, Discovery Laboratory, Organic Chemistry Division-III Indian Institute of Chemical Technology, Hyderabad 500 007, India. E-mail: prkgenius@iict.res.in; Fax: +91-040-27160387; Tel: +91-040-27160123

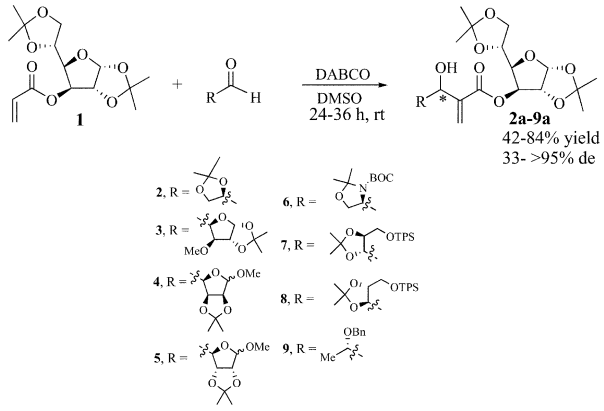
Received (in Cambridge, UK) 28th July 2004, Accepted 27th August 2004
First published as an Advance Article on the web 30th September 2004

The strategy of double asymmetric induction was utilized in Baylis–Hillman reaction for the first time by the coupling of chiral aldehydes with chiral acrylate (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-3-acrylate) to obtain corresponding adducts with high *syn* diastereoselectivities (de >90%) in moderate to good yields.

Baylis–Hillman reaction[1] is a widely recognized protocol for the preparation of multifunctional products with a newly created center and these adducts constitute versatile synthetic intermediates in organic synthesis.[2] Recently, we have demonstrated the single asymmetric induction in Baylis–Hillman reaction using either monosaccharide derived acrylate as chiral auxiliary[3] or sugar derived aldehydes as chiral electrophiles[4] to obtain moderate to good diastereoselectivities. However, the concept of 'double asymmetric induction', which plays a decisive role in the stereochemical control for an asymmetric aldol,[5] epoxidation,[6] hydrogenation[7]and Diels–Alder reactions,[8] remains unexplored in the asymmetric Baylis–Hillman reaction. In continuation of our recent interest in asymmetric Baylis–Hillman reactions,[3,4,9] herein a conceptually related stratagem *viz.* 'double asymmetric induction' is conceived as a mechanistic probe for the first time to achieve higher diastereoselectivity by coupling a chiral aldehyde with chiral acrylate (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-3-acrylate, **1**) under the standard (DABCO–DMSO, rt) reaction conditions, and the results are reported.

Initially, the double asymmetric induction was examined by coupling (*R*)-glyceraldehyde (**2**) as the chiral aldehyde with chiral acrylate (**1**) in THF, dichloromethane and dioxane–water[10] under the standard base (DABCO) catalyzed reaction conditions at ambient temperature. However, hydrolysis of acrylate was observed in THF and dioxane–water. Indeed, the desired adduct **2a** was formed when the same reaction was conducted in sulfolane[11] (yield 65%, de 66%) or DMSO (yield 71%, de 90%). DMSO was elected as the solvent for all further reactions (Table 1) since a higher yield and better diastereoselectivity was obtained for adduct **2a** (Scheme 1). Subsequently, aldehydes **3**–**9** on Baylis–Hillman reaction with **1** under the standardized conditions resulted in adducts **3a**–**9a** (Table 2).

Inspection of the data revealed that sterically more demanding aldehydes **2**–**7** exhibited high diastereoselectivity (>90% de). The de of the adducts was determined by ^{1}H NMR spectra, wherein the relative integrations of separable protons were compared. For instance, the ^{1}H NMR spectrum of the adduct **2a** revealed H-1 at δ 5.83 as a doublet (J = 3.8 Hz) for the major isomer, while the same proton resonated at δ 5.78 as a doublet (J = 3.8 Hz) for the minor isomer with a relative integration of 9.5:0.5 (de 90%). Similarly H-3 was observed at δ 5.26 as a doublet (J = 2.3 Hz) for the major isomer while for the minor isomer it resonated at δ 5.18 as a doublet (J = 2.3 Hz), with an integral ratio of 9.5:0.5. The allylic proton resonated at δ 4.54 as an unresolved doublet (J = 4.5 Hz) however comparison of J values with the earlier compound[9b] *prima facia* indicated *syn* diastereoselectivity in the present case, in contrast to the previous study.



Scheme 1

The next task was to conclusively prove that uniformly *syn* selectivity was the major stereochemical outcome for all adducts. Accordingly, an alternative strategy was undertaken to determine the absolute stereochemistry at the newly created center of the adduct **7a**. Aldehyde **7** was treated with ethyl acrylate (Scheme 2) under the same set of reaction conditions to obtain adduct **10** (58%, de 30%) with the *anti* form being the major isomer[4] (also see ESI†).

Table 1 Baylis–Hillman reaction of (*R*)-glyceraldehyde (**2**) with sugar derived acrylate (**1**) in different solvents

No.	Solvent	Time/h	Yield (%)	de (%)
1	THF	48	0[a]	
2	CH_2Cl_2	48	0	
3	Dioxane–water	48	0[a]	
4	Sulfolane	24	65	66
5	DMSO	24	71	90

[a] Acrylate hydrolysis was observed.

Table 2 Baylis–Hillman reaction of chiral aldehydes with sugar derived acrylate (**1**)[a]

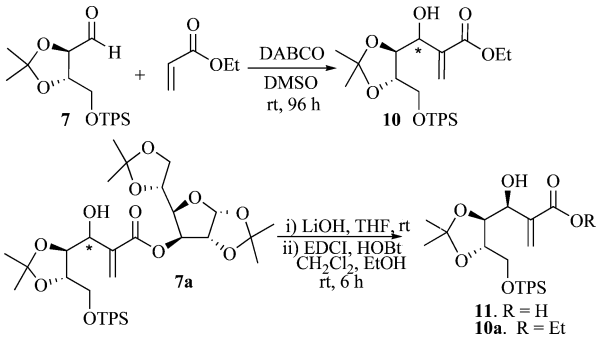
No.	Aldehyde	Time/h	Product, yield[b] (%)	de[c] (%)
1	**2**	24	**2a**, 71	90
2	**3**	28	**3a**, 43	>95
3	**4**	30	**4a**, 42	>95
4	**5**	24	**5a**, 44	>95
5	**6**	24	**6a**, 59	>95
6	**7**	24	**7a**, 73	>95[d]
7	**8**	36	**8a**, 78	33
8	**9**	24	**9a**, 84	40

[a] All reactions were carried out using aldehyde (1 mmol), chiral acrylate (1.5 mmol) and DABCO (1 mmol) in DMSO (0.5 mL) at ambient temperature. [b] Isolated yield. [c] As determined by ^{1}H NMR spectroscopy. [d] Confirmed by HPLC analysis.

† Electronic supplementary information (ESI) available: Experimental section. See http://www.rsc.org/suppdata/cc/b4/b411548a/

‡ IICT Communication No. 040608.

DOI: 10.1039/b411548a



Scheme 2 Establishment of absolute stereochemistry.

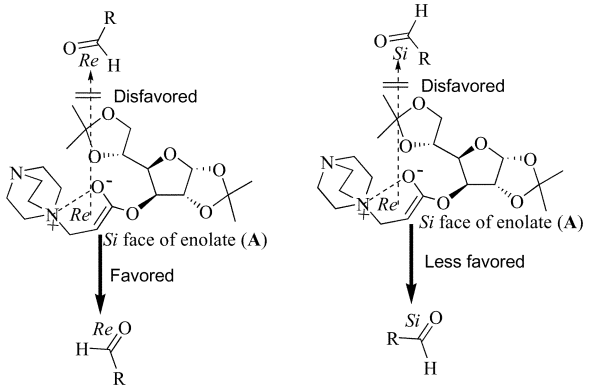
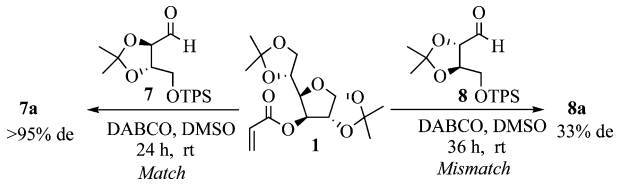


Fig. 1 Schematic representation of diastereofacial interactions.

Hydrolysis of **7a** afforded acid **11** (74%) which on esterification[12] (EDCI–HOBt–EtOH–CH_2Cl_2, rt) gave **10a** (60%). The ^{1}H NMR spectrum of **11** revealed the allylic proton resonating at δ 4.60 as a doublet (J = 4.5 Hz) indicative of a *syn* relation between the newly created center and the existing one. The same reasoning was further strengthened when an HPLC analysis (Chiral OD column, 2.25 nm, 5% ^{i}PrOH–*n*-hexane) of ester **10a** was carried out wherein the major isomer showed retention times of 8.3 min while the minor isomer had 8.8 min as the retention time with diastereomeric ratio as 9.75:0.25. However **10** showed retention times of 8.3 min for the minor isomer and 8.8 min for the major isomer (3.5:6.5) which implied that **10a** had an apparent reversal of selectivity (*syn* as the major isomer) under the influence of the 'double asymmetric induction' Baylis–Hillman reaction protocol. Thus the newly created stereogenic center for **7a** was unambiguously assigned as '*R*'. The absolute configuration of major isomers in all other compounds (**2a–6a** and **9a**) was assigned as '*R*' by analogy.

The observed high selectivity can be rationalized as the cumulative effect of steric inhibitions posed by the chiral aldehyde (for *e.g.* **7**) and chiral acrylate (**1**). *Syn* selectivity can be attributed to the interaction of the *Si*-face of enolate (**A**) with the *Re*-face of aldehyde (Fig. 1). The *Re* face of the enolate is unapproachable due to steric restrictions of the acetonide moieties and ammonium ion. Similarly, the *Si* face of the aldehyde is comparatively hindered thus paving way for *Si–Re* interactions (favored, *match*) between enolate and aldehyde respectively leading to the *syn* adduct as an exclusive



Scheme 3

product. The poor selectivity encountered in the case of aldehydes **8** and **9** could be explained due to low steric bias of these aldehydes thus making the *Si*-face also available (*mismatch*) for the enolate attack.

Thus it is clear that the extent and directionality of the reaction could be controlled by the right choice of chiral aldehyde and chiral acrylate. It is also pertinent to mention that the acid **11** obtained from **7a** (de >95%) had an $[\alpha]_D$ –19.9 (*c* 1.0, $CHCl_3$) while the corresponding acid **11a** obtained from **8a** (de ~33%) had $[\alpha]_D$ +6.3 (*c* 1.0, $CHCl_3$) confirming that the present protocol though while preferentially giving *syn* adducts, shows varied diastereoselectivities depending upon the 'match' or 'mismatch' pair[13] (Scheme 3) and that the acids (esters) obtained from their respective adducts **7a** and **8a** (only major isomer) share an enantiomeric relationship (ESI†).

In conclusion, we have successfully demonstrated the use of 'double asymmetric induction' as a potential mechanistic probe to obtain a reversal of selectivity, in contrast to the single asymmetric induction, to achieve high diastereoselectivities by the proper selection of match pairs of chiral aldehydes and chiral acrylates, thus leading to a cumulative enhancement of selectivities in asymmetric Baylis–Hillman reactions.

Two of the authors (R. S. and V. K.) thank CSIR, New Delhi for financial support in the form of fellowships.

Notes and references

1 (*a*) D. Basavaiah, P. D. Rao and R. S. Hyma, *Tetrahedron*, 1996, **52**, 8001; (*b*) E. Ciganek, *Org. React.*, 1997, **51**, 201; (*c*) D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811.
2 L. J. Brzezinski, S. Rafel and J. W. Leahy, *J. Am. Chem. Soc.*, 1997, **119**, 4317.
3 P. Radha Krishna, V. Kannan, A. Ilangovan and G. V. M. Sharma, *Tetrahedron: Asymmetry.*, 2001, **12**, 829.
4 P. Radha Krishna, V. Kannan, G. V. M. Sharma and M. H. V. Ramana Rao, *Synlett*, 2003, 888.
5 (*a*) S. Masamune, W. Choy, J. S. Petersen and R. S. Lawrence, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1; (*b*) S. V. Lev, L. R. Cox and J. M. Worrall, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3349.
6 J. S. Brimacombe, R. Hanna and A. K. M. S. Kabir, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2421.
7 M. Terada, N. Savo and K. Mikami, *Synlett*, 1995, 411.
8 K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2000, **39**, 3558.
9 (*a*) P. Radha Krishna, V. Kannan and P. V. Narasimha Reddy, *Adv. Synth. Catal.*, 2004, **346**, 603; (*b*) P. Radha Krishna, M. Narsingam and V. Kannan, *Tetrahedron Lett.*, 2004, **45**, 4773.
10 C. Yu, B. Liu and L. Hu, *J. Org. Chem.*, 2001, **66**, 5413.
11 P. Radha Krishna, A. Manjuvani, V. Kannan and G. V. M. Sharma, *Tetrahedron Lett.*, 2004, **45**, 1183.
12 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.
13 S. G. Davies, G. J. Hermann, M. J. Sweet and A. D. Smith, *Chem. Commun.*, 2004, 1128.