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Synthesis of enantiomerically enriched Baylis–Hillman alcohols from their acetates: combination of kinetic resolution during the salt formation with $(DHQD)_2PHAL$ and following asymmetric induction during hydrolysis with $NaHCO_3$ as a water surrogate

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Abstract—Enantiomerically enriched Baylis–Hillman alcohols **2a–d** (*S*) were prepared in 25–42% yields with optical purities of 54–92% ee by using the combined concept of kinetic resolution during the salt formation of racemic Baylis–Hillman acetates **1a–d** with $(DHQD)_2PHAL$ and the asymmetric induction during the S_N2' type reaction with sodium bicarbonate as a water surrogate.

The Baylis–Hillman reaction allows the direct preparation of α-methylene-β-hydroxycarbonyl compounds by base-catalyzed reaction of α,β-unsaturated carbonyl compounds with aldehydes.[1] Much effort has been devoted to the synthesis of the Baylis–Hillman adducts in an enantioselective or diastereoselective manner.[2–6] By using the modified acrylic acid derivatives with chiral alcohols or chiral amines, limited success has been achieved.[2] A remarkable improvement was reported by Leahy and co-workers by using Oppolzer's chiral sultam-derived acrylamide in the Baylis–Hillman reaction.[2a] The use of chiral catalyst, tertiary amines[3,4] or tertiary phosphines,[5] has also been studied with low % ee. Recently, Hatakeyama and co-workers have reported an unprecedented level of asymmetric induction using the cinchonidine-derived chiral amine catalyst, (3*R*,8*R*,9*S*)-10,11-dihydro-3,9-epoxy-6′-hydroxycinchonane.[4] They obtained Baylis–Hillman adducts in 31–58% yields with 91–99% ee by using this catalyst.

Trost et al. have reported on a deracemization process of the Baylis–Hillman carbonate with phenols in the presence of a palladium catalyst and a chiral phosphine ligand.[6] The best result was up to 92% ee (yield = 69%) for *p*-methoxyphenol and is given as an example in this paper. More recently, Basavaiah and co-workers have published the asymmetric synthesis of the propargyl ether of the Baylis–Hillman adduct via the deracemization process.[7] In situ generation of the quinidinium salt followed by the nucleophilic substitution reaction with propargyl alcohol gave the product in 32–47% isolated yield with 25–40% enantiomeric purity.

Baylis–Hillman acetates or bromides can form the quarternary ammonium salt, which can be used as an electrophile toward many nucleophiles.[7,8] The formation of ammonium salt is quantitative for DABCO (1,4-diazabicyclo[2.2.2]octane) in a short time.[8,9] The reaction of the ammonium salt and nucleophile gave the allylic substitution product in good yield.[8] We intended to study a deracemization type process with oxygen and nitrogen nucleophiles in the presence of a chiral cinchona alkaloid in this context in order to obtain better results than in Basavaiah's paper.[7]

We initially examined the reaction of *p*-methoxyphenol and the Baylis–Hillman acetate **1b** in the presence of cinchonidine, $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ in aqueous THF (see Table 1). To our disappointment, however, the chemical yield of the product **3a** was low (11–48%). Moreover, the % ee of the product did not exceed 38% (entries 1–3 in Table 1). Thus, we next examined other nucleophiles such as *p*-toluenesulfonamide and methanesulfonamide under similar reaction

Keywords: Baylis–Hillman alcohol; kinetic resolution; cinchona alkaloid; water surrogate; asymmetric induction.

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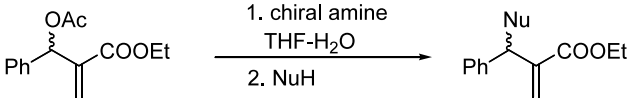
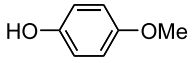
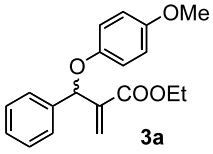
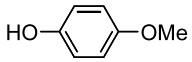
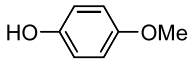
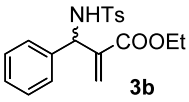
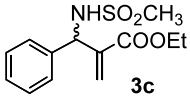
Table 1. Effect of chiral amine and nucleophile on the deracemization of **1b**



1b **3a-c**

entry	chiral amine conditions	nucleophile	product	yield (%) % ee (S:R)[a]
1	1. cinchonidine (1.2 equiv.) THF/H_2O, rt, 2 days 2. nucleophile (1.0 equiv.) rt, 4 days		 **3a**	48 18 (41:59)
2	1. $(DHQD)_2PHAL$ (0.5 equiv.) THF/H_2O, rt, 2 days 2. nucleophile (2.0 equiv.) rt, 4 days		**3a**	11 38 (69:31)
3	1. $(DHQ)_2PHAL$ (0.5 equiv.) THF/H_2O, rt, 2 days 2. nucleophile (2.0 equiv.) 40-50 °C, 4 days		**3a**	21 28 (36:64)
4	1. $(DHQD)_2PHAL$ (0.5 equiv.) THF/H_2O, rt, 2 days 2. nucleophile (2.0 equiv.) 40-50 °C, 4 days	$TsNH_2$	 **3b**	12 70 (85:15)
5	1. $(DHQ)_2PHAL$ (0.5 equiv.) THF/H_2O, rt, 2 days 2. nucleophile (2.0 equiv.) 40-50 °C, 4 days	$TsNH_2$	**3b**	9 44 (28:72)
6	1. $(DHQD)_2PHAL$ (0.1 equiv.) THF/H_2O, rt, Et_3N (1 mL), 2 days 2. nucleophile (2.0 equiv.) 40-50 °C, 1 day	$TsNH_2$	**3b**	48 28 (64:36)
7	1. $(DHQD)_2PHAL$ (0.5 equiv.) THF/H_2O, rt, 2 days 2. nucleophile (2.0 equiv.) 40-50 °C, 4 days	$CH_3SO_2NH_2$	 **3c**	10 70 (85:15)

[a]Determined by HPLC (CHIRALCEL OD) and the assignment of S/R is arbitrary. Hexane/IPA = 9:1 for **3a** and hexane/EtOH = 19:1 for **3b** and **3c.**

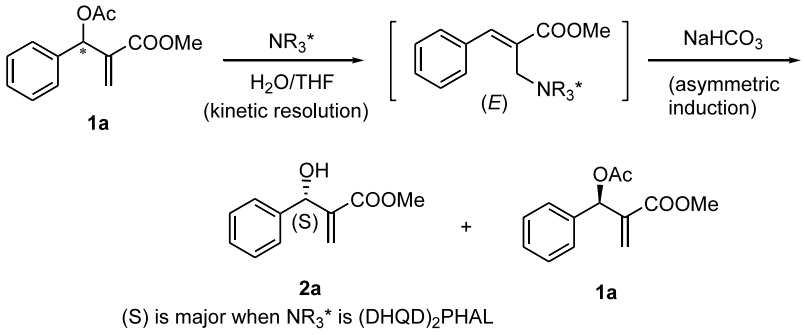
conditions (entries 4–7 in Table 1). We found that the % ee reached up to 70% when we used sulfonamide as the nucleophile. However, the chemical yields of the products were quite low. The low yield might be due to the incomplete and slow salt formation[9] and low reactivity of sulfonamide in the reaction medium. Recently, we have reported the facile synthesis of Baylis–Hillman adducts of *N*-tosylimines from the Baylis–Hillman acetates of benzaldehydes via the achiral version using DABCO.[8c] The salt formation was complete when we used DABCO as previously mentioned and the following substitution reaction with *p*-toluenesulfonamide occurred in good yield. Due to incomplete and slow salt formation in the cases of cinchona alkaloids,[9] the use of larger amounts of chiral amine did not improve the yield. The use of aqueous DMF in order to quicken the reaction and improve the yields failed due to the fast formation of the rearranged acetate. The use of triethylamine improves the chemical yields; however, as shown in entry 6, the % ee was dramatically decreased.[7] Low % ee (4% yield, 8% ee, not shown in Table 1) with *N*-methyl *p*-toluenesulfonamide as the nucleophile implies that a certain type of interaction such as hydrogen bonding (between the incoming nucleophile and the ammonium salt) might be involved for the asymmetric induction.

The unfavorable data for the deracemization type process made us try another approach for the synthesis of a Baylis–Hillman adduct in an enantiomerically enriched form. Kinetic resolution of the Baylis–Hillman adduct with acetic anhydride in the presence of a chiral amine catalyst was examined.[10,11] The reaction of the Baylis–Hillman adduct **2b** (racemic) in the presence of acetic anhydride, triethylamine and $(DHQD)_2PHAL$ was quenched at around half conversion. However, HPLC analysis of the remaining alcohol (41%) or the generated acetate (45%) showed that they are completely racemic mixtures. Without triethylamine, acetylation reaction was quite slow.

In another experiment, we examined the deracemization type process with triphenylsilanol or sodium bicarbonate as a water surrogate in the presence of commercially available chiral amine catalyst (Scheme 1). As Trost et al. have reported in a similar experiment, triphenylsilanol was ineffective as a water surrogate.[12] When we used sodium bicarbonate interesting results were observed. The reaction of the Baylis–Hillman acetate **1a** in aqueous THF in the presence of sodium bicarbonate and $(DHQD)_2PHAL$ (0.2 equiv.) was examined (entry 1 in Table 2). At the point of half-conversion (around 3.5 days), the separated alcohol (42%) showed 84% ee, while the remaining acetate (24%) showed 53% ee.[13] Appreciable amounts of rearranged alcohol and unreacted ammonium salt were observed as the side products. As shown in Table 2, the use of other chiral amine catalysts and water surrogates showed similar results. We used $(DHQD)_2PHAL$, $(DHQ)_2PHAL$, $(DHQD)_2$-AQN and $(DHQD)_2PYR$ as the chiral amine catalyst. As a water surrogate, $NaHCO_3$, $KHCO_3$, Na_2CO_3 and Cs_2CO_3 were examined.

It is difficult to say from the results whether the first salt-formation step or the second S_N2'-type stage is the reason for the asymmetric induction. There might be a combined interaction. Thus, we examined the salt formation reaction between the Baylis–Hillman acetate **1b** (racemic) and $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$. The remaining Baylis–Hillman acetate was separated and its % ee was examined after the reaction at room temperature for 2 days with chiral cinchona alkaloid (0.2 equiv.). The Baylis–Hillman acetates **1b** were isolated in 62 and 72%, respectively. Their % ee was 27 and 6% ee, respectively. The results mean that the difference in reactivity for the salt formation (kinetic resolution) is present between the two enantiomeric acetates (*R*) and (*S*). Moreover, $(DHQD)_2PHAL$ is more effective than $(DHQ)_2PHAL$.

The structure of the generated ammonium salt from $(DHQD)_2PHAL$ and **1b** would be *E*-form as previously reported by us and Basavaiah et al.[7,8] As mentioned in the above paragraph, maximum % ee of the recovered acetate would not exceed 27% if there were only kinetic resolution factor. Thus, the observed data (vide supra, entry 1 in Table 2, 84% ee for the Baylis–Hillman alcohol and 53% ee for the recovered acetate) must result from the combined effects of kinetic resolution during salt formation and the asymmetric induction process during the hydrolysis of the ammonium salt



Scheme 1.

Table 2. Effects of chiral catalyst and water surrogate on the deracemization of **1a**

Entry	Catalyst	Water surrogate	Time/temp. (°C)	**2a**	**1a**
1	$(DHQD)_2PHAL$ (0.2 equiv.)	$NaHCO_3$ (3.0 equiv.)	3.5 days/40–50	**42%**[a], **84% ee (*S*)**	24%, 53% ee (*R*)
2	$(DHQD)_2PHAL$ (0.2 equiv.)	$NaHCO_3$ (3.0 equiv.)	16 days/rt	60%, 81% ee (*S*)	Not isolated
3	$(DHQD)_2PHAL$ (0.2 equiv.)	$KHCO_3$ (2.0 equiv.)	3.5 days/40–50	27%, 79% ee (*S*)	17%, 56% ee (*R*)
4	$(DHQD)_2PHAL$ (0.2 equiv.)	Na_2CO_3 (3.0 equiv.)	3.5 days/40–50	33%, 75% ee (*S*)	35%, 52% ee (*R*)
5	$(DHQD)_2PHAL$ (0.2 equiv.)	Cs_2CO_3 (3.0 equiv.)	3.5 days/40–50	25%, 71% ee (*S*)	43%, 66% ee (*R*)
6	$(DHQD)_2AQN$ (0.2 equiv.)	$NaHCO_3$ (3.0 equiv.)	3.5 days/40–50	39%, 72% ee (*S*)	24%, 53% ee (*R*)
7	$(DHQD)_2PYR$ (0.2 equiv.)	$NaHCO_3$ (3.0 equiv.)	3.5 days/40–50	15%, 76% ee (*S*)	41%, 39% ee (*R*)
8	$(DHQD)_2PHAL$ (0.2 equiv.)	$NaHCO_3$ (2.0 equiv.)	40 h/40–50	31%, 79% ee (*S*)	52%, 22% ee (*R*)
9	$(DHQ)_2PHAL$ (0.2 equiv.)	$NaHCO_3$ (2.0 equiv.)	40 h/40–50	8%[b], 53% ee (*R*)	51%, 10% ee (*S*)

[a] $[\alpha]_D^{22} = +85.5°$ (*c* 1.11, MeOH).
[b] $[\alpha]_D^{22} = -56.9°$ (*c* 1.11, MeOH).

with $NaHCO_3$ by the chiral ammonium moiety of the salt. Asymmetric induction in the nucleophilic substitution stage with sodium bicarbonate could be another reason for the 84% ee. In fact, when the alcohol was isolated over 50%, the % ee was not reduced significantly (entry 2 in Table 2, 60% yield, 81% ee). Thus, without affecting the % ee, the desired Baylis–Hillman alcohol could be theoretically obtained in over 50% yield.

The reaction of the Baylis–Hillman acetate and $(DHQD)_2PHAL$ produced a quarternary ammonium salt with *E*-configuration as previously reported.[7,8] Salt formation of the (*S*) isomer occurs faster than the (*R*) form (vide infra). Sodium bicarbonate then attacks the electrophilic β-carbon toward the *si* face and subsequently the (*S*) form of the Baylis–Hillman alcohol was obtained as a major product (Fig. 1). Hydrogen bonding between the hydrogen atom of the bicarbonate and the oxygen atom of the $(DHQD)_2PHAL$ moiety would cause the approach of the bicarbonate ion toward the *si* face. To obtain greater insight on the hydrogen bonding effect, we examined the reaction with sodium carbonate, potassium bicarbonate and cesium carbonate. However, we could not find any significant changes in chemical yields and in % ees (Table 2). The reaction in THF, instead of using aqueous THF in order to maximize the hydrogen bonding, failed due to the incomplete salt formation in dry THF and subsequent low yield of the alcohol product.

The distance between the oxygen atom of the methoxy group at the quinoline moiety and the carbon atom at the benzylic position of the ammonium salt is estimated to be about 7.38 Å in the energy-minimized conformation (MM2 calculation). Considering the size of the bicarbonate anion (about 3.24 Å by MM2) and normal H-bonding distance (about 1.79 Å),[14] the distance between the oxygen atom of bicarbonate and the reaction center (benzylic carbon) is calculated as 2.35 Å. In other words, the bicarbonate ion fits well into the roomy pocket of the ammonium salt as shown in Fig. 1. The counter cation, sodium, potassium or cesium, did not affect the results significantly.[12] The effect of the anion, bicarbonate or carbonate, was also not observed.[12]

We then examined the reaction of some Baylis–Hillman acetate **1a–d** as shown in Table 3. As compared in entries 1 and 2, the reaction of **1a** at room temperature gave the improved % ee (up to 92% ee). However, low yield (25%) and long reaction time diminished the value. Other Baylis–Hillman acetates **1b–d** showed similar results. When we used the aliphatic Baylis–Hillman acetate derived from hexanal, elimination of acetic acid followed by subsequent Diels–Alder reaction was the principle pathway.[8c]

The absolute configuration of the obtained Baylis–Hillman alcohol **2a** was deduced from the optical rotation by comparison with that reported.[15] The optical rotation of the (*R*)-form of the Baylis–Hillman adduct **2a** was reported as −111.1°. In our case, we obtained +85.5° for the isolated alcohol (entry 1 in Table 3, 42%, 84% ee). The optical rotation value can be estimated as 77% ee based on the reported data, which was in agreement with the HPLC data (*S*-form is major, 84% ee). When we used $(DHQ)_2PHAL$ (entry 9 in Table 2) the optical rotation of the alcohol was −56.9°, indicating the major isomer is the (*R*)-form as expected.

As stated above, we presumed the reaction mechanism as follows. Salt formation between the acetate and chiral amine, although incomplete, must be the first step. Nucleophilic attack of sodium bicarbonate at the benzylic position occurred in a stereoselective manner. Direct hydrolysis of the acetate by sodium bicarbonate could not be excluded completely, which could diminish the optical purity of the products. However, the possibility of direct hydrolysis with sodium bicarbonate was excluded experimentally. As a blank test, direct hydrolysis of the acetate group into alcohol in the absence of $(DHQD)_2PHAL$ was never observed ($NaHCO_3$, aq. THF, 40–50°C, 3 days). Thus, our conclusion is as follows: The (*S*) form of acetate reacts faster than the (*R*) form with $(DHQD)_2PHAL$. The generated ammonium salt reacts with sodium bicarbonate preferentially at the *si* face to give the (*S*) form of Baylis–Hillman alcohol as the major product. Most of the (*R*) form acetate remained intact.

In summary, we could obtain the enantiomerically enriched Baylis–Hillman alcohols in 25–42% yield with optical purity of 54–92% ee by using the combined concept of kinetic resolution during salt formation and the asymmetric induction during the S_N2' type reaction with sodium bicarbonate as a water surrogate. Such a combined concept should inspire new avenues for other asymmetric synthesis.

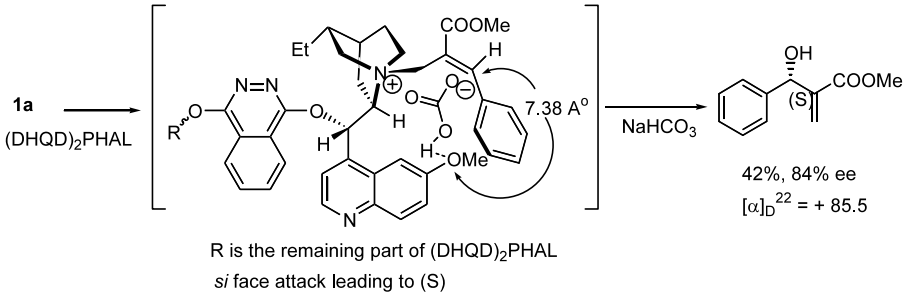
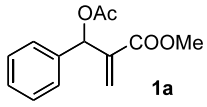
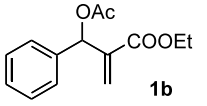
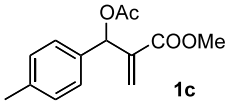
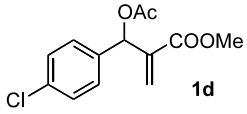


Figure 1. Proposed TS model for the (*S*) selectivity.

Table 3. Deracemization of the Baylis–Hillman acetates

entry	B-H acetate **1**	conditions	B-H alcohol **2** yield (%)	B-H alcohol **2** % ee[a]	recovered **1** yield (%)	recovered **1** % ee[a]
1	 **1a**	$(DHQD)_2PHAL$ (0.2 equiv.) H_2O/THF (1:2), 40-50 °C $NaHCO_3$ (3.0 equiv.), 3.5 days	42	84 (S) $[\alpha]_D^{22}$ +85.5 ° (c 1.11, MeOH)	24	53
2	**1a**	$(DHQD)_2PHAL$ (0.2 equiv.) H_2O/THF (1:2), rt $NaHCO_3$ (3.0 equiv.), 13 days	25	92 (S)	21	80
3	 **1b**	$(DHQD)_2PHAL$ (0.2 equiv.) H_2O/THF (1:2), rt $NaHCO_3$ (3.0 equiv.), 13 days	37	70 (S)	21	64
4	 **1c**	$(DHQD)_2PHAL$ (0.1 equiv.) H_2O/THF (1:2), 40-50 °C $NaHCO_3$ (3.0 equiv.), 4 days	28	54 (S) $[\alpha]_D^{20}$ +2.6 ° (c 0.05, MeOH)	59	nd[b]
5	 **1d**	$(DHQD)_2PHAL$ (0.2 equiv.) H_2O/THF (1:2), rt $NaHCO_3$ (3.0 equiv.), 6 days	40	70 (S) $[\alpha]_D^{20}$ +2.9 ° (c 0.05, MeOH)	26	nd[b]

[a]Determined by HPLC analysis. For entries 1-4, hexane/EtOH = 19:1 was used. For entriy 5, hexane/IPA = 98:2 was used. [b]Not determined.

Acknowledgements

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11. For the symmetric acetylation of the Baylis–Hillman adducts with vinyl acetate catalyzed by *Pseudomonas AK*,[11a] selective hydrolysis of the Baylis–Hillman acetates

by pig-liver esterase,[11b] and other kinetic resolution technique,[11c] see: (a) Burgess, K.; Jennings, L. D. *J. Org. Chem.* **1990**, *55*, 1138; (b) Basavaiah, D.; Rao, P. D. *Synth. Commun.* **1994**, *24*, 917; (c) Takagi, M.; Yamamoto, K. *Tetrahedron* **1991**, *47*, 8869.

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13. Typical procedure: To a stirred solution of the Baylis–Hillman acetate **1a** (234 mg, 1.0 mmol) and $(DHQD)_2PHAL$ (156 mg, 0.2 mmol) in aqueous THF (10 mL, H_2O/THF = 1:2) was added sodium bicarbonate (252 mg, 3.0 mmol). The reaction mixture was stirred at 40–50°C for 3.5 days. After usual workup and column chromatographic purification (hexane/ether/dichloromethane = 80:10:10) the Baylis–Hillman alcohol (**2a**, 81 mg, 42%) and the remaining acetate (**1a**, 56 mg, 24%) were isolated. Enantiomeric excess (ee) was determined by HPLC analysis (DAICEL CHIRALCEL OD, hexane/EtOH = 19:1, 1.0 mL/min). The retention time (t_R) of the alcohol was 9.31 min for the (*R*) enantiomer and 8.66 min for the (*S*) isomer (vide infra). Enantiomeric excess of **2a** was calculated as 84% from the two peak areas. The optical rotation of the Baylis–Hillman alcohol **2a** was determined as $[\alpha]_D^{22} = +85.5°$ (*c* 1.11, MeOH). We presumed the absolute configuration of the major isomer was (*S*) from the sign of specific rotation based on the reported data.[15] The value of optical rotation corresponds to 77% ee based on the reported data of Drewes ($[\alpha]_D^{26} = -111.1°$ (*c* 1.11, MeOH) for the (*R*) isomer),[15] which was in agreement with our HPLC data (84% ee).
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