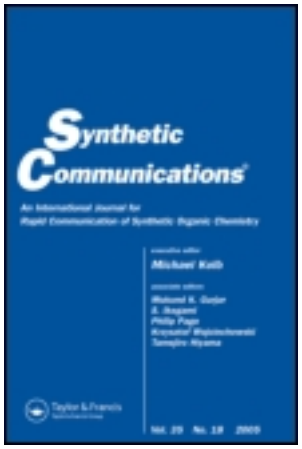

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A Nonenzymatic Kinetic Resolution of (±)-trans-2-Arylcyclohexanols via Esterification Using Polymer-Supported DCC, DMAP, and 3β-Acetoxyetienic Acid

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A NONENZYMATIC KINETIC RESOLUTION OF (±)-*trans*-2-ARYLCYCLOHEXANOLS VIA ESTERIFICATION USING POLYMER-SUPPORTED DCC, DMAP, AND 3β-ACETOXYETIENIC ACID

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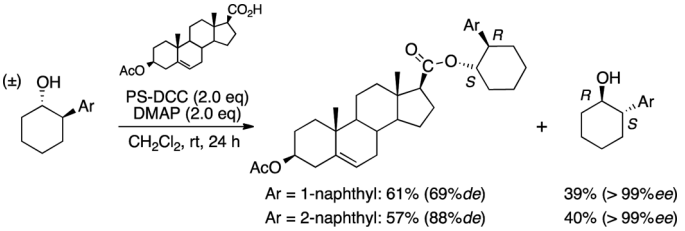
GRAPHICAL ABSTRACT



Abstract *A nonenzymatic kinetic resolution of (±)-*trans*-2-arylcyclohexanols was carried out by esterification using polymer-supported N,N′-dicyclohexylcarbodiimide (DCC), dimethylaminopyridine (DMAP), and 3β-acetoxyetienic acid. The efficiency of the kinetic resolution was comparable to the enzymatic method when arylcyclohexanols bearing a condensed-aromatic ring were used.*

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Keywords Esterification; kinetic resolution; nonenzymatic; polymer-supported DCC

INTRODUCTION

The optically active *trans*-2-arylcyclohexanols[1] are known to be useful chiral auxiliaries in asymmetric Michael addition,[2] Diels–Alder reaction,[3] and sulfoxide syntheses.[4] We have reported a novel method to determine the absolute configuration of various *trans*-2-arylcyclohexanols using ^{1}H NMR observation of the intramolecular CH/π shielding effect of the corresponding chiral 3β-acetoxyetienic acid esters.[5] The absolute configuration of the chiral center of the hydroxyl group would be (*S*)-isomer, if a significant change in chemical shift [δ −0.25–0.12 ppm] of the CH_3 protons at the 18 position of the chiral ester was observed in the ^{1}H NMR spectrum.

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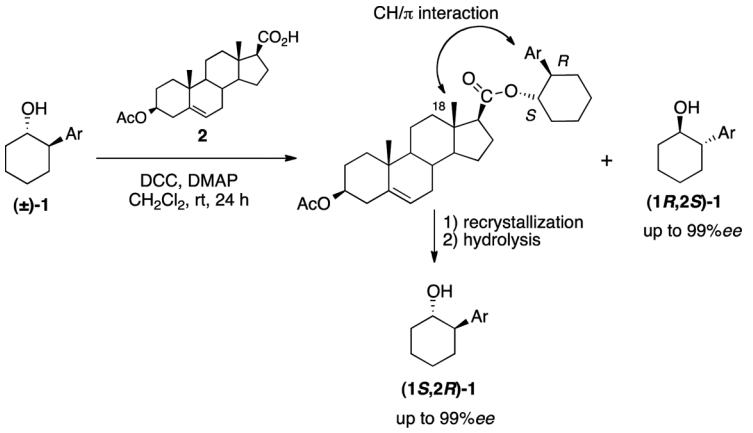
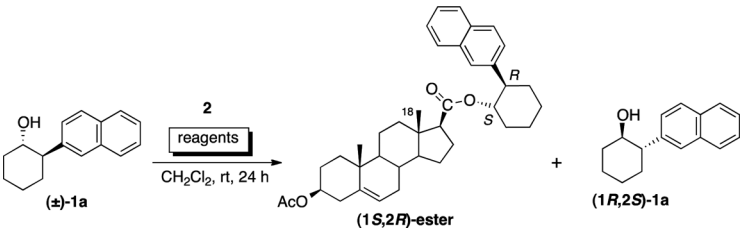


Scheme 1. Nonenzymatic kinetic resolution of (±)-arylcyclohexanols using condensation reaction with chiral acid **2**.

The numbering positions on the steroid ring and hexane ring are respectively depicted by the positions of 3β-acetoxyetienic acid and 2-arylcyclohexanols before esterification for the simple discussion. During the course of that study, we found that the (1*S*,2*R*)-*trans*-arylcyclohexanols always predominantly proceeded to give the corresponding esters in the coupling reaction. We have also reported an effective nonenzymatic kinetic resolution of racemic *trans*-2-arylcyclohexanols[6] using 3β-acetoxyetienic acid,[7] *N,N*-dicyclohexylcarbodiimide (DCC), and *N,N*-dimethyl-4-aminopyridine (DMAP) as shown in Scheme 1.[8] There are methods using simple chiral carboxylic acids by way of DCC esterification that are known to give good results, but their selectivities are not necessarily high.[9] Here, we report a modified kinetic resolution of (±)-*trans*-2-arylcyclohexanols using a polymer-supported condensation reagent (PS-DCC: *N*-benzyl-*N*-cyclohexyl carbodiimide on polystyrene, DMAP, and 3β-acetoxyetienic acid. [PS-DCC (*N*-Benzyl-*N*′-cyclohexylcarbodiimideon polysttylene) is commercially available from Aldrich (529.0 USD / 25 g)]. The advantages of our method are (1) the use of easily accessible chiral auxiliary and (2) the adequate *s* values[10] obtained in the kinetic resolutions. Also, our modified method provides a more practical workup process compared to the previous conditions in our seminal paper.[8]

DISCUSSION

First, we examined the effect on reactivity of different polymer-supported reagents in the kinetic resolution of (±)-*trans*-2-(2-naphthyl)cyclohexanol **1a** (Scheme 2). PS-DCC and PS-carbodiimide (*N*-cyclohexylcarbodiimide-*N*-propyloxymethylpolystyrene) were used as the polymer-supported condensation reagents, and PS-DMAP was used as a nucleophilic catalyst. [PS-DMAP (*N*-Benzyl-4-(-methylamino)pyridine, polymer-bound) is commercially available from Aldrich (372.5 USD / 25 g)]. As shown in Table 1, we found that combinations of PS-DCC and DMAP or PS-carbodiimide and DMAP gave similar resolution efficiencies as



Scheme 2. Nonenzymatic kinetic resolution of (±)-*trans*-2-(2-naphthyl)cyclohexanol **1a**.

our initial method (Table 1, entries 2 and 3). On the other hand, the esterification reaction did not proceed at all when PS-DMAP was used as a nucleophilic catalyst (Table 1, entries 4–6). Interestingly, kinetic resolution using PS-DCC/DMAP proceeded with a selectivity comparable to our homogeneous conditions.[8] The (1*S*,2*R*)-*trans*-2-(2-naphthyl)cyclohexanol **1a** predominantly reacted to give the corresponding ester, and this was confirmed using, as discussed earlier, the CH/π interaction[11] in the ^{1}H NMR spectrum. The chemical shift of the C18-CH_3 in the ester was −0.248 ppm and agreed with the (1*S*,2*R*)-ester, which was confirmed previously by x-ray crystallographic analytical data. (The crystal structure of the compound (1*S*,2*R*)-ester (Ar = 2-naphthyl): $C_{38}H_{48}O_4$ has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number). The *s* values observed were similar to the homogeneous condition using DCC/DMAP,[8] and enantiomerically pure (1*R*,2*S*)-*trans*-2-(2-naphthyl)cyclohexanol **1a** was obtained in 40% and 39% yield respectively (Table 1, entries 2 and 3). As previously reported, the diastereomeric ratio of the (1*S*,2*R*)-2-naphthyl ester can be

Table 1. Non-enzymatic kinetic resolution of (±)-*trans*-2-(2-naphthyl)-l-cyclohexanol **1a** using polymer-supported reagents and chiral acid **2**

		(1*S*,2 *R*)-Ester		(1 *R*,2*S*)-1		
Entry	Reagents (2.0 eq)	Yield (%)	*de* (%)[a]	Yield (%)	*ee* (%)[b]	Selectivity (*s* value)[c]
1	DCC/DMAP	58	52	32	>99	30.5
2	PS-DCC/DMAP	57	88	40	>99	34.9
3[d]	PS-DCC/DMAP	49	61	46	79	24.5
4[e]	PS-DCC/DMAP	66	56	31	>99	14.5
5	PS-Carbodiimide/DMAP	60	67	39	>99	21.9
6	DCC/PS-DMAP	trace	—	—	—	—
7	PS-DCC/PS-DMAP	trace	—	—	—	—
8	PS-Carbodiimide/PS-DMAP	trace	—	—	—	—

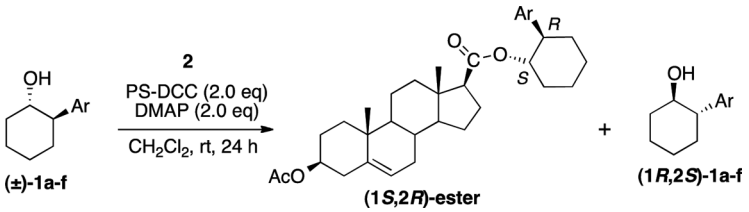
[a]The *de* value was determined by ^{1}H NMR spectra.

[b]The *ee* value was determined by HPLC analysis (CHIRAL CEL OD, hexane/^{i}PrOH = 95/5, flow rate; 1.0 ml/min.).

[c]*s* values were calculated according to Kagan's method. See: Ref. 10. $s = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$, C = conversion.

[d]The reaction was conducted for 20 h.

[e]The reaction was conducted for 30 h.



Scheme 3. Nonenzymatic kinetic resolution of (±)-*trans*-2-arylcyclohexanols.

elevated to 99%*de* by recrystalization, and the removal of the chiral auxilliary leads to the corresponding enantiomerically pure (1*S*,2*R*)-arylcyclohexanols.[5]

Table 2 shows the results of the kinetic resolution for (±)-*trans*-2-arylcyclohexanols **1a–f** by esterification using chiral acid **2** in the presence of PS-DCC/DMAP. All reactions proceeded at room temperature and were treated after 24 h to give the corresponding acylated products and substrate alcohols with enantiomeric excess. The efficiency for the kinetic resolution was significantly high when the arylcyclohexanols bearing a condensed-aromatic ring were used. The enantiomerically pure (1*R*,2*S*)-*trans*-2-arylcyclohexanols were easily attainable when the Ar function was 2-naphthyl or 1-naphthyl (Table 2, entries 1 and 2). These results seem to suggest that a high electron density of the aromatic moiety and/or the spreadability of the π plane is important to achieve a high selectivity. This tendency was also observed in the corresponding homogeneous reaction.[8] It goes without saying that the PS-DCC urea was separated effectively by filtration after the reaction.

The present nonenzymatic kinetic resolution method of (±)-*trans*-2-arylcyclohexanols using PS-DCC and an easily accesible 3β-acetoxyetienic acid **2** will be useful for large-scale syntheses. This methodology is also useful in determining the stereochemistry of resolved alcohols as well. The application of our new method to the kinetic resolution of various acyclic aryl alcohols is now being investigated.

Table 2. Nonenzymatic kinetic resolution of (±)-*trans*-2-arylcyclohexanols **1a–f** using PS-DCC/DMAP and chiral acid **2**

		(1*S*,2*R*)-Ester		(1*R*,2*S*)-1		
Entry	Ar	Yield (%)	*de* (%)[a]	Yield (%)	*ee* (%)[b]	Selectivity (*s* value)[c]
1	2-Naphthyl: **1a**	57	88	40	>99	34.9
2	1-Naphthyl: **1b**	61	69	39	>99	21.5
3	Ph: **1c**	49	66	50	56	6.3
4	*p*-Tolyl: **1d**	61	69	38	58	3.8
5	*p*-chlorophenyl: **1e**	62	56	31	67	4.3
6	*p*-Methoxyphenyl: **1f**	48	73	40	63	10.0

[a]The *de* was detennined by ^{1}H NMR.

[b]The *ee* was determined by HPLC analysis (**la, lb**: CHIRAL CEL OD, hexane/^{i}PrOH = 95/5, flow rate: 1.0 ml/min, **lc:** CHIRAL CEL OD, hexane/^{i}PrOH = 99/1, flow rate: 0.5 ml/min, **ld–f:** CHIRAL CEL OJ, hexane/PrOH = 99/1, flow rate: 1.0 ml/min).

[c]The *s* was calculated according to Kagan's method. See: Ref. 10. $s = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$, C = conversion.

EXPERIMENTAL

Typical Procedure for the Kinetic Resolution and Purification

To a solution of (±)-*trans*-2-(2-naphthyl)-1-cyclohexanol **1a** (20 mg, 0.09 mmol), 3β-acetoxyetienic acid[5] **5** (47.8 mg, 0.13 mmol), and PS-dicyclohexylcarbodiimide (177 mg, 0.18 mmol) in dry CH_2Cl_2 (3 ml) was added *N,N*-Dimethyl-4-aminopyridine (21.6 mg, 0.18 mmol) at room temperature. The reaction mixture was stirred for 24 h at ambient temperature. After filteration of PS-DCC urea by a filter paper (Kiriyamaglass Co. Ltd. No. 5C), the reaction mixture was washed with 1 M HCl and 1 M aqueous NaOH. Then the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silicagel (eluent: hexane/AcOEt = 5/1) to give (1*S*,2*R*)-2-naphthylester (28.6 mg, 57%, 88% *de*) and (1*R*, 2*S*)-**1** (7.9 mg, 40%, 99% *ee*).

Compound (1*R*,2*S*)-1a: (1*R*,2*S*)-*trans*-2-(2-Naphthyl)cyclohexanol

Colorless crystals; mp 91.0–92.0 °C; 99% *ee* [the *ee* was determined by HPLC analysis (Daicel Chiralcel OD; hexane/^{i}PrOH = 95/5; flow rate: 1.0 ml/min; 25 °C; t_R 16.1 min)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.84–7.79 (m, 3H), 7.71 (s, 1H), 7.50–7.38 (m, 3H), 3.79 (m, 1H), 2.61 (m, 1H), 2.17 (m, 1H), 1.91–1.26 (m, 7H).

(1*S*,2*R*)-2-Naphthyl Ester (88% *de*): (3*S*,10*R*,13*S*,17*S*)-(*trans*-2-(2-Naphthyl)cyclohexyl)-3-acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene-17-carboxylate

Colorless solid; mp 194.0–194.5 °C.

Assigned Value from (1*S*,2*R*)-Ester

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.81–7.73 (m, 3H, overlap with signals of the other diastereomer), 7.62 (s, 1H, overlap with signals of the other diastereomer), 7.44–7.33 (m, 3H, overlap with signals of the other diastereomer), 5.26 (m, 1H, overlap with signals of the other diastereomer), 5.09 (m, 1H, overlap with signals of the other diastereomer), 4.55 (m, 1H, overlap with signals of the other diastereomer), 2.86 (m, 1H, overlap with signals of the other diastereomer), 2.27 (m, 2H, overlap with signals of the other diastereomer), 2.23–0.66 (m, 26H, overlap with signals of the other diastereomer), 1.97 (s, 3H), 0.69 (s, 3H), −0.25 (s, 3H).

Assigned Value from (1*R*,2*S*)-Ester

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.81–7.73 (m, 3H, overlap with signals of the other diastereomer), 7.62 (s, 1H, overlap with signals of the other diastereomer), 7.44–7.33 (m, 3H, overlap with signals of the other diastereomer), 5.26 (m, 1H, overlap with signals of the other diastereomer), 5.09 (m, 1H, overlap with signals of the other diastereomer), 4.55 (m, 1H, overlap with signals of the other diastereomer), 2.86 (m, 1H, overlap with signals of the other diastereomer), 2.27 (m, 2H, overlap

with signals of the other diastereomer), 2.23–0.66 (m, 26H, overlap with signals of the other diastereomer), 2.03 (s, 3H), 0.98 (s, 3H), 0.43 (s, 3H).

(1*S*,2*R*)-2-Naphthyl Ester (Isolated)

Colorless crystals; mp 198.0–199.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.81–7.73 (m, 3H), 7.62 (s, 1H), 7.44–7.33 (m, 3H), 5.26 (m, 1H), 5.09 (m, 1H), 4.55 (m, 1H), 2.86 (m, 1H), 2.27 (m, 2H), 1.97 (s, 3H), 2.23–0.66 (m, 26H), 0.69 (s, 3H), −0.25 (s, 3H); IR (KBr): 1720 cm^{-1}. Elemental analysis calcd. (%) for $C_{38}H_{48}O_4$ (568.8): C, 80.24; H, 8.51. Found: C, 79.90; H, 8.70.

(1*R*,2*S*)-2-Naphthyl Ester (Isolated)

Colorless crystals; mp 180.0–181.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.81–7.73 (m, 3H), 7.64 (s, 1H), 7.44–7.33 (m, 3H), 5.34 (m, 1H), 5.09 (m, 1H), 4.55 (m, 1H), 2.86 (m, 1H), 2.27 (m, 2H), 2.03 (s, 3H), 2.23–0.66 (m, 26H), 0.98 (s, 3H), 0.43 (s, 3H); IR (KBr): 1727 cm^{-1}.

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