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REVERSAL OF DIASTEREOSELECTIVITY – CATALYST- AND SOLVENT-EFFECTS ON THE STEREOCHEMICAL OUTCOME IN THE ACYLATION OF SEVERAL *TRANS*-1,2-SUBSTITUTED CYCLOHEXANOLS*

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Abstract

The ability to control the diastereoselectivity of reactions allows their application to laboratory- as well as industrial-sized syntheses. Thus, understanding the underlying mechanistic principles that govern diastereoselective reactions is imperative. It has been shown that during a specific acylation reaction of racemic *trans*-1,2-substituted cyclohexanols with racemic acylating agents, a simple achiral amine can lead to the reversal of diastereoselectivity. Here we present further investigation into the system by varying the substituent of the cyclohexanol, the identity of the achiral additive, the catalyst load and the solvent. The reactions were investigated using NMR spectroscopy to determine the diastereomeric ratio of the products and computational results contributing to the mechanistic investigation of the observed stereodifferentiation are discussed as well.

Keywords: Acylation, Reversal of Diastereoselectivity, Achiral Catalyst, Solvent Dependence

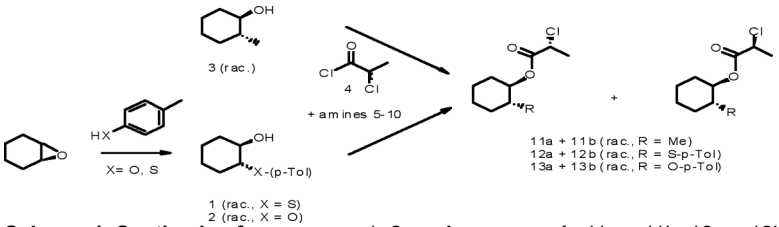
Introduction

Enantiomers and their action as biologically active compounds have provided countless challenges ranging from separation, (1-4) characterization, and medical testing (5) all the way to specific enrichment during synthesis (6). Stereoselective reactions are important tools in synthesizing useful and configurationally pure compounds. Diastereo- and enantioselectivity have been demonstrated in esterifications using enzymes and chiral catalysts (7). Examples of achiral catalysts showing similar effects exist (8). However, such achiral catalyst influences have not been reported for the formation of esters from secondary alcohols to the best of our knowledge. Previous studies in our laboratories have identified pyridine as a novel example for an achiral catalyst capable of reversal of diastereoselectivity in the acylation of (±)-*trans*-2-substituted cyclohexanols with (±)-2-chloropropionyl chloride (9). Here, we present our results from further investigations into this phenomenon.

Experimental

General.

Cyclohexene, *p*-thiocresol, *p*-cresol, NBS, cyclohexene oxide, 2-chloropropionyl chloride and pyridine were purchased from Sigma-Aldrich (St. Louis, MO, USA). Racemic *trans*-2-methylcyclohexanol and 2,4,6-trimethylpyridine were purchased from Alfa Aesar (Ward Hill, MA, USA). Dimethylaminopyridine was obtained from Avocado Chemicals. Unless otherwise noted, commercial reagents were used without further purification. Column chromatography was performed on silica gel (Sorbent Technologies, Norcross, GA, USA, 40-75 ?m). NMR spectra were acquired on a JEOL ECA-600MHz instrument using the residual solvent peak for referencing. High Resolution mass spectra were acquired on a JEOL AccuTOF DART Mass Spectrometer (Peabody, MA, USA) with a resolving power of 7,500, using polyethyleneglycol as an internal reference to give accurate mass measurements.



Scheme 1. Synthesis of precursors 1, 2, **and compounds** 11a + 11b, 12a + 12b, 13a + 13b.

Substituted cyclohexanols.

Compound [1]: [(±)-*trans*-2-(*p*-tolylsulfanyl)-cyclohexanol]

To a solution of cyclohexene (10.2 mL, 100 mmol) in aqueous THF (200 mL, THF/H_2O 3:1) NBS (21.72 g, 122 mmol) was added slowly and stirred at rt overnight. Diethyl ether (200 mL) was added to the reaction mixture followed by NaOH solution (10% w/w, 100 mL). The mixture was stirred at rt overnight. The aqueous layer was separated and extracted with ether (3 x 25 mL). The organic layers were combined and dried over Na_2SO_4. The organic layer containing the cyclohexene oxide was decanted from the drying agent and concentrated to 50 mL. Subsequently, *p*-thiocresol (13.68 g, 110 mmol) was added followed by borax (2.07 g, 10.0 mmol) and water (50 mL). The mixture was stirred at 50 °C (water bath) for 2 h. The organic solvent was removed on a rotavap, and the remaining aqueous solution was mixed with aq. NaOH (5% w/w, 150 mL) and stirred at rt for 30 minutes. The mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the extracts were combined and dried over Na_2SO_4. Filtration and evaporation of the solution yielded a yellow viscous liquid that crystallized at 4 ºC overnight. The crude product was purified *via* recrystallization from hexane and the purified product was obtained as white crystalline solid (17.11 g, 77%). ^{1}H NMR (600 MHz, $CDCl_3$): ? 7.35 (dt, 1.8 Hz, 7.8 Hz, 2H, Ar), 7.10 (br d, 7.8 Hz, 2H, Ar), 3.27 (dt, 4.2 Hz, 9.6 Hz, H-1), 3.04 (broad s, 1H, OH), 2.66 (ddd, 4.2 Hz, 10.2 Hz, 12.0 Hz, H-2), 2.33 (s, 3H, Tolyl-CH_3), 2.07 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 1.26 (m, 4H,CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): ? 138.28 (Ar-C_q), 134.83 (Ar-CH), 134.60 (Ar-CH), 129.94 (Ar-CH), 129.64 (Ar-CH), 128.33 (Ar-C_q), 71.70 (C1), 56.58 (C2), 33.66 (C6), 32.45 (C3), 26.12 (C5), 24.22 (C4), 21.05 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{13}H_{19}OS$ $[M + H]^+$ 223.1152, found 223.1161; *m/z* calculated for $C_{13}H_{19}OS$ $[M - OH]^+$ 205.1056, found 205.1042.

* Parts of this work were presented at the National Conference for Undergraduate Research in La Crosse, WI in spring 2013.

Compound [2]: [(±)-*trans*-2-(*p*-tolyloxy)-cyclohexanol] To 15 mL of a saturated solution of NaOH in ethanol (pH 14) was added cyclohexene oxide (2.0 mL, 20.0 mmol) and *p*-cresol (2.1 mL, 20.0 mmol) with stirring and the reaction was heated to 80 ºC with vigorous stirring for 24 hours. The solution was then cooled and neutralized using conc. HCl acid. The brown liquid was then diluted with 15 mL of CH_2Cl_2 and transferred to a separatory funnel. The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (2 x 10 mL). The combined organic layers (yellowish liquid) were dried over Na_2SO_4. The drying agent was filtered off and the solvent evaporated to give 2.65 g of an off-white solid. The crude product was recrystallized from hexane to yield 2.41 g (11.7 mmol, 58%) of white needle-like crystals. ^{1}H NMR (600 MHz, $CDCl_3$): ? 7.08 (m, 2H, Ar), 6.85 (dt, 2.7 Hz, 8.4 Hz, 2H, Ar), 3.93 (ddd, 4.2 Hz, 8.4 Hz, 10.2 Hz, H-1), 3.70 (ddd, 4.8 Hz, 8.4 Hz, 10.8 Hz, H-2), 2.43 (broad s, 1H, OH), 2.29 (s, 3H, Tolyl-CH_3), 2.11 (m, 2H, CH2), 1.74 (m, 2H, CH_2), 1.33 (m, 4H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): ? 155.78 (Ar-C_q), 130.67 (Ar-C_q), 130.78 (2C, Ar-CH), 116.62 (2C, Ar-CH), 82.75 (C-1), 73.61 (C-2), 32.12, 29.34, 24.40, 24.01, 20.55 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{13}H_{19}O_2$ $[M+H]^+$ 207.1380, found 207.1373, *m/z* calculated for $C_{13}H_{17}O$ $[M-OH]^+$ 189.1284, found 189.1278.

Acylation of substituted cyclohexanols.

(±)-*trans*-2-substituted cyclohexanols [**1-3**] (1.0 mmol) were dissolved in 6 mL of solvent (CH_2Cl_2, unless noted otherwise). If applicable, the amine catalyst was added immediately afterwards. The reaction was initiated by the addition of (±)-2-chloropropionyl chloride [**4**]. Reaction conditions, such as temperature and reaction duration, were adjusted and reaction progress was monitored by TLC (hexane/EtOAc 95:5). The reaction mixture was evaporated to remove solvent and amine catalyst (except in the case of DMAP) and then redissolved in 10 mL of CH_2Cl_2. The solution was washed with aq. $NaHCO_3$ (2 x 10 mL) and DI water (10 mL), then dried over Na_2SO_4, and evaporated to give the crude product, which was subjected to column chromatography (hexane/EtOAc 95:5). The products were all isolated as clear yellow oils.

Compound [11a] + [11b]: [(±)-(*trans*-2-(*p*-tolylsulfanyl) cyclohexyl) 2-chloropropanoate]: Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.30-4.21 ppm). ^{1}H-NMR (600 MHz, $CDCl_3$): ? (ppm) 7.30 (m, 2H, Ar), 7.15 (m, 2H, Ar), 4.80 (dt, 4.2 Hz, 9.0 Hz, H-1), 4.30/4.26 (q, 10.2 Hz, 1H, C**H**(CH_3)Cl), 3.10 (*dt*, 4.2 Hz, 9.6 Hz, H-2), 2.32 (s, 3H, tolyl-CH_3), 2.05 (m, 2H, H-3a), 1.70 (m, 2H), 1.67/1.65 (d, 10.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.48-1.38 (m, 2H, H-6a,b), 1.38-1.23 (m, 2H, CH_2, H-3b). ^{13}C NMR (150 MHz, $CDCl_3$): ? 169.47/169.33 (C=O), 137.63/137.61 (Ar-C_q), 133.54/133.45 (Ar, 2C), 130.10/130.05 (Ar-C_q), 129.73/129.70 (Ar, 2C), 76.39/76.26 (C-1), 53.07/52.78 (**C**H(CH_3)Cl), 50.24/50.17 (C-2), 31.58/31.40 (C-6), 30.82/30.55 (C-3), 24.86/24.64, 23.42/23.27 (CH(**C**H$_3$)Cl), 21.69/21.54, 21.15 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{16}H_{21}ClO_2S$ $[M]^{+?}$ 312.0951, found 312.0935; *m/z* calculated for $C_{13}H_{19}OS$ $[M - {}^?O_2C\text{-}CH(CH_3)Cl]^+$ 205.1046, found 205.1016.

Compound [12a + 12b]: [(±)-(*trans*-2-(*p*-tolyloxy) cyclohexyl) 2-chloropropanoate]: Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.30-4.26 ppm). ^{1}H NMR (600 MHz, $CDCl_3$): ? 7.06 (m, 2H, Ar), 6.84 (m, 2H, Ar), 5.02 (ddd, 4.2 Hz, 7.8 Hz, 9.6 Hz, H-1), 4.30/4.26 (q, 7.2 Hz, C**H**(CH_3)Cl), 4.19 (ddd, 4.2 Hz, 7.8 Hz, 9.0 Hz, H-2), 2.27 (s, 3H, tolyl-CH_3), 2.10 (m, 2H), 1.76 (m, 2H), 1.59/1.56 (d, 7.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.55-1.24 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): ? 169.70 (C=O), 155.99 (Ar-C_q), 130.62 (Ar-C_q), 129.99 (2C, Ar-CH), 116.40 (2C, Ar-CH), 77.53 (C-2), 75.77 (C-1), 52.96 (**C**H(CH_3)Cl), 29.65, 29.30, 23.03, 22.88, 21.58 (CH(**C**H$_3$)Cl), 20.59 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{16}H_{22}ClO_3$ $[M+H]^+$ 297.1252, found 297.1200, *m/z* calculated for $C_{13}H_{17}O$ $[M - O_2C\text{-}CH(CH_3)Cl]^+$ 189.1284, found 189.1257.

Compound [13a + 13b]: [(±)-(*trans*-2-methylcyclohexyl) 2-chloropropanoate]: Mixture of diastereomers (ratio of diastereomers determined using doublet signals for CH(C**H$_3$**)Cl at 1.68/1.67 ppm). The doublets for CH(C**H$_3$**)Cl overlapped to appear as a triplet, so the *dr* was determined from the integration of the side peaks. To confirm the validity of this method, a homonuclear decoupling experiment was performed (for spectra, see SI) to collapse the signals into singlets which could be integrated to give the measured ratio within reasonable experimental error. ^{1}H NMR (600 MHz, $CDCl_3$): ? 4.45 (m, H-1), 4.37/4.36 (q, 7.2 Hz, C**H**(CH_3)Cl), 1.97 (m, 1H), 1.75 (m, 2H), 1.68/1.67 (d, 6.9 Hz, CH(C**H$_3$**)Cl), 1.64-1.55 (m, 2H), 1.35-1.20 (m, 3H), 1.07 (m, 1H), 0.91 (d,

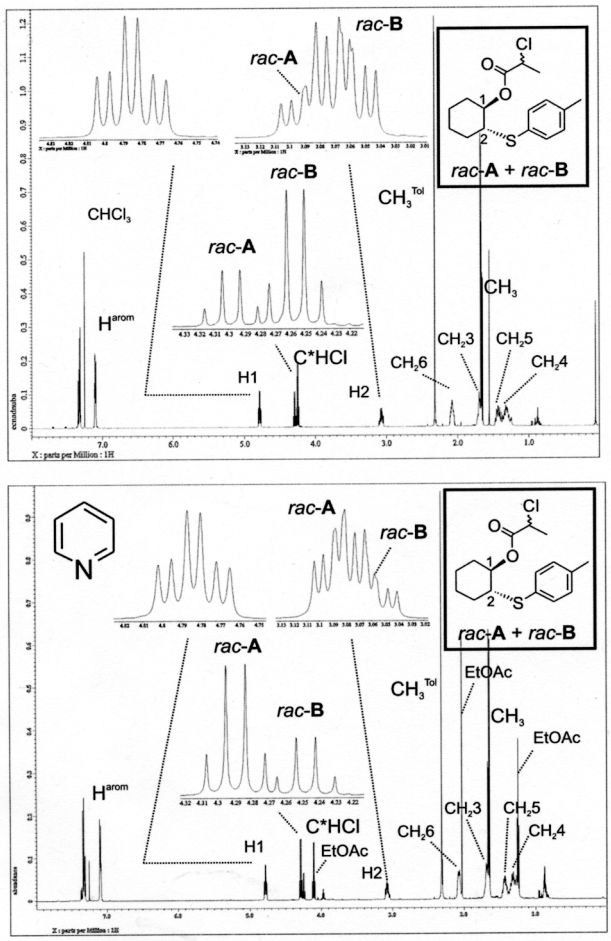


Figure 1. ^{1}H-NMR spectra of the isolated (*rac.*) 11a + 11b **from the reaction a) without pyridine and b) with pyridine. Inset: quartet signals of C**H**(CH$_3$)Cl showing diastereomeric ratio.**

Table I. Data from ^{1}H-NMR integration in $CDCl_3$. Reactions run in CH_2Cl_2 as solvent at 1.0 mmol scale. (*(a) Assignment of A and B arbitrary, for determination of *dr*, see Experimental.)

Entry	Alcohol	ROH:Acyl	Catalyst	- mol%	Isolated Yield	dr (A:B)[a]
1	1	1:1.1	-/-		40%	1:2.0
2	1	1:1.1	pyridine	10	61%	1:1.2
3	1	1:1	pyridine	20	41%	1:1.1
4	1	1:1.1	pyridine	51	45%	1.5:1
5	1	1:1	pyridine	80	52%	2.2:1
6	1	1:1.1	pyridine	104	51%	2.3:1
7	1	1:1	pyridine	151	66%	2.2:1
8	1	1:1.1	pyridine	201	61%	2.5:1
9	1	1:1	pyridine	308	43%	2.2:1
10	1	1:1	DMAP	10	35%	1:1.7
11	1	1:1	DMAP	20	37%	1:1.3
12	1	1:1	DMAP	51	46%	1.7:1
13	1	1:1	DMAP	100	47%	2.6:1
14	1	1:1	DMAP	197	50%	2.2:1
15	1	1:1.1	collidine	10	36%	1:1.0
16	1	1:1	collidine	97	43%	2.7:1
17	1	1:1	DBU 107		24%	1.1:1
18	1	1:1	DIPEA	98	41%	1.1:1
19	1	1:1	DIPEA	48	30%	1:1.0
20	1	1:1	TEA 103		46%	1:1.1
21	2	1:1.1	-/-		46%	1:1.6
22	2	1:1.1	pyridine	110	63%	3.4:1
23	2	1:1	DIPEA	57	27%	1.3:1
24	3	1:1	-/-		52%	1:1.6
25	3	1:1	pyridine	50	30%	1:1.3
26	3	1:1	pyridine	100	56%	1:1.2
27	3	1:1	DIPEA	55	17%	1:1.9

6.6 Hz, 2H, Cy-CH_3), 0.89 (d, 6.6 Hz, 1H, Cy-CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): ? 169.84 (C=O), 80.36/80.24 (C-1), 53.12/52.89 (**C**HClCH$_3$), 37.31/37.20, 34.74, 33.51, 31.48, 25.35/25.27, 24.68, 21.70/21.48 (CHCl**C**H$_3$). HRMS: *m/z* calculated for $C_{10}H_{18}ClO_2$ $[M + H]^+$ 205.0990, found 205.1040.

Results and Discussion

The (±)-*trans*-2-substituted cyclohexanols [**1**] and [**2**] were prepared from cyclohexane oxide (see Experimental Section). Acylation reactions proceeded with the (±)-*trans*-2-substituted cyclohexanols [**1**]-[**3**] and the acyl chloride [**4**] (Scheme 1) in the presence or absence of amine catalysts, such as pyridine [**5**], DMAP (4-(dimethylamino)pyridine) [**6**], collidine (2,4,6-trimethylpyridine) [**7**], DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) [**8**], DIPEA (diisopropylamine) [**9**] and TEA (triethylamine) [**10**]. After chromatographic purification of the products, the ^{1}H-NMR spectra were integrated to calculate the diastereomeric ratio (Figure 1, Table I).

The diastereoselectivity of the simple acylation reaction can be reversed by the introduction of an achiral amine catalyst (entries 6 and 13 for [**1**] and entry 22 for [**2**]). However, in the case of the less sterically demanding methyl substituent in [**3**], no reversal of diastereoselectivity was observed (Entries 25-26).

The diastereomeric ratio of the product of the acylation of [**1**] was found to be dependent on the catalyst/promoter load for pyridine (Entries 2-9) and its derivatives (Entries 10-14 and 15-16). This load-dependence was less significant when

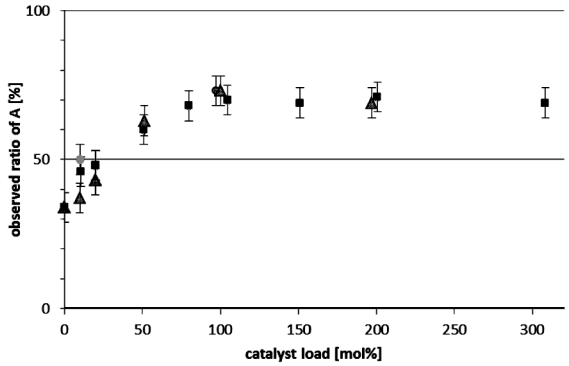


Figure 2. Observed catalyst-load dependence of *dr* of the acylation product of 1 with 2-chloro propionylchloride 4 with pyridine (black squares), DMAP (dotted triangles) and collidine (gray circles) as catalysts.

employing the bulky base [**9**] (Entries 18-19), or in the acylation of [**3**]. The catalyst/promoter load-dependent *dr* in the respective reactions was plotted in Figure 2 and appeared to show a near-linear dependence in the range of 0–100 mol%, with the maximum observed diastereoselectivity observed for 0 mol% and 100 mol% catalyst-loading respectively. This appears to be *inconsistent* with pyridine acting simply as a catalyst and would indicate that it plays a more essential role in the reaction pathway, when specific substituents (OTol, STol) are present in *trans*-2-position on the cyclohexanol substrate. The observed *dr* for the different pyridine-derived catalysts/promoters [**5**]-[**7**] were qualitatively similar (see Figure 2), suggesting that the observed diastereoselectivity for all three may be the result of matched/mismatched pairings of similar reaction pathways.

However, for the bulky bases [**8**]-[**10**], no significant or even moderate selectivity was observed (Entries 17-19) for substrate [**1**], indicating that here, the reaction pathway is likely different from the pyridine-promoted reaction. This would be expected as the bulky bases should not be able to form an acyl-*nitrogen*-intermediate.

Additionally, the solvent-dependence of the diastereoselectivity in the acylation was investigated. The results were summarized in Table 2 and showed that for the tolylsulfanyl-substituted cyclohexanol, the uncatalyzed

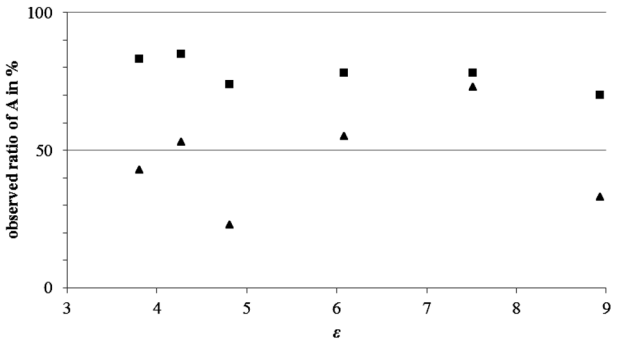


Figure 3. Observed solvent dependence of *dr* of the acylation product of 1 with 2-chloro propionylchloride 4 plotted against the dielectric constant *?* in different solvents with (black squares) and without (gray triangles) pyridine present at approx. 100 mol% (see Table II).

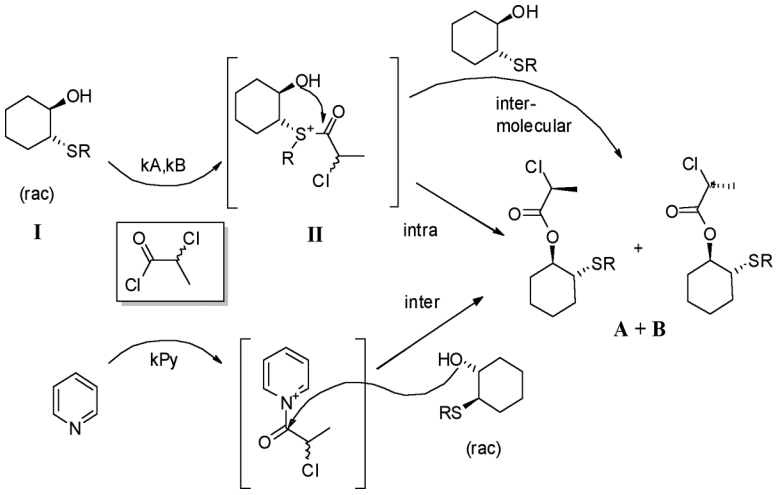
Table II. Data from solvent variation in the acylation reaction between 1 and 4. *(a) *?*: dielectric constant (10). b) Assignment of A and B arbitrary, for determination of *dr*, see Experimental.)

Entry	Solvent	ε^a	Catalyst -	mol%	Isolated Yield	*dr* (A:B)[b]
1	CH_2Cl_2	8.93	-/-		40%	1:2.0
2			pyridine	104	51%	2.3:1
3	THF	7.52	-/-		23%	3.0:1
4			pyridine	100	68%	3.45:1
5	EtOAc	6.08	-/-		51%	1.2:1
6			pyridine	102	31%	3.5:1
7	$CHCl_3$	4.81	-/-		53%	1:3.29
8			pyridine	110	59%	2.7:1
9	iPr_2O	3.81	-/-		17%	1.42:1
10			pyridine	97	42%	5.7:1
11	Et_2O	4.27	-/-		23%	1:1.3
12			pyridine	102	65%	4.9:1

reaction was strongly influenced by the type of solvent used, as large variations in *dr* were observed. In the case of THF, the diastereoselectivity of the reaction was reversed when compared to dichloromethane. However, as can be seen in Figure 3, these changes in diastereoselectivity are not the result of the change in the solvent-polarity (as given by its dielectric constant *?*) alone.

In the pyridine-promoted reaction (100 mol%), only little change in *dr* was observed, which may be a result of the faster reaction in the presence of pyridine, leaving little solvent influence. As a general trend, in the presence of pyridine, larger *dr* were seen in less polar solvents, however this is not the case for the reaction in the absence of pyridine.

The mechanism of the reaction is potentially very complicated and several distinct reaction pathways might contribute to the overall reaction as well as the specific solvent in which the reaction took place. It has to be clearly stated at this point that the results described here only represent the beginning of the mechanistic investigation. We have previously shown (9) that the presence of basic pyridine does not cause a change in diastereomeric ratio via post-reaction enolization and epimerzation of the chiral center in the ester side chain.



Scheme 2. Possible reaction pathways for stereodifferentiation of ester formation on *trans*-2-substituted cyclohexanols.

The most straightforward mechanistic scenario is the direct acylation of the hydroxyl group by racemic acyl chloride [**4**] via a standard tetrahedral intermediate and the subsequent removal of HCl. By necessity, the approach of the racemic [**4**] to the racemic cyclohexanol scaffold will lead to diastereomeric transition states and intermediates, which are different in their respective free energies. This, in turn, will lead to differences in stabilities and, hence, differences in reaction rates. Such a simplified scenario would also assume that the nearly non-polar solvent CH_2Cl_2 has no influence on the reaction and all mechanistic steps are "intrinsic."

In a mechanistic alternative, acylation could occur first at the heteroatom of the 2-substituent, especially in the case of soft and polarizable sulfur (Scheme 2). Intermediate **II** can itself react as an acylating reagent and react in intermolecular fashion with another *c*-hexanol molecule or it could undergo an intramolecular acyl-transfer to the adjacent hydroxyl group of **II**. In both cases, diastereomeric intermediates will favor different reaction pathways towards **A** and **B**.

The alternative reaction condition included pyridine, which will cause the reaction medium to be slightly basic. While not basic enough to cause complete deprotonation of alcohols, pyridine will generate some alkoxide as opposed to neutral alkanol. Alkoxide is a more potent nucleophile than neutral alkanol, especially the case of an almost non-polar environment where the solvation shell around the nucleophile is minimal and nucleophilicity parallels basicity. We found vastly higher reaction rates in all pyridine-catalyzed/promoted cases where the reaction at room temperature was nearly complete before an NMR sample could be prepared compared to pyridine-free experiments which required up to 24 hours for completion. It is also known that pyridine is an effective catalyst for the transfer of acyl groups to hydroxyl groups. The presence of pyridine during the acylation of alcohols with acetic anhydride for example causes the formation of acylpyridinium species, which are more powerful acylating reagents than acetic anhydride itself. An even better catalyst is DMAP (11) because of the dimethylamino-group's ability to stabilize the positive charge at the heterocyclic nitrogen after acylation. Therefore, it can be assumed that acylpyridinium species contribute to the esterification of the hydroxyl group in *c*-hexanol and lead to acceleration of the reaction rates. The additional influence on diastereoselectivity overall could potentially be a result of steric or stereoelectronic (dipole/p-stacking) effects and consequential rate differences in diastereoselective acyl transfer from the acylpyridinium species **III** (Scheme 2) to the chiral scaffold. The experimentally observed product distribution of approximately 70:30 in the most pronounced cases implied that catalyst/promoter-load, the solvent polarity, and the presence or absence of a heteroatom in the substituent at C2 played a significant role.

At this point, detailed computational studies have not been carried out and the absolute stereochemistry of the products has not been established. The diastereomers would have to

be separated, crystallized, and subjected to X-Ray diffraction. Efforts are currently underway in our laboratory to address these questions.

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