Kinetic resolution of *trans*-cycloalkane-1,2-diols *via* Steglich esterification†

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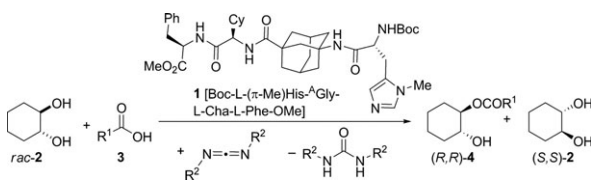
We describe the efficient and highly enantioselective kinetic resolution of *trans*-cycloalkane-1,2-diols utilizing an enantioselective Steglich reaction with a variety of carboxylic acids that form the corresponding anhydrides *in situ*.

Esterification is one of the key reactions that ubiquitously appear both in nature and in organic synthesis.[1] While biosynthetic ester formation generally proceeds through a mixed anhydride consisting of the transferred acyl function and ATP,[2] the chemist's often employed variant is the Steglich esterification using acids and carbodiimides in the presence of 4-dimethylaminopyridine (DMAP) as a nucleophilic catalyst.[3] This reaction is viewed as proceeding through an *O*-acyl isourea intermediate[4] that is converted into a symmetrical anhydride of the corresponding acid.[5] As we recently showed that *trans*-cycloalkane-1,2-diols (**2**)[6] can be kinetically resolved utilizing anhydrides and an oligopeptide catalyst (such as **1**, Scheme 1), we envisaged a Steglich-type protocol by using a variety of achiral carboxylic acids (**3**) for the resolution of *rac*-**2**. Using the acids instead of the anhydrides is a clear advantage when a particular anhydride cannot be prepared (as for, *e.g.*, formic acid, **3a**) or is generally not readily available (as for, *e.g.*, phenylacetic acid, **3g**).

There are many highly selective acylation protocols for alcohols,[7] yet, to the best of our knowledge, none that use carboxylic acids with carbodiimides, *i.e.*, an enantioselective Steglich esterification. On the other hand, there are only a few reports on the generation of anhydrides for the resolution of alcohols or acids[8] and the generalization of these protocols would expand the versatility of this important reaction.

Of a variety of simple, chiral, and highly lipophilic oligopeptides[9] bearing an *N*-π-methyl histidine catalytic moiety **1** has been shown to be very effective in catalyzing the kinetic resolution of **2**[6] and the desymmetrization of *cis*-1,2-diols[10] by enantioselective acylation using various anhydrides. The origin of the observed high enantioselectivities was proposed to arise from the preferential binding of one *trans*-1,2-diol enantiomer to the peptide catalyst in the rate-limiting stereodifferentiating step;[6] independent computations provided convincing evidence for this proposal.[11] These findings led us to re-examine the Steglich esterification protocol and its adaptation to an enantioselective version.

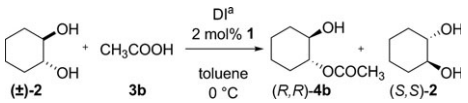


Scheme 1 The Steglich reaction catalyzed by nucleophilic catalyst **1**.

To probe this idea we first applied a modified Steglich protocol to the enantioselective kinetic resolution of (±)-**2** using nucleophilic oligopeptide **1** in place of DMAP of the original reaction. Indeed, the same high enantioselectivity levels of the present protocol as compared to reactions utilizing the pre-formed anhydrides[6] underscores the *in situ* anhydride formation and the high utility of this transformation.

We first optimized the conditions for the kinetic resolution of (±)-**2** using acetic acid and dialkylcarbodiimides in toluene with 2 mol% of **1** at 0 °C (Table 1). Nonpolar toluene has proven to be the best solvent for this transformation probably because of intermediate salt formation and tight ion pair association at the acylium ion stage required for stereoinduction; DCM can also be employed but gives a lower *S*-value for **4b**. The choice of carbodiimide is not critical but the highest enantioselectivity for the resolved diol was obtained with diisopropylcarbodiimide (DIC). Remarkably, a comparison of the acetylation of **2** with DMAP *vs.* **1** shows that our catalyst not only is much more active but also that diacylation,

Table 1 Kinetic resolution of *trans*-cyclohexane-1,2-diol (±)-**2** under various conditions; optimization studies



Molar ratio					*ee* (%)		
(±)-**2**	**3b**	**DI**[a]	*t*/h	C (%)[b]	(*R*,*R*)-**4b**	(*S*,*S*)-**2**	*S*[e]
1	1	DCC, 1.0	14	51	87	91	45
1	1	DIC, 1.0	14	54	83	97	44
1	1	EDC, 1.0	14	46	89	76	39
1	2	DIC, 1.2	10	55	81	>99	>50
1	2	DIC, 2.0	7	56	80	>99	>50
1	2	DIC, 1.2	8[c]	56	76	98	33
1	2	DIC, 1.2	24[d]	9	77	8	8

[a] DI = Diimide, equiv. given. [b] Conversion. [c] At r.t. [d] In DCM. [e] *S*-values (selectivity factors) determined by the method of Kagan and Fiaud.[12]

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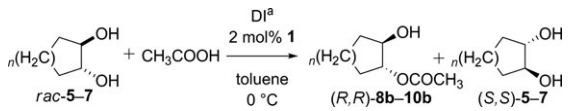
Table 2 Kinetic resolution of cyclic *trans*-1,2-diols



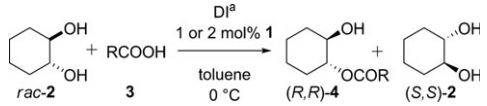
n	*t*/h	C (%)[b]	*ee* (%)		*S*[c]
1	10	76	**8b**, 32	**5** >99	11
3	16	55	**9b**, 82	**6** >99	>50
4	18	55	**10b**, 81	**7** >99	>50

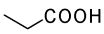
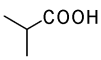
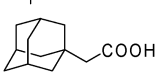
[a] DI = Diimide, here: DIC. [b] Conversion. [c] *S*-values (selectivity factors) determined by the method of Kagan and Fiaud.[12]

as observed to some extent in the reaction with DMAP, does *not* occur. The optimized conditions were applied to the kinetic resolution of other cyclic *trans*-1,2-diols (Table 2). The selectivities remained high in all cases and compare very well to the analogous reaction of the diols with the anhydrides, which can be rationalized on the basis of the uncatalyzed rapid anhydride formation.

The next step was the variation of the acid to probe the generality and utility of this esterification protocol (Table 3). Apart from electron-donor substituted benzoic acids, the present protocol is of broad utility. Phenylacetic acid (**3g**) was the most reactive, and the kinetic resolution was complete after only two hours, which is about five times faster than the acetylation.

Table 3 Kinetic resolution of *trans*-cyclohexane-1,2-diols (**2**) using various acids



Carboxylic acid				*ee* (%)		
		t/h	C (%)[b]	**4**	**2**	*S*[f]
3a	HCOOH	7	67[d]	41	83	6
3b	CH_3COOH	15	55	83	>99	>50
		15	(51, 39)[c]	82	98	45
3c		15	55	83	>99	>50
		41	(48, 43)[c]	90	98	>50
3d		24	54	85	>99	>50
		45	(55, 41)[c]	90	98	>50
3e		48	4[e]	86	4	14
3f		48	60[e]	57	85	9
3g	$PhCH_2COOH$	2	57	75	>99	>50
		2	(54, 41)[c]	82	>99	>50
3h	PhCOOH	48	38[e]	60	36	6
3i	*p*-Cl-PhCOOH	48	58[e]	60	84	10
3j	*p*-CH_3O-PhCOOH	48	n. d.[e]	n. d.	3	n. d.

[a] DI = Diimide, here: DIC. [b] Conversion determined by chiral GC. [c] Preparative reaction at 1 mmol scale with 1 mol% of **1**, isolated product yields of **2** and **4** in %. [d] Doubled solvent volume. [e] 2 equiv. of DIC used. [f] *S*-values (selectivity factors) determined by the method of Kagan and Fiaud.[12]

Sterically hindered acids (**3e**) and (**3f**) react more slowly; substituted benzoic acids generally react quite sluggishly, owing to the increased stability of the intermediate acylium ions. This is apparent from a comparison of the conversion times for **3h–j**. As found for the use of isobutyric anhydride,[13] isobutyric acid **3d** leads to the highest *ee* for **4**.

We have shown here that the much utilized Steglich esterification protocol can be readily adapted to the enantioselective acylation of 1,2-*trans*-cycloalkane diols utilizing a short peptide catalyst with a catalytically active His-moiety and a broad variety of carboxylic acids. The mechanistic details are currently being elucidated and will be recorded in full in due course. The adaptation of this strategy to monoalcohols and possibly other nucleophiles will require the development of other catalysts, for which the current platform is a highly promising starting point.

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