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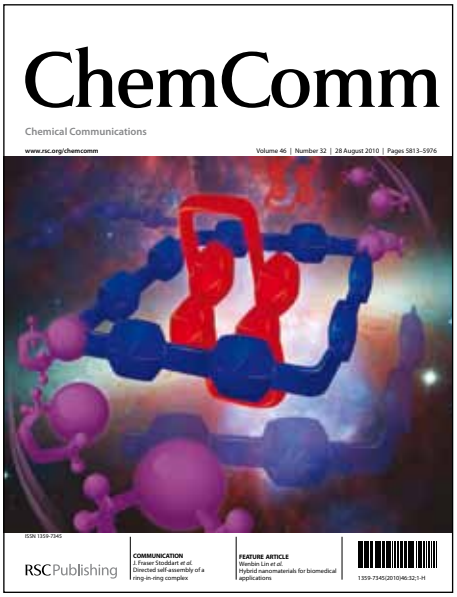

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En Route to Multicatalysis: Kinetic Resolution of *trans*-Cycloalkane-1,2-diols *via* Oxidative Esterification†‡

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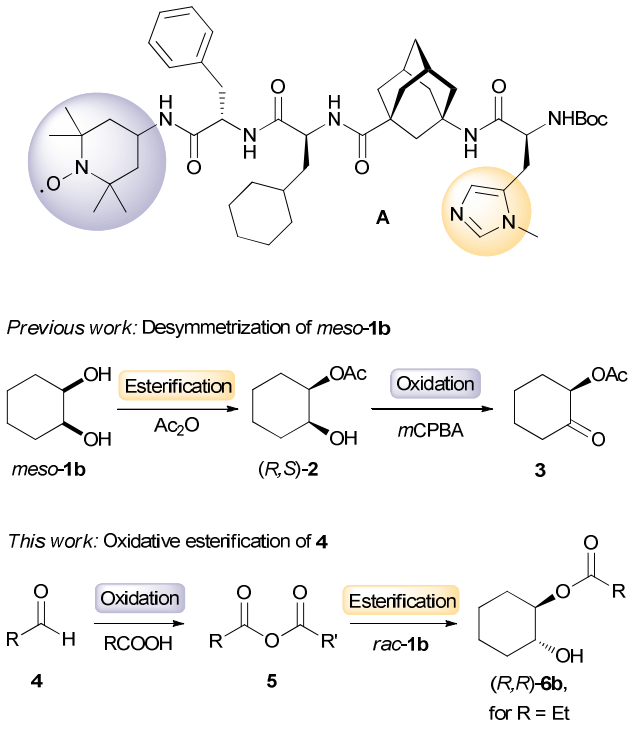
We demonstrate the application of a multicatalyst to the oxidation of a broad variety of aldehydes and subsequent enantioselective esterification of the incipient acids with (±)-*trans*-cycloalkane-1,2-diols. This reaction operates well with a multicatalyst bearing two independent catalytic moieties that provide monoprotected 1,2-diols in one pot.

Multicatalysts carry distinct catalytic moieties on a backbone that allows modular synthesis, for instance, an oligopeptide. The combination of several catalytic moieties gives rise to reactivity and operational simplicity not attainable with multiple single catalysts, and complex molecules can be prepared from simple starting materials with high efficiency.[1] An obvious challenge with this concept is the mutual compatibility of the catalytic moieties and the versatility as well as generality of a multicatalyst, for instance, in changing a particular reaction order. Based on the concept of *retrocatalysis*[1] we designed peptide catalyst **A** (**Scheme 1**) as a multicatalyst, and it has previously been applied as an efficient multicatalyst for the one-pot desymmetrization of *cis*-cycloalkane-1,2-diols (e.g., *meso*-**1b**) and oxidation of the configurationally unstable monoacetate (*R*,*S*)-**2**.[2] Therefore, we envisioned **A** also to be a promising catalyst for a reverse reaction sequence, for instance, the oxidation of aldehydes followed by an enantioselective esterification (**Scheme 1**).

One-pot oxidative esterifications of aldehydes have become a conceptually and economically attractive alternative to traditional ester synthesis.[3] Thus, there are several examples for oxidative esterifications of aldehydes activated by transition-metal catalysts[4] or *N*-heterocyclic carbenes.[5] Recently, Szpilman *et al.* reported an efficient TEMPO[6] (**B**) catalyzed oxidation of aldehydes activated with carboxylic acid **7e** (**Table 1**) to give mixed anhydrides that can be converted to esters *in situ*.[7] We envisaged redesigning this oxidative esterification protocol as an application for multicatalyst **A**. Before using **A** we first elaborated the single-step reactions with **B** and oligopeptide **C**[8] to determine the feasibility of the individual reactions and for optimization as well as comparison with existing procedures.



Scheme 1 Versatility of multicatalyst **A**

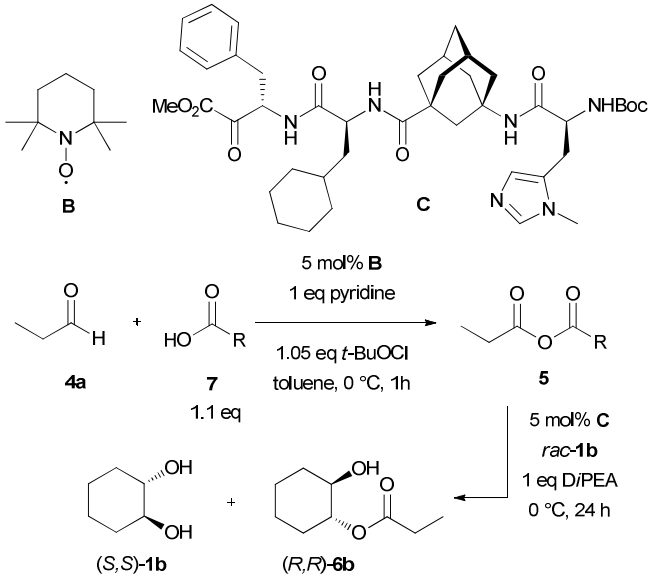
Recently, we have shown that oligopeptide catalysts[9] bearing an *N*-π-methyl histidine moiety (e.g., **C**) highly efficiently transfer acyl groups enantioselectively onto *trans*- and *cis*-cycloalkane-1,2-diols.[10] Peptide catalyst **C** also led to the first realization of an enantioselective Steglich esterification.[11] Using an aldehyde instead of the acid is advantageous because aldehydes are typically more soluble in organic solvents, easier to purify, more reactive and therefore a more practical intermediate in multistep syntheses.

We optimized the reaction conditions for the enantioselective oxidative esterification with propanal (**4a**) and tested various acids (**7a**□**f**) as activators for **4a** (**Table 1**). Toluene has proven to be the

best solvent for the kinetic resolution of diols with **C** and we used it therefore also for the oxidation step.[8] Complete conversion of **4** was achieved using a stoichiometric amount of pyridine, 1.1 equiv. 4-nitrobenzoic acid, 5 mol% **B** and 1.05 equiv. of the oxidant, *t*-BuOCl, at a concentration of 1 M in toluene after 1 h. An excess of pyridine or catalytic amounts of the acid accelerated the background reaction and resulted in lower enantioselectivities. The esterification requires relatively high dilution[8, 12] (0.005 M) to achieve high enantioselectivities for **1b** and **6b**.

Under optimized reaction conditions **7a** and **7b** provided the highest conversions of *rac*-**1b** within 24 h. The best enantioselectivities were achieved with acid **7a**. Acids **7e** and **7f** with higher pK_a values[13] showed lower conversion. To identify the ratios of the mixed and symmetric anhydrides of **4a** and **7a** formed during the reaction NMR studies were undertaken.[14] The anhydrides formed in a ratio of approximately 3:1:1 of mixed anhydride relative to the symmetric anhydrides of **4a** and **7a**. Further investigations are necessary to determine which of the formed anhydrides is faster transferred onto the acylation moiety.

Table 1 Screening of various acids (**7a**–**f**) under optimized reaction conditions



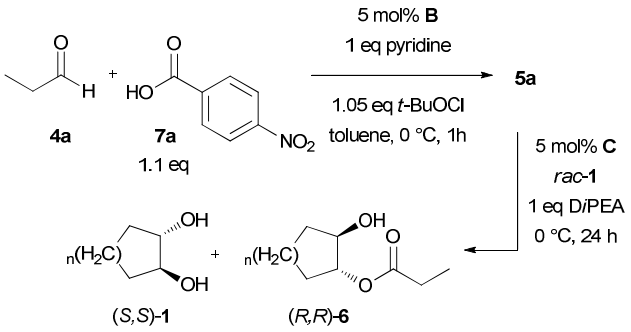
R		C[a] /%	*ee* /%		*S*[b]
			1	**6**	
7a	*p*- $NO_2C_6H_4$	49	81	86	33
7b	2-CH_3-6-$NO_2C_6H_3$	38	48	78	13
7c	2,4,6-$(Cl)_3C_6H_2$	28	29	73	9
7d	2,4,6-$(CH_3)_3C_6H_2$	27	28	78	11
7e	$C(CH_3)_3$	23	27	90	25
7f	1-adamantyl	12	12	92	27

[a] Conversion of *rac*-**1b** determined by chiral GC after 24 h reaction time for esterification, 0.1 mmol **4a**. [b] *S* = selectivity factors.[15]

To expand the substrate scope we tested various *trans*-cycloalkane-1,2-diols **1** in the kinetic resolution with 1 equiv. acyl source affording the corresponding hydroxy ester with high enantioselectivities and good yields (**Table 2**). The selectivities depend on the ring size of the substrate, with *trans*-cyclooctane-1,2-diol (**1d**) showing the highest and *trans*-cyclopentane-1,2-diol (**1a**) the lowest selectivity.[8]

Various aldehydes were employed to probe the generality and utility of this oxidative esterification protocol. To determine the time for full conversion of the aldehyde, we followed the conversion by NMR (see Supporting Information for details). Owing to the low solubility of **7a** in the reaction mixture, we used **7c** for the NMR investigations, assuming that the time for full conversion of **4** with **7c** and **7a** are similar (**Table 1**). Sterically hindered aldehydes require longer reaction times: For **4a** the oxidation completes in 1 h, while isopentanal (**4c**) required 9 h and isobutanal (**4d**) 18 h. Aromatic aldehydes proved to be more reactive than aliphatic ones. However, benzaldehyde showed insufficient conversion under these conditions; this is due to the increased stability of the anhydride intermediate that we had prepared separately and which does not react under our standard conditions.

Table 2 Kinetic resolution of *trans*-cycloalkane-1,2-diols **1a**–**1d**

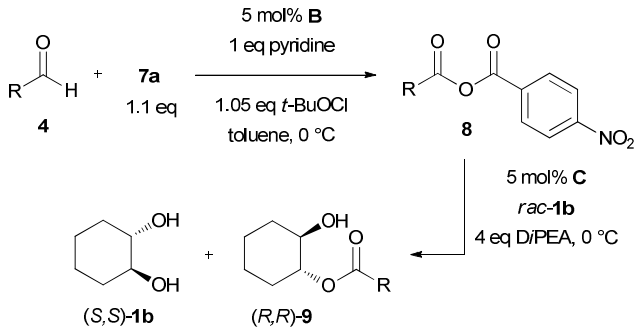


Diol	n	C[a] (Yield **1**, **6**) /%	*ee* /%		*S*[b]
			1	**6**	
1a	1	70 (n.d., n.d.)	76	31	4
1b	2	47 (46, 43)	81	88	39
1c	3	49 (48, 43)	86	88	43
1d	4	50 (39, 47)	94	93	> 50

[a] Conversion determined by chiral GC and HPLC, 1.0 mmol **4a**.
[b] *S* = selectivity factors[15], n.d. = not determined.

After having determined the time for full conversion, aromatic and aliphatic aldehydes were oxidized to their corresponding mixed anhydrides and tested in the kinetic resolution of *rac*-**1b**. Aldehydes **4b**–**d**, **g**, **h** afforded high enantioselectivities and good yields. Cyclohexanal **4e** gave lower selectivities while pivaldehyde (**4f**) showed insufficient conversion due to the increased steric hindrance.

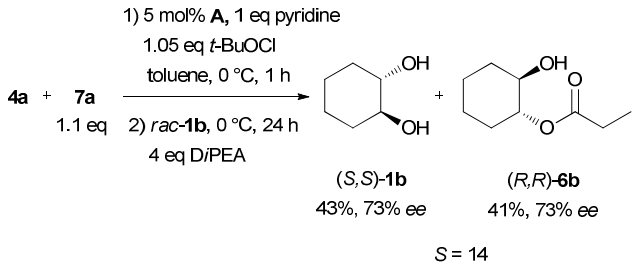
Table 3 Enantioselective oxidative esterification of *rac*-**1b** using various aldehydes **4b**–**i**



Aldehyde		t/h[a]	C[b] (Yield **1b**, **9**) /%	*ee* /% **1b**	**8**	*S*[c]
4b	Decanal	1/24	47 (48, 42)	79	88	38
4c	Isopentanal	9/24	48 (43, 46)	76	82	24
4d	Isobutanal	18/6[d]	44 (43, 40)	72	90	40
4e	Cyclohexanal	18/18[d]	46 (37, 35)	52	62	7
4f	Pivaldehyde	24/48[d]	4 (n.d.,n.d.)	4	92	25
4g	$Ph(CH_2)_2CHO$	0.5/6[d,e]	50 (44, 44)	85	82	27
4h	$PhCH_2CHO$	0.5/6[d,e]	35 (58, 27)	50	93	47
4i	PhCHO	18/48[d,e]	7 (n.d.,n.d.)	6	78	9

[a] Reaction time for oxidation and esterification. [b] Conversion determined by chiral GC and HPLC, 1.0 mmol **4**. [c] *S* = selectivity factors.[15] [d] 2 equiv. of generated anhydride. [e] Concentration for oxidation was 0.1 M. n.d. = not determined.

With these promising results at hand, our attention turned to the multicatalyst approach. We used 5 mol% of multicatalyst **A** instead of *individual* catalysts **B** and **C** and applied it to the enantioselective oxidative esterification of **4a** (**Scheme 2**). To keep the catalyst deprotonated at all times it is necessary to use an excess (4 equiv.) of D*i*PEA for the esterification step. We obtained 43% of **1b** and 41% of **6b** with good enantioselectivities (73% *ee*, for both **1b** and **6b**, respectively; *S* = 14) with **A**. Thus, the enantioselectivities as compared to the individual catalysts **B** and **C** are only slightly lower, and we consider this a proof-of-principle for our multicatalyst concept.



Scheme 2 Kinetic resolution of *rac*-**1b** with multicatalyst **A**

We have shown that a variety of aldehydes can be activated by 4-nitrobenzoic acid and oxidized with TEMPO to furnish mixed anhydrides that can be enantioselectively transferred onto *trans*-cycloalkane-1,2-diols with good yields and enantioselectivities with catalyst **C**. The protocol with individual catalysts can be unified with multicatalyst **A**[2] that was designed utilizing the *retrocatalysis* concept,[1] with only slightly reduced enantioselectivities. A natural extension of this work would be the use of alcohols as the starting materials as this would constitute direct alcohol cross-coupling.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and spectra. See DOI: 10.1039/c000000x

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