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Inversion of enantioselectivity in quinine-mediated desymmetrization of glutaric *meso*-anhydrides

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ABSTRACT

An unexpected inversion of enantioselectivity, dependent on the degree of quinine loading, was observed during the desymmetrization of glutaric *meso*-anhydrides. Decrease in catalyst loading from 1.6 equiv to 0.1 equiv caused a clear inversion of stereochemistry—from about 40% ee of (*R*)-configuration to about 40% ee of the opposite enantiomer. The effect of various carboxylic acid additives was also studied.

1. Introduction

Desymmetrization of *meso* compounds has proven to be a valuable approach in the synthesis of chiral compounds.[1] The first catalytic ring-opening of cyclic anhydrides was reported by Oda[2] and shortly thereafter by Aitken;[3] methanol was used as a nucleophile in the presence of 10 mol % of a cinchona alkaloid. Oda examined the opening of glutaric and succinic anhydrides and observed that stereochemistry and enantioselectivity are highly dependent on a specific substrate/alkaloid combination. Aitken noticed that, in the case of complex epoxy-anhydride, an increase in the catalyst loading from 10 to 50 mol % increases the enantioselectivity from 38% to 76%. Finally, Bolm and co-workers developed a highly enantioselective protocol for the desymmetrization of *meso*-anhydrides promoted by a stoichiometric amount of quinine or quinidine.[4] A variety of succinic anhydrides were tested and it was observed, without exception, that quinine catalyzes nucleophilic attack of the *pro*-(*R*) carbonyl group while quinidine always exhibited the opposite selectivity.[5] In parallel, Deng developed an excellent method based on a catalytic amount of commercially available modified cinchona alkaloid.[6] Very recently, a new generation of cinchona-based thiourea catalysts have been developed.[7] However, while modified cinchona catalysts provide outstanding results with succinic anhydrides, the same catalyst loading gives inferior results when applied to glutaric anhydrides,[6] which are more demanding substrates. Thus, in the case of glutaric anhydrides, especially when larger quantities of products are needed, the use of a stoichiometric quantity of easily available, inexpensive and recoverable unmodified alkaloid is still the best choice. During our recent work on pregabalin synthesis[8] where quinine-mediated ring-opening of 3-isobutylglutaric anhydride was the key step, we noticed an unexpected inversion of enantioselectivity, which was dependent on the catalyst loading. Herein, we elaborate upon those results.

2. Results and discussion

When we initiated the synthesis of pregabalin **3** there were only a few reported enantioselective catalytic desymmetrizations of 3-substituted glutaric anhydrides. Seebach[9] reported opening of anhydride **6** catalyzed with Ti-TADDOLate with 50% ee, Oda[2] reported the opening of **4** and **5** with natural cinchona alkaloids with 5–33% ee, and Deng[6] of **4** and **6** in combination with modified cinchona alkaloids with 82–91% ee. Moreover, to achieve 82–83% ee of products possessing an (*R*)-configuration, 0.3 equiv of bulky, expensive $(DHQ)_2AQN$ was required. Therefore, although this was not verified on glutaric anhydrides, we decided to apply Bolm's methodology.[4] Preliminary experiments revealed that hemi-ester **2** with an (*R*)-configuration could be obtained using stoichiometric quantities of quinine, benzyl or cinnamyl alcohols as nucleophiles at −25 °C with 65–70% ee. (Scheme 1). However, Oda reported the (*S*)-configuration in the quinine-mediated opening of **4** and **5** with low enantioselectivity (7%). We initially assigned the discrepancy in stereochemistry to high nucleophile loading (MeOH, 10 equiv) and reaction conditions (room temperature). From Oda's, Aitken's and Bolm's studies on succinic anhydrides it can be concluded that a free alkaloid base is responsible for the stereoselection, whilst protonated base (product–base complex), still catalytically active, produces mainly racemates. Indeed, when *cis*-1,2-cyclohexane dicarboxylic acid anhydride **7** was subjected to a quinine-mediated desymmetrization with benzyl alcohol, the enantioselectivity dropped from 75% to 3% ee when the catalyst loading was reduced from 1.6 equiv to 0.1 equiv (Fig. 1).

In contrast, 3-substituted glutaric anhydrides showed a different behaviour (Fig. 2). Decreasing the quinine loading caused a clear inversion of stereochemistry—from about 40% ee of (*R*)-configuration to about 40% ee of the opposite one. As we reported ear-

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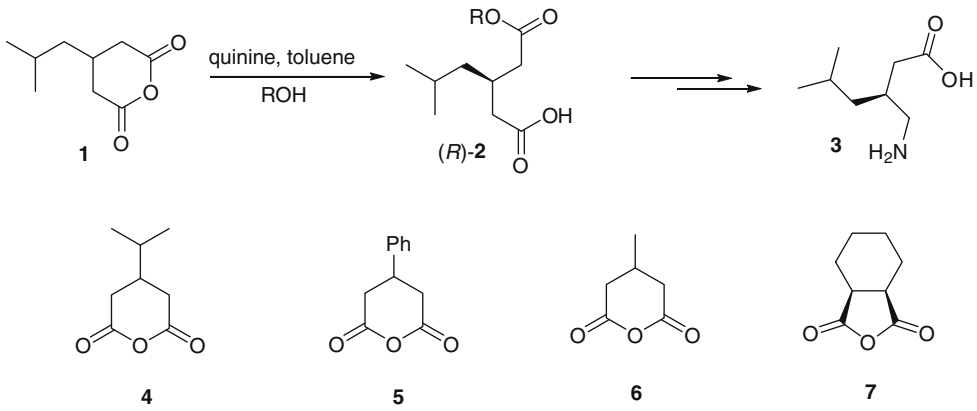


Scheme 1.

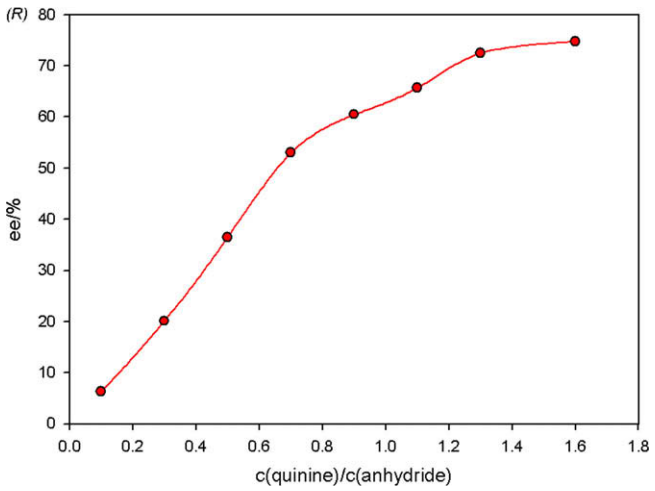


Figure 1. Influence of quinine loading on the desymmetrization of *cis*-1,2-cyclohexane dicarboxylic acid anhydride **7**. Conditions: constant anhydride concentration (100 mg scale, 0.05 M in toluene), 0.1–1.6 equiv of quinine, 1.5 equiv of benzyl alcohol, rt, 20 h.

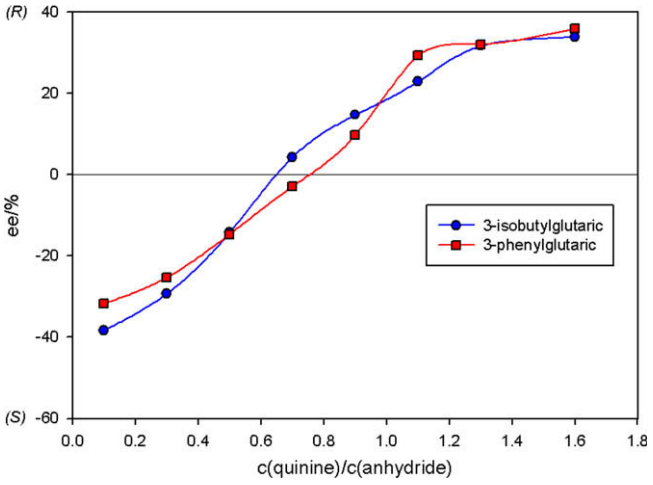
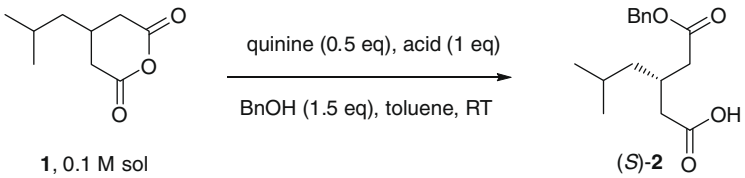


Figure 2. Influence of quinine loading on the desymmetrization of 3-substituted glutaric anhydrides **1** and **5**. Conditions: constant anhydride concentration (100 mg scale, 0.05 M in toluene), 0.1–1.6 equiv of quinine, 1.5 equiv of benzyl alcohol, rt, 20 h.

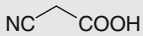
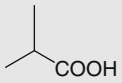
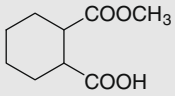
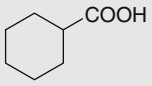
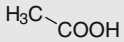
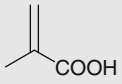
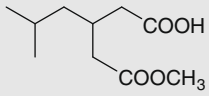
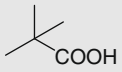
lier,[8] the enantioselectivity of the reaction can significantly be improved upon by lowering the reaction temperature when the alkaloid is employed in stoichiometric quantities. In the case of low catalyst loading, lowering the temperature causes a minor improvement in enantioselectivity, but a drastic reduction in the reaction rate. To verify whether a specific product–base complex or the geometry of anhydride itself was responsible for the inversion of stereochemistry, various aliphatic acids were tested as additives in the opening of **1** (Scheme 2). The results, summarized in Table 1, clearly show that the pK_a of the acid has a major influence on the stereoselectivity of the reaction, while the influence of the acid structure is almost negligible. For example, cyclohexane-1,2-dicarboxylic acid monomethyl ester **11**, a product of anhydride **7** opening, has the same effect on enantioselectivity as acetic acid **12**.

In addition, the influence of aromatic acids as additives was also studied (Table 2). Although the influence of the pK_a is observed (acids **26** and **27**) their structure seems to be of greater importance. The best enantioselectivities were achieved with acids **24**, **25**, **33**, **34** and **36** possessing a phenylacetic acid substructure and also with 2-thiophene-acetic acid **35**, which can be considered as phenylacetic acid congener. Obviously, π–π interactions between the aromatic ring of the acid additive and the quinoline moiety can additionally stabilize the catalyst conformation in a manner



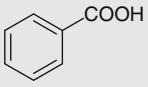
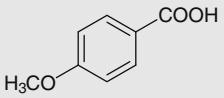
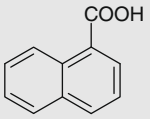
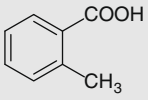
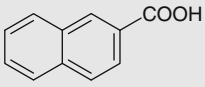
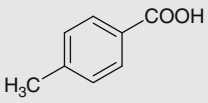
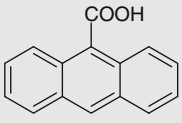
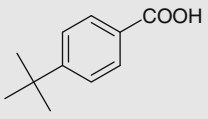
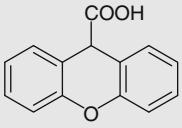
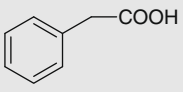
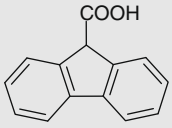
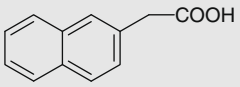
Scheme 2.

Table 1
Influence of aliphatic acid additive on the desymmetrization of 3-isobutylglutaric anhydride **1**

	Acid	pK_a[10]	ee[a] (%)		Acid	pK_a[10]	ee[a] (%)
8		0.52	Rac	**14**	$CH_3(CH_2)_6COOH$	4.89	42
9		2.45	27	**15**	$CH_3(CH_2)_{10}COOH$		43
10	HCOOH	3.75	29	**16**		4.84	43
11			35	**17**		4.90	45
12		4.76	36	**18**			45
13			40	**19**		5.03	47

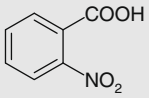
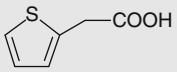
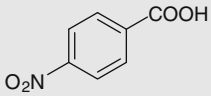
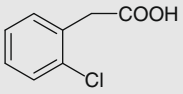
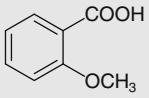
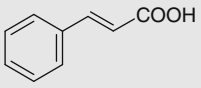
[a] Determined by chiral HPLC on Chiralcel AS (EtOH/hexane/TFA = 2/98/0.1).

Table 2
Influence of aromatic acid additive on the desymmetrization of 3-isobutylglutaric anhydride (**1**)

	Acid	pK_a[10]	ee[a] (%)		Acid	pK_a[10]	ee[a] (%)
20		4.19	47	**29**		4.5	42
21		3.70	37	**30**		3.91	45
22		4.17	38	**31**			45
23			15	**32**		4.38	50
24			63	**33**		4.31	54
25			53	**34**			48

(*continued on next page*)

Table 2 (*continued*)

	Acid	pK_a[10]	ee[a] (%)		Acid	pK_a[10]	ee[a] (%)
26		2.16	21	**35**			55
27		3.41	17	**36**		4.07	50
28		4.08	36	**37**		4.44	45

[a] Determined by chiral HPLC on Chiralcel AS (EtOH/hexane/TFA = 2/98/0.1).

dependent upon the steric interactions of acid and base in the complex. The inversion of enantioselectivity caused by carboxylic acid additives was also observed in Pd- or Pt-cinchona-catalyzed hydrogenations and was explained by a change in the reaction mechanism.[11] Hydrogen-bonding interactions and the conformational behaviour of cinchonidine were studied both theoretically and experimentally (NMR).[12] It was found that the population density of the Open(3) conformer, which is already the most populated one at room temperature in apolar solvents, was significantly increased by the addition of 2-methyl-2-hexenoic acid. However, this observation cannot explain the inversion of enantioselectivity in the desymmetrization of 3-substituted glutaric anhydrides, which obviously also involves a switch of reaction mechanism. On the other hand, neither of the two proposed possible mechanisms of amine-catalyzed alcoholytic opening of *meso* cyclic anhydrides, general base catalysis or nucleophilic catalysis,[13] can give a full explanation; anhydride shape should also be taken into account.

3. Conclusion

The observed inversion of enantioselectivity in the quinine-mediated desymmetrization of 3-substituted glutaric *meso*-anhydrides, in a manner dependent on catalyst loading, seems to be specific to these anhydrides. The study of carboxylic acid additives revealed that enantioselectivity can be increased to >60% ee of (*S*)-product—a level which might be of synthetic interest. This finding may also contribute to a better understanding of the mechanism of the cinchona-catalyzed desymmetrizations of cyclic anhydrides.

Acknowledgement

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