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Catalytic Enantioselective Desymmetrization of *meso*-Glutaric Anhydrides Using a Stable Ni_2-Schiff Base Catalyst

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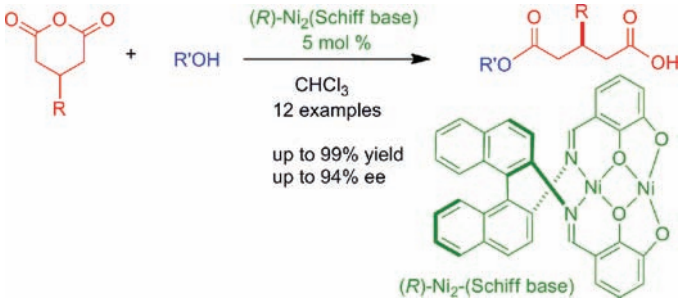
ABSTRACT



We describe the desymmetrization of *meso*-glutaric anhydrides to chiral hemiesters using a bench-stable homodinuclear Ni_2-(Schiff base) complex as the catalyst in good to excellent yield (up to 99%) and enantioselectivity (up to 94%). Using the opposite enantiomer of the catalyst, we obtained the same yield and enantioselectivity with the opposite configuration, thereby gaining access to both hemiester enantiomers.

Stereoselective catalytic desymmetrization of *meso*-anhydrides is a versatile tool in organic synthesis for the construction of many bioactive scaffolds[1] and provides direct access to chiral compounds containing two chemically different carbonyl groups. Of particular importance is the desymmetrization of *meso*-glutaric anhydrides, as the resultant hemiesters are key intermediates in many pharmacologically important molecules (Figure 1).[2] In our pursuit of an enantioselective total synthesis of caprazamycin B, we envisioned desymmetrization of 3-methyl glutaric anhydride as a key transformation.

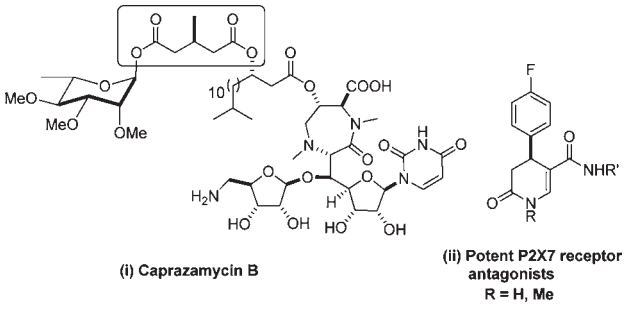


Figure 1. Structures of pharmacologically important compounds.

Although there are a number of methods for the enantioselective ring opening of *meso*-cyclic succinic anhydrides[3] (mostly using cinchona alkaloid-derived catalysts),

(1) For reviews on desymmetrization of *meso*-anhydrides, see: (a) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131. (b) Willis, M. C. *J. Chem. Soc., Perkins Trans. 1* **1999**, 1765. (c) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327. (d) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683.

(2) (a) Igarashi, M.; Nakagawa, N.; Doi, N.; Hattori, S.; Naganawa, H.; Hamada, M. *J. Antibiot.* **2003**, *56*, 580. (b) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 569. (c) Jacob, B. U.S. Pat. Appl. Publ. 20100160384, 2010.

(3) (a) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7872. (b) Youk, S. H.; Oh, S. H.; Rho, H. S.; Lee, J. E.; Lee, J. W.; Song, C. E. *Chem. Commun.* **2009**, 2220. (c) Manzano, R.; Andrés, J. M.; Muruzábal, M.-D.; Pedrosa, R. *J. Org. Chem.* **2010**, *75*, 5417. (d) Wang, S.-X.; Chen F,-E. *Adv. Synth. Catal.* **2009**, *351*, 547. (e) Schmitt, E.; Schiffers, I.; Bolm, C. *Tetrahedron* **2010**, *66*, 6349.

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desymmetrization with *meso*-glutaric anhydrides as substrates using the same catalysts results in lower enantioselectivity.

Recently, Song et al. reported enantioselective alcoholysis of *meso*-glutaric anhydrides using a cinchona-based sulfonamide catalyst.[4] Although this synthetic method affords chiral hemiesters with good enantioselectivity, substrates having bulky 3-substituents such as OTBDPS, OTBDMS, and *i*-Bu are generally used, and there is only one example for a simple methyl-substituted glutaric anhydride. Moreover, quinine and quinidine (pseudoenantiomer of quinine)-derived cinchona organocatalysts do not have similar reactivity and enantioselectivity in the desymmetrization reactions.[5] Given the importance of these hemiesters, however, a practical and more convenient method for providing access to both enantiomers just by changing the absolute configuration of the catalyst is desirable.

Initial screening of various metal catalysts (Figure 2)[6] developed by our group for the methanolysis of 3-methyl glutaric anhydride led us to select homodinuclear (*R*)-Ni_2-(Schiff base) complex (III)[6d−f] as a promising catalyst for this reaction (Scheme 1).

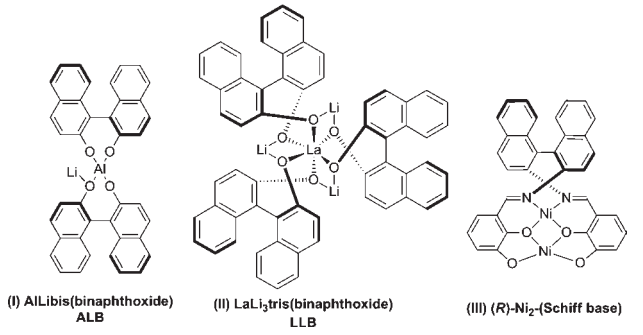
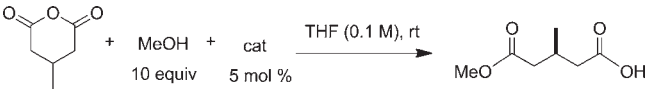


Figure 2. Structures of various metal catalysts.

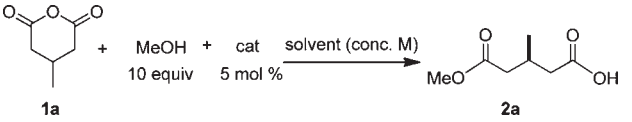
Once we determined the catalyst system, we then screened various solvents for the desymmetrization reaction using 3-methyl glutaric anhydride and methanol as the substrate. In general, the reaction gave slightly better enantioselectivity and yield with halogenated solvents such as $CHCl_3$ and CH_2Cl_2 (Table 1, entries 5 and 6). The reaction also gave almost similar enantioselectivity when using 1,4-dioxane and THF as solvents (Table 1, entries 1 and 2).

Scheme 1. Catalyst Screening



cat = (*R*)-ALB, 12 h, 95% yield, racemic
(*R*)-LLB, 4 h, 48% yield, racemic
(*R*)-Ni_2-(Sciff base), 18 h, 88% yield, 85% ee

Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	solvent	conc. (M)	temp	time (h)	yield (%)[b]	ee (%)[c]
1	THF	0.1	rt	18	88	85
2	1,4-dioxane	0.1	rt	18	93	85
3	EtOAc	0.1	rt	18	82	85
4	acetone	0.1	rt	18	80	84
5	$CHCl_3$	0.1	rt	18	95	86
6	CH_2Cl_2	0.1	rt	18	95	85
7	toluene	0.1	rt	18	95	70
8	MTBE	0.1	rt	18	95	80
9	Et_2O	0.1	rt	18	93	79
10	$CHCl_3$	0.1	0 °C	24	88	90
11	$CHCl_3$	0.1	-20 °C	20	86	94
12	$CHCl_3$	0.1	-20 °C	40	90	94
13	$CHCl_3$	0.5	-20 °C	15	94	94
14	$CHCl_3$	0.5	-20 °C	20	94	94

[a] The reaction was performed using 0.2 mmol of **1a** and catalyst III. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] ee was determined by chiral HPLC analysis (see Supporting Information).

On the other hand, use of toluene, MTBE, and diethyl ether (entries 7, 8, and 9) as solvents afforded lower enantioselectivity but good yield.

In the next step, using $CHCl_3$ as the solvent, we studied the effect of reaction temperature and concentration. Decreasing the reaction temperature from room temperature to −20 °C led to an increase in the enantioselectivity to 94%, which is the best enantioselectivity reported to date for 3-methyl glutaric anhydride as the substrate (Table 1, entries 10 and 11) in non-enzymatic reactions. Also, increasing the concentration from 0.1 to 0.5 M reduced the reaction time in contrast to many urea- and thiourea-based organocatalysts as they generally require higher dilutions

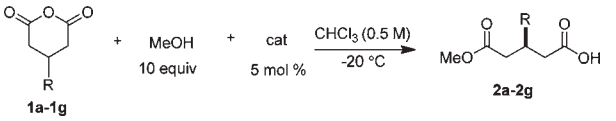
(4) Park, S. E.; Nam, E. H.; Jang, H. B.; Oh, J. S.; Some, S.; Lee, Y. S.; Song, C. E. *Adv. Synth. Catal.* **2010**, *352*, 2211.

(5) (a) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542. (b) Peschiulli, A.; Gun'ko, Y.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 2454. (c) Kim, H. S.; Song, Y.-M.; Choi, J. S.; Yang, J. W.; Han, H. *Tetrahedron* **2004**, *60*, 12051.

(6) (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. (b) Arai, T.; Sasai, H.; Aoe, K.-i.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104. (c) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117. (d) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (e) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255. (f) Xu, Y.; Lu, G.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3353.

to avoid hydrogen-bonding aggregates (Table 1, entries 13 and 14).[3a,3d,7] Further increases in concentration reduced the enantioselectivity.

Table 2. Desymmetrization of Various Anhydrides[a]



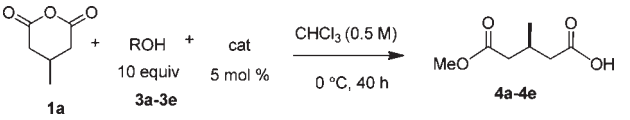
entry	anhydrides	product	time (h)	yield (%)[b]	ee (%)[c]
1	1a	2a	15	91	94
2	1b	2b	28	99	90
3	1c	2c	15	93	80
4	1d	2d	48	83	83
5	1e	2e	15	92	88
6	1f	2f	15	85	89
7[d]	1g	2g	24	86	75

[a] The reaction was performed using 0.2 mmol of anhydride and catalyst III. [b] Isolated yields. [c] ee was determined using chiral HPLC analysis (see Supporting Information). [d] 0.05 M $CHCl_3$ solution was used.

After successfully optimizing the reaction conditions, we attempted the desymmetrization of other anhydrides with methanol (10 equiv) and 5 mol % of the catalyst to show the generality of our methodology (Table 2). First, ethyl-substituted glutaric anhydride was subjected to the desymmetrization reaction, which gave the corresponding hemiester in almost quantitative yield with good enantioselectivity (Table 2, entry 2). Phenyl-substituted glutaric anhydride gave the resultant hemiester with slightly lower enantioselectivity (80% ee) in 93% isolated yield (Table 2, entry 3), whereas other aryl-substituted glutaric anhydrides (Table 2, entries 5 and 6) gave better enantioselectivity with good yield.

(7) Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. *Chem. Commun.* **2008**, 1208.

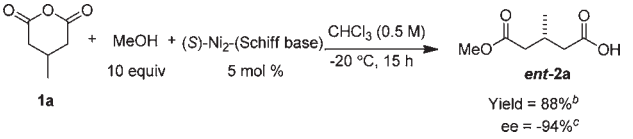
Table 3. Alcoholysis of 3-Methyl Glutaric Anhydride **1a**[a]



entry	alcohol	product	time (h)	yield (%)[b]	ee (%)[c]
1	EtOH 3a	4a	15	88	90
2	1-PrOH 3b	4b	15	90	92
3	BnOH 3c	4c	48	91	90
4[d]	BnOH 3c	4c	72	80	91
5	3d	4d	15	88	90
6	3e	4e	15	98	91

[a] The reaction was performed using 0.2 mmol of **1a** and catalyst III. [b] Isolated yields. [c] ee was determined by chiral HPLC analysis (see Supporting Information). [d] Reaction was performed at −20 °C for 72 h.

Scheme 2. Synthesis of the Opposite Enantiomer of Hemisester **2a**[a]



[a] The reaction was performed using 0.2 mmol of **1a**. [b] Isolated yields. [c] ee was determined by chiral HPLC analysis (see Supporting Information).

Of particular importance is the 4-fluorophenyl-substituted glutaric anhydride **1e**,[8] which is a potential synthetic precursor for the synthesis of potent P2X7 receptor antagonists.[2c] Given the importance of fluoro compounds in medicinal chemistry, we also attempted the desymmetrization of 3-trifluoromethyl-substituted glutaric anhydride. Only moderate enantioslectivity was observed (Table 2, entry 7), but this is notable as the first example of desymmetrization with 3-trifluoromethyl glutaric anhydride as the substrate.

We next attempted the desymmetrization reaction with various alcohols using anhydride **2a** as the substrate. The reaction was slow under the standard conditions

(8) Huang, X; Zhu, J; Broadbent, S. *Tetrahedron Lett.* **2010**, *51*, 1554.

($CHCl_3$, −20 °C; Table 2, entry 4); therefore, we performed the alcoholysis of 3-methyl glutaric anhydride at 0 °C. The reaction gave almost similar enantioselectivity at 0 °C and at −20 °C (Table 3, entries 3 and 4). In general, the enantioselectivity remained almost the same (90−92%) for most of the alcohols (Table 3). Propargyl alcohol derived hemiester **4e** was obtained in excellent yield (Table 3, entry 5).

Finally, to show the versatility of our reaction, we performed the desymmetrization reaction using the (*S*)-Ni_2-(Schiff base) complex (opposite enantiomer) as the catalyst. As expected, 3-methyl glutaric anhydride **1a** afforded an almost similar yield and the same enantioselectivity (Scheme 2, ***ent*-2a**). This widens the scope for access to both of the enantiomers of hemiesters and provides a major advantage over many of the previous methods.

In summary, we developed a practical and more convenient method for the desymmetrization of 3-substituted glutaric anhydrides using a bench-stable and commercially available Ni_2-(Schiff base) complex[9] as the catalayst. Other advantages include easy access to both hemiester enantiomer of using the corresponding Ni_2-(Schiff base) complex as the catalyst. Moreover, the hemiesters can be isolated in good purity using simple workup procedures without column chromatographic purification (see Supporting Information). Studies of the desymmetrization of anhydrides using other nucleophiles are underway.

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Note Added after ASAP Publication. In the version published ASAP on February 16, 2012 the toc/abstract graphic and Figure 2 contained an error. The corrected version was reposted on February 21, 2012.

Supporting Information Available. Characterization of new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) Purchased from Wako Pure Chemical Co. Ltd., Osaka, Japan.

The authors declare no competing financial interest.