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Facile Synthesis of Versatile Enantioenriched α-Substituted Hydroxy Esters through a Brønsted Acid Catalyzed Kinetic Resolution

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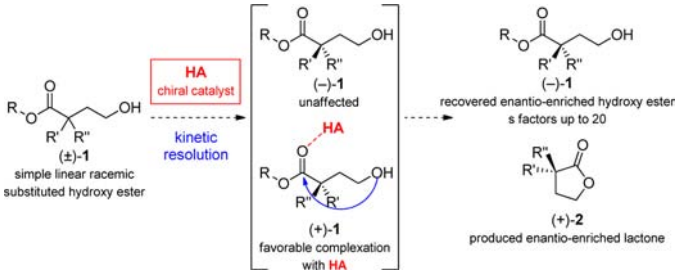
ABSTRACT



An efficient synthesis of enantioenriched α-substituted γ-hydroxy esters via a kinetic resolution event is described. Bulky racemic esters in the presence of a chiral Brønsted acid selectively lactonize to yield a recoverable enantioenriched hydroxy ester and lactone. These esters are highly versatile building blocks that can readily be converted to synthetically useful materials.

Enantioenriched α-substituted γ-hydroxy esters such as (−)-**1** are versatile molecules with two distinct functional group handles for further manipulation. Previous syntheses of these molecules are nearly nonexistent, likely due to the propensity of nonbulky esters to lactonize or epimerize. Select examples include a hydroboration/oxidation of an α-substituted allylic ester prepared by an asymmetric Cu-catalyzed S_N2'-addition[1] and an organocatalyzed Friedel–Crafts alkylation of an α,β-unsaturated ester/aldehyde followed by reduction.[2] Stabilization of these versatile building blocks through the use of a bulky ester and a facile enantioselective synthesis would likely lead to the widespread use of these molecules in the preparation of important biological molecules including natural products or drug candidates.

Enzyme catalyzed enantioselective transesterifications are attractive reactions.[3] However, primary alcohols are often particularly problematic in the process. Our strategy for the preparation of enantioenriched primary alcohol containing building blocks such as (−)-**1** takes advantage of the different rates of intramolecular tranesterification of the enantiomers of (±)-**1** in the presence of a chiral Brønsted acid catalyst (Scheme 1). By using bulky esters we reduce the inherent instability of the substrates so that lactonization is slowed and will only occur in the presence of a strongly activating acid catalyst. The two enantiomers can then be separated via the selective lactonization of one of the enantiomers over the other. This kinetic resolution leads to a generalized and scalable process for the preparation of stable enantioenriched hydroxy ester building blocks.

The use of chiral Brønsted acids is a rapidly growing field of organocatalysis.[4] In the proposed lactonization reaction, we envisioned that the chiral acid would serve to activate substrates through either a hydrogen bonding

(1) den Hartog, T.; Maciá, B.; Minnard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2010**, 999–1013.

(2) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371.

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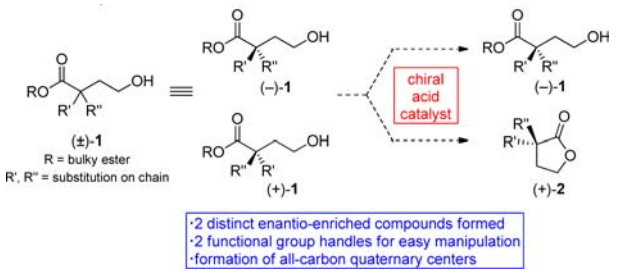
Scheme 1. Kinetic Resolution of Hydroxy Ester with Chiral Acid Catalyst



event or full Brønsted acid catalysis (through coordination to the carbonyl and/or the alcohol). Typical catalysts are based on thiourea, TADDOL, or BINOL (Figure 1) and have been used in a variety of enantioselective transformations.[5] In particular, there have been several recent examples using chiral phosphoric acids in kinetic resolution processes.[6]

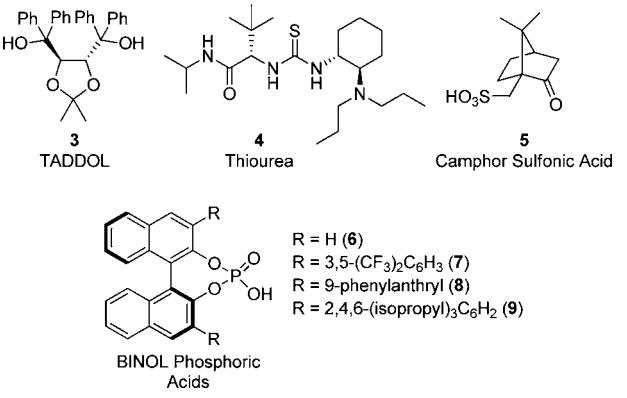
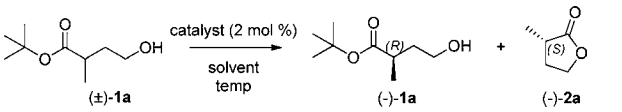


Figure 1. Chiral hydrogen bonding catalysts.

Initial optimization of the process focused on α-methyl hydroxy *tert*-butyl ester (±)-**1a** (Table 1). Hydroxy ester (±)-**1a** was cooled to 5 °C in dichloromethane and treated with a variety of chiral hydrogen bonding acid catalysts, monitoring lactonization by gas chromatography. TADDOL (**3**) and thiourea based acids **4** (Table 1, entries 1 and 2) were not effective at catalyzing the lactonization of hydroxy ester (±)-**1a**. Camphor sulfonic acid (**5**) and unsubstituted BINOL phosphoric acid **6** were both capable of inducing lactonization; however, they did not produce either lactone **2a** or recovered hydroxy ester **1a** with any enantioenrichment (Table 1, entries 3 and 4).

Table 1. Initial Optimization[a]



entry	catalyst	solvent	temp (°C)	time (h)	% conv	ee%, **1a**	ee%, **2a**	*s*
1	**3**	CH_2Cl_2	5	6	3	0	0	n/a
2	**4**	CH_2Cl_2	5	12	1	0	n/a	n/a
3	**5**	CH_2Cl_2	5	6	18	0	0	n/a
4	**6**	CH_2Cl_2	5	19	75	0	0	n/a
5	**7**	CH_2Cl_2	5	24	71	17	32	1
6	**8**	CH_2Cl_2	5	24	23	8	29	4
7	**9**	CH_2Cl_2	5	24	40	58	31	25
8	**9**[b]	CH_2Cl_2	5	24	42	57	68	15
9	**9**	toluene	5	24	41	64	41	19
10	**9**	THF	5	48	2	0	n/a	n/a
11	**9**	Et_2O	5	48	2	0	10	n/a
12	**9**	hexanes	5	48	47	39	45	4
13	**9**	toluene	rt	4	50	73	68	14
14	**9**	toluene	−5	48	67	>98	32	15
15	**9**	toluene	−20	720	47	71	49	19

[a] Typical reaction conditions: 0.06 mmol of (±)-**1a**, 0.001 mmol of catalyst, in 10 mL of solvent at set temperature and time. Conversion and % ee's determined by GC analysis with a chiral support unless indicated otherwise. [b] Catalyst **9** washed with HCl before use.[7]

Gratifyingly, when 2,2′-aryl substituted BINOL-derived phosphoric acids were examined we began to see selectivity in the process (Table 1, entries 5−8), with the triisopropyl phenyl catalyst **9** being the most selective. At 40% conversion, lactone (−)-**2a** was found to have an ee of 68% and the recovered starting material (−)-**1a** had an ee of 57% giving a selectivity factor of 25.[8] Next, we performed a limited solvent screen. Predictably, nonpolar solvents such as toluene (Table 1, entry 9) and hexanes (Table 1, entry 12) performed at similar rates and selectivities to CH_2Cl_2, while polar aprotic solvents such as THF (Table 1, entry 10) and Et_2O (Table 1, entry 11) were ineffective, presumably due to interruption of hydrogen bonding between the catalyst and substrate. Varying the temperature of the reaction had little difference on the selectivity factor of the reaction; however, the reaction time was significantly affected (Table 1, entries 13−15). Using optimized conditions (Table 1, entries 7 and 9) we consistently were able to achieve selectivity factors of ∼20 and with test substrate **1a**.[9]

(5) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568. (b) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal, V. H. *Nature* **2003**, *424*, 146. (c) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902. (d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357. (e) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.

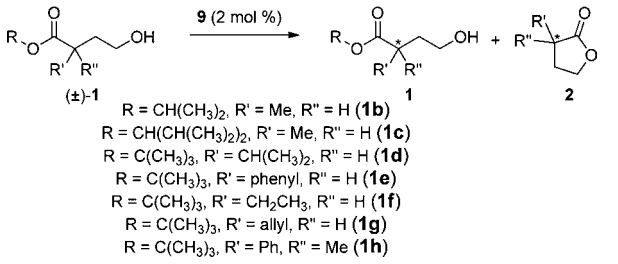
(6) Select recent examples: (a) Mandai, H.; Murota, K.; Mitsudo, K.; Suga, S. *Org. Lett.* **2012**, *14*, 3486–3489. (b) Lu, G.; Birman, V. B. *Org. Lett.* **2011**, *13*, 356–358.

(7) For a discussion on the impact of trace metals in chiral phosphoric acids, see: Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 3823–3826.

(8) (a) The selectivity factor (*s*) was determined using the equation $s = k_{rel(fast/slow)} = \ln[(1 - c)(1 - ee_s)]/\ln[(1 - c)(1 + ee_s)]$, where c = conversion and ee_s is the ee of the recovered starting material. This equation was developed by Kagan; see: Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Ed.; Wiley & Sons: New York, 1988; Vol. 18, pp 249−330. (b) The absolute configuration of stereocenter in (−)-**2a** was determined based on comparison of optical rotation to literature values (see Supporting Information), and that of (−)-**1a** was determined by comparison of the optical rotation of lactone formed by treatment of (−)-**1a** with TFA (see Scheme 4 and Supporting Information).

(9) Use of **enant-9** gave recovered hydroxy ester (+)-**1a**.

Table 2. Substrate Scope[a]



entry	substrate	solvent	temp (°C)	time (h)	% conv	ee%, **1**	ee%, **2**	*s*
1	**1b**	CH_2Cl_2	5	8	68	21	24	1.4
2	**1c**	CH_2Cl_2	35	144	50	14	27	1.5
3	**1d**	hexanes	5	72	56	52	37	3.9
4	**1e**	toluene	5	40	71	50	26[b]	2.3
5	**1f**	CH_2Cl_2	rt	24	67	85	n/a	6.1
6	**1g**	CH_2Cl_2	5	72	63	86	50	7.9
7	**1h**	CH_2Cl_2	5→rt	232	53	83	66[b]	16.7

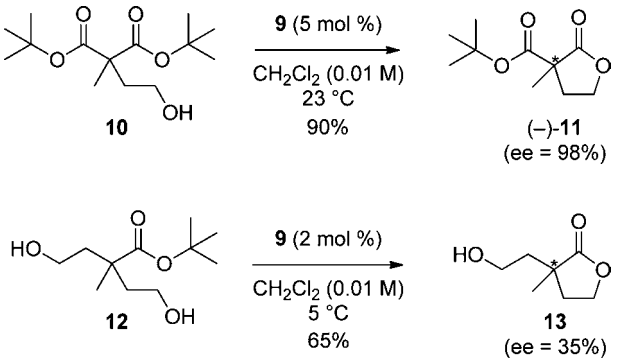
[a] Typical reaction conditions: 0.06 mmol of (±)-**1**, 0.001 mmol of **9**, in 10 mL of solvent at set temperature and time. Conversion and % ee's determined by GC analysis with a chiral support column unless indicated otherwise. [b] Ee determined by HPLC analysis with a chiral support column.

With our optimum conditions in hand we set out to explore the scope of the reaction (Table 2). We first explored other ester functionalities. The smaller isopropyl ester **1b** showed drastically reduced selectivity and reaction time (Table 2, entry 1, $s = 1.4$). However the bulkier 2,4-dimethyl-3-pentanol ester **1c** was prohibitively slow and needed heat to progress to lactone while showing little selectivity (Table 2, entry 2, $s = 1.5$). Thus, we focused on the initial *tert*-butyl esters.

Hydroxy esters with bulky α-substituents such as isopropyl **1d** (Table 2, entry 3, $s = 3.9$) or phenyl **1e** (Table 2, entry 4, $s = 2.3$) were found to be poor substrates in the resolution; however substrates with small to moderately sized α-substitution such as ethyl **1f** (Table 2, entry 5, $s = 6.1$) proceeded through the resolution with moderate to good selectivities. Most excitingly, easily manipulated α-allyl substrate **1g** (Table 2, entry 6, $s = 7.9$) yielded product with good enantioselectivity and the di-α-substituted substrate **1h** (Table 2, entry 7, $s = 16.7$) produced an enantioenriched hydroxy ester with a challenging all-carbon quaternary center.

The desymmetrization of prochiral substrates, an important variant of kinetic resolutions, is not limited by the inherent yield constraints of classical kinetic resolutions.[10] Gratifyingly, symmetric substrates such as **10** or **12** were compatible with the reaction conditions yielding enantioenriched lactones (−)-**11** and **13** (Scheme 2). Prochiral diester **10** was converted to enatioenriched ester (−)-**11** in excellent yield (90%) and selectivity (ee = 98%). Regrettably, the lactonization of prochiral diol **12** to lactone **13** in the presence of chiral catalyst **9** was not as successful. While the yield was still good (65%), the selectivity was diminished (ee = 35%), likely due to the increased rate of the reaction.[11] Both lactones (−)-**11** and **13** contain an all-carbon quaternary stereocenter that would be difficult to install using other methodologies. Studies are currently underway to employ lactone (−)-**11** in the synthesis of a biologically important molecule.

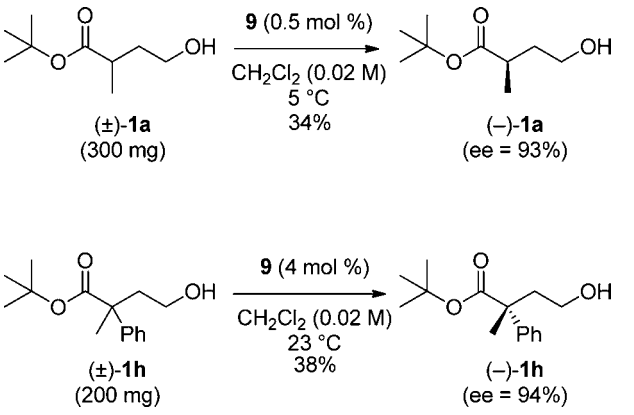
Scheme 2. Desymmetrization of Prochiral Substrates



We next sought to show the utility of the kinetic resolution process on a larger, more synthetically relevant scale than for the initial screenings (Scheme 3). Starting with 300 mg of (±)-**1a** we obtained 102 mg (34% isolated yield) of (−)-**1a** with an enantiopurity of 93% using only 0.5 mol % of the catalyst. The α-quaternary substrate (±)-**1h** (200 mg) produced 76 mg (38% yield) of (−)-**1h** with an enantiopurity of 94%.[12]

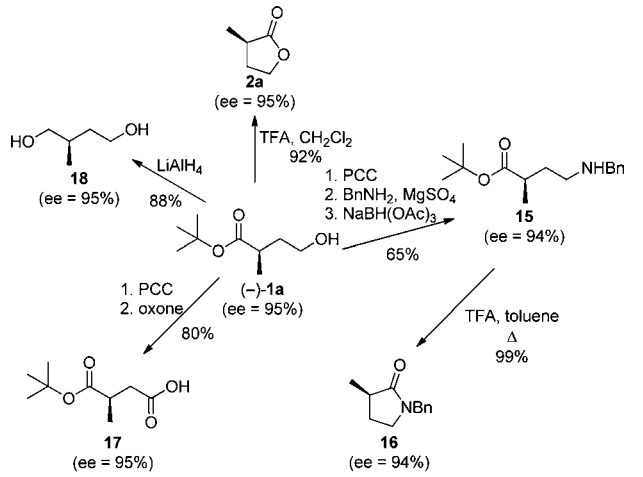
Enantioenriched hydroxy esters of the type described here are highly versatile building blocks that are suitable for either incorporation directly into a biologically relevant molecule or conversion into a multitude of other small molecules (Scheme 4). Commercially available lactone **2a** is easily prepared by treatment of (−)-**1a** with acid in high

Scheme 3. Scale



(10) Garciá-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313–354.

Scheme 4. Easy Access to Enantioenriched Building Blocks



yield and no loss of enantioselectivity. Amino ester **15** was prepared in three steps with minimal loss of enantioselectivity and can easily be converted to lactam **16**. Oxidation of alcohol (−)-**1a** generated carboxylic acid **17**, and reduction afforded diol **18**. These newly formed enantioenriched molecules can then be manipulated further and incorporated into more complex molecules. In particular diol **18** has been used in numerous natural product syntheses.[13]

In summary, we report an efficient and generalized procedure for the preparation of enantioenriched α-substituted hydroxy esters through a kinetic resolution. This process is easily scalable and requires catalyst loadings as low as 0.5 mol %. Generation of all-carbon quaternary centers in high enantioselectivities is readily achieved. Current work is directed toward expanding the scope of this reaction and examining the mechanism in more detail.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) Reaction was complete after 12 h at 5 °C.

(12) The absolute configuration of the stereocenter in (−)-**1h** was determined based on comparison to literature values of recovered lactone (−)-**2h** (see Supporting Information).

(13) Select recent examples: (a) Liu, H.; El-Salfiti, M.; Chai, D. I.; Auffret, J.; Lautens, M. *Org. Lett.* **2012**, *14*, 3648–3651. (b) Francais, A.; Leyva, A.; Etxebarria-Jardi, G.; Ley, S. V. *Org. Lett.* **2010**, *12*, 340–343. (c) Lautens, M.; Stammers, T. A. *Synthesis* **2002**, 1993–2012.

The authors declare no competing financial interest.