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Silylation-Based Kinetic Resolution of α-Hydroxy Lactones and Lactams

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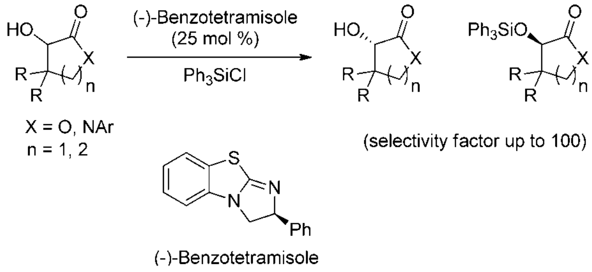
ABSTRACT



A silylation-based kinetic resolution has been developed for α-hydroxy lactones and lactams employing the chiral isothiourea catalyst (−)-benzotetramisole and triphenylsilyl chloride as the silyl source. The system is more selective for lactones than lactams, and selectivity factors up to 100 can be achieved utilizing commercially available reagents.

Enantiomerically pure α-hydroxy lactones and lactams are highly desirable chiral building blocks for the synthesis of biologically active compounds[1] and natural products[2] and have been used as chiral auxiliaries in a variety of reactions.[3] While a number of asymmetric synthetic methods[3,4] have been developed to produce these compounds, including enzymatic kinetic resolutions,[5] until recently there has been very little work with nonenzymatic kinetic resolutions of these substrates. Currently, there are two examples of nonenzymatic kinetic resolutions of lactones which include a Cu-catalyzed carbamoylation[6] and an isothiourea-catalyzed acylation.[7] However, to the best of our knowledge, a successful nonenzymatic resolution of α-hydroxy lactams remains unreported. Herein, we describe the expansion of the substrates employed in silylation-based kinetic resolutions to include α-hydroxy lactones and lactams, as well as a few amides and esters. The method employs commercially available reagents to resolve a variety of synthetically useful substrates and achieves selectivity factors[8] up to 100.

The use of silicon in asymmetric reactions is an emerging field. Until recently, the use of silicon based reagents for the production of chiral secondary alcohols has been limited to asymmetric hydrosilylation of a prochiral ketone.[9] An alternate and powerful method to produce enantioenriched secondary alcohols is the kinetic resolution

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[8] Selectivity factor (s) = (rate of the fast reacting enantiomer)/(rate of slow reacting enantiomer).

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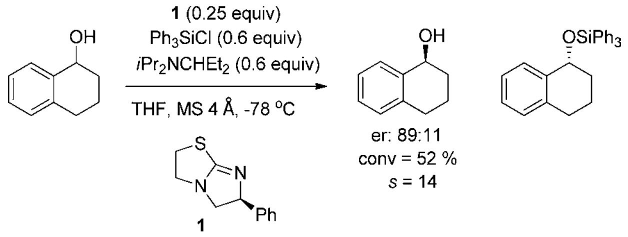
[11] (a) Rendler, S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 248. (b) Weickgenannt, A.; Mewald, M.; Oestreich, M. *Org. Biomol. Chem.* **2010**, *8*, 1497.

10.1021/ol402982w

of racemic alcohols,[10] but relatively few examples of silylation-based kinetic resolutions have been explored,[11] despite the many synthetic advantages (tunable reactivity, ease of protection, and selective deprotection).[12] The substrates that have been targeted with enantioselective silylation thus far include diols,[13] 1,2,3-triols,[14] pyridyl substituted alcohols,[15] simple alcohols,[16] and β-hydroxy esters.[17] Recently, we reported a synthetically useful silylation-based kinetic resolution of secondary cyclic alcohols (Scheme 1).[18] This methodology utilizes the chiral isothiourea (−)-tetramisole (**1**) as a chiral Lewis base to activate triphenylsilyl chloride.[19] Moderate to high selectivity factors (*s* up to 25) were obtained for a variety of monofunctional, cyclic, secondary alcohols. Unfortunately, when acyclic secondary alcohols, such as 1-phenylethanol, were attempted nearly all selectivity was lost.

Scheme 1. Reaction Conditions for Silylation-Based Resolutions of Cyclic 2° Benzylic Alcohols

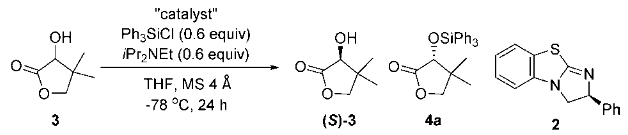


In order to expand the substrate scope of our silylation-based kinetic resolution, we concluded that a successful substrate class would possess many of the same topologies as cyclic benzylic alcohols (Scheme 1): a relatively planar substrate with a π-system adjacent to the alcohol. We hypothesized α-hydroxy lactones or lactams could be amenable to resolution based on the position of the carbonyl and inherent conformational rigidity.

Initially, reaction conditions were developed using commercially available pantolactone **3** as the model substrate. Conditions similar to our previous work were employed, with the exception of a change in the base from diisopropyl-3-pentyl amine to Hünig's base because of the limited availability of the former. When catalysts **1** and (−)-benzotetramisole **2**[27] were tested, little to no conversion was observed (Table 1, entries 1 and 2). When the reaction was warmed from −78 to −40 °C using **2** as the catalyst, only minor amounts of product formed, but some selectivity was achieved (Table 1, entry 3). Utilizing catalyst **2**, the concentration was almost tripled which led to an increase in conversion to ~40% and an impressive selectivity factor of 28 (Table 1, entry 4). In an attempt to increase the conversion further, the catalyst loading was increased to 25 mol %, resulting in a slight increase in conversion to 52% and a selectivity factor of 36 (Table 1, entry 6). When catalyst **1** was applied under the exact same conditions there was little conversion (Table 1, entry 5); thus, catalyst **2** was chosen for subsequent studies.

An investigation into the effect of different silyl groups, solvents, and bases revealed that the previously determined conditions were still the optimum choice (triphenylsilyl chloride, THF, and Hünig's base).[21] As was seen in our previous paper, the phenyl groups on the silyl chloride play a critical role in affecting the selectivity of the reaction. When silyl chlorides were employed that contained fewer or no phenyl groups, the selectivity of the reaction dramatically decreased. Solvents such as dichloromethane, toluene, or DME provided high conversions, but selectivity factors were significantly decreased (s = 7, 10, and 5, respectively). Other bases that were investigated, such as triethylamine, triisobutylamine, and tribenzylamine, resulted in a decrease in product formation as well as a slight decrease in selectivity. Employing the optimal conditions on a preparative scale kinetic resolution of **3** showed similar results to the smaller scale runs.[22]

Table 1. Reaction Optimization Conditions for Pantolactone



entry	catalyst (equiv)	concn [M][a]	% conv[b]	s[b]
1	**1** (0.2)	0.16	<5%	–
2	**2** (0.2)	0.16	<5%	–
3[c]	**2** (0.2)	0.16	9%	18
4	**2** (0.2)	0.42	41%	28
5	**1** (0.25)	0.42	6%	–
6	**2** (0.25)	0.42	52%	36

[a] Concentration with respect to substrate. [b] See ref 20. [c] Reaction was run at −40 °C for 19 h.

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(13) (a) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67. (b) Zhao, Y.; Mitra, A. W.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8471. (c) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8167.

(14) You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 547.

(15) (a) Rendler, S.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7620. (b) Klare, H. F. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9335. (c) Rendler, S.; Plefka, O.; Karatas, B.; Auer, G.; Fröhlich, R.; Mück-Lichtenfeld, C.; Grimme, S.; Oestreich, M. *Chem.—Eur. J.* **2008**, *14*, 11512. (d) Weickgenannt, A.; Mewald, M.; Muesmann, T. W. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2223.

(16) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243.

(17) Patel, S. G.; Wiskur, S. L. *Tetrahedron Lett.* **2009**, *50*, 1164.

(18) Sheppard, C. I.; Taylor, J. L.; Wiskur, S. L. *Org. Lett.* **2011**, *13*, 3794.

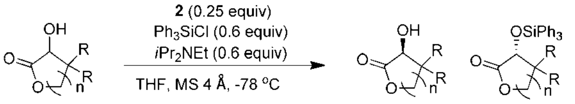
(19) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

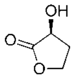
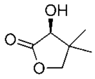
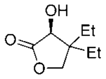
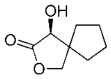
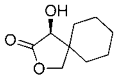
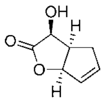
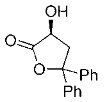
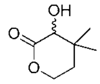
(20) (a) Conversions and selectivity factors are based on the ee of the recovered starting materials and products. See ref 10a. (b) Selectivity factors are an average of two runs. Conversions are from a single run.

(21) See Supporting Information.

(22) (a) Molecular sieves were added to prevent hydrolysis of Ph_3SiCl and aid in reproducibility. (b) Kinetic resolution of 1.04 g of **3**: s = 28 with 50% conversion and recovered alcohol with an er of 92:8.

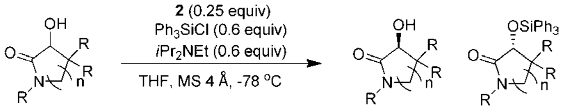
Table 2. Substrate Scope of the Silylation-Based Kinetic Resolution of α-Hydroxy Lactones

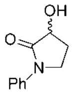
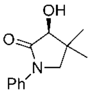
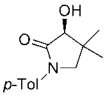
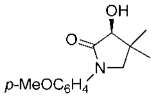
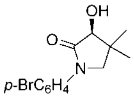
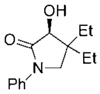
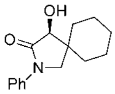


entry	recovered alcohol	*t* (h)	er of recovered alcohol	% conv[a]	*s*[a]
1		24	82:18	57	5.8
2		24	96:4	52	36
3		48	82:18	40	100
4		48	94:6	53	23
5		48	98:2	53	48
6		48	90:10	58	7.8
7		24	53:47	56	1.2
8		48	--	<5[b]	--

[a] See ref 20. [b] Conversion determined by ^{1}H NMR.

Table 3. Scope of the Silylation-Based Kinetic Resolution of α-Hydroxy Lactams



entry	recovered alcohol	*t* (h)	er of recovered alcohol	% conv[a]	*s*[a]
1		24	rac	57[b]	1.0
2		48	84:16	47	14
3		48	60:40	22	7.1
4		48	66:34	32	6.8
5		48	62:38	34	3.3
6		48	60:40	20	20
7[c]		72	97:3	56	24

[a] See ref 20. [b] Conversion determined by ^{1}H NMR. [c] Reaction performed with 0.75 equiv of Ph_3SiCl and iPr$_2$NEt.

With the optimized reaction conditions obtained from the resolution of **3**, the substrate scope was explored. When α-hydroxy-*γ*-butyrolactone (Table 2, entry 1) was resolved, a decrease in selectivity was observed presumably due to a decrease in steric bulk at the *β*-position. In order to test this hypothesis, a variety of lactones possessing sterically hindered groups in the *β*-position were synthesized.[23] As predicted, changing the *β*,*β*-dimethyl group in **3** to a *β*,*β*-diethyl group resulted in a dramatic increase in selectivity to an *s* of 100 (Table 2, entry 3). This result is the highest selectivity factor obtained to date for the triphenyl silylation-based kinetic resolution of secondary alcohols.[18] Spiro cyclic lactones (Table 2, entries 4 and 5) were also resolved with a high degree of selectivity. The cyclohexane substituted spiro lactone (Table 2, entry 5) was more selective than the cyclopentane substituted one (Table 2, entry 4), presumably due to the increased sterics of the six-membered ring. A fused bicyclic lactone was also explored with moderate selectivity (Table 2, entry 6). Interestingly, when the lactone was substituted in the *γ*-position with sterically large phenyl groups (Table 2, entry 7) nearly all selectivity was lost. Finally, when the *β*,*β*-disubstituted lactone ring was expanded from a five- to a six-membered ring (Table 2, entry 8), the substrate became too sterically hindered and no conversion was obtained. Unfortunately, the corresponding unsubstituted six-membered ring lactone decomposed under the reaction conditions and therefore could not be examined.

Next, α-hydroxy lactams were examined. These *N*-aryl substituted lactams were prepared in one step from the corresponding lactone and an aryl amine.[24] The lactams were universally less selective than their lactone counterparts. Unfortunately, complete loss of enantioselectivity was observed for the *N*-phenyl lactam with no substituents

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(23) Hata, H.; Morishita, T.; Akutsu, S.; Kawamura, M. *Synthesis* **1991**, 289.

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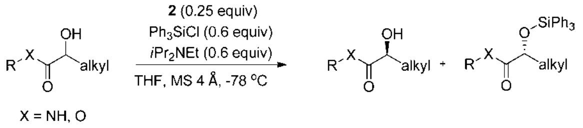
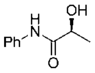
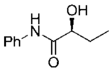
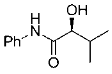
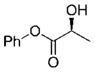
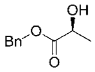
Table 4. Scope of the Silylation Kinetic Resolution of Amides and Esters



entry	recovered alcohol	*t* (h)	er of recovered alcohol	% conv[a]	*s*[a]
1		24	81:19	47	8.5
2		24	83:17	54	6.6
3		24	79:21	49	7.3
4		24	83:17	57	3.9
5		24	81:19	53	5.6

[a] See ref 20.

in the β-position (Table 3, entry 1). Even though amides are known to catalyze silylation reactions,[12] no product was detected when the reaction was run with the same unsubstituted substrate in the absence of catalyst **2**. This shows that the lack of selectivity is not due to an uncontrolled background reaction.

Similar to the lactones, increasing sterics in the β-position of the lactams increased the selectivity. As the substituents were changed from methyl to ethyl to a six-membered spiro ring (Table 3, entries 2, 6, and 7), the selectivity factors increased from 14 to 20 to 24 respectively. However, the reactions became sluggish as the sterics increased in the β-position; therefore, more equivalents of silyl chloride and base were employed to force higher conversions (Table 3, entry 7). The effect of electronics on the *N*-aryl group was investigated by substituting electron-donating (methyl, methoxy) and an electron-withdrawing group (bromo) in the para position (Table 3, entries 3−5). Surprisingly, a decrease in selectivity was observed for both electron-withdrawing and -donating substituents. The selectivity factor for electron-donating groups dropped by a factor of 2, while electron-withdrawing groups decreased the selectivity factor even further (s = 7.1, 6.8, and 3.3, respectively).

As shown in Table 2 (entry 3 vs 7), the reaction is sensitive to the position of sterics on the substrates. Substituents in the β-position are advantageous to selectivity, whereas sterics in the γ-position are detrimental. The *N*-aryl group[25] seems to alter the selectivity of the reaction resulting in a decrease in enantio-discrimination as compared to the lactone counterparts. Presumably, this is the result of a change in sterics on the substrates due to the phenyl group rotating out of the lactam plane to form a carbonyl−π interaction.[25b] The interaction would be more pronounced with the bromo substituted phenyl group, resulting in the low selectivity observed.

Acyclic esters and amides were also explored employing the standard reaction conditions developed (Table 4). Previously, acyclic substrates, such as 1-phenylethanol, were slow to silylate and displayed no enantio-discrimination.[18] The *N*-phenyl amides and *O*-phenyl and *O*-benzyl ester in Table 4 did show a small amount of selectivity with decent conversions. The small improvement of the amides over previous acyclic substrates is presumably due to the high energy barrier of rotation around the N−C bond providing some degree of planarity.[26] The amides showed no sensitivity to substituents next to the alcohol (Table 4, entries 1−3), but were slightly more selective than the esters (Table 4, entries 4 and 5). This is probably the result of the increased barrier of rotation for the amides vs the esters.

In conclusion, silylation-based kinetic resolutions have been expanded to include synthetically valuable α-hydroxy carbonyl compounds employing an isothiourea catalyst and commercially available reagents. This is one of the few nonenzymatic kinetic resolutions of α-hydroxy lactones and the first nonenzymatic kinetic resolution of α-hydroxy lactams. Selectivity factors up to 100 were obtained by including sterics adjacent to the alcohol, and spiro containing lactones and lactams were efficiently resolved under these conditions. It was discovered that sterics elsewhere on the ring proved detrimental, and acyclic amides and esters were tolerated in this system with limited selectivity. Further studies to elucidate the mechanism, including a linear free energy relationship and computational studies, are currently underway in our laboratory.

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Note Added after ASAP Publication. Reference 27 was added December 12, 2013.

Supporting Information Available. Experimental procedures, characterization data, NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.