ORGANIC LETTERS

2011
Vol. 13, No. 15
3794–3797

Silylation-Based Kinetic Resolution of Monofunctional Secondary Alcohols

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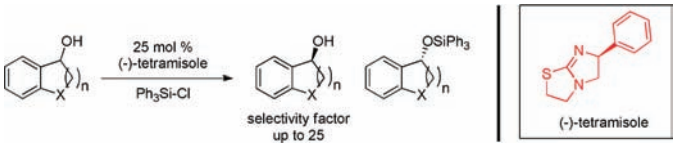
Received May 11, 2011

ABSTRACT



The nucleophilic small molecule catalyst (−)-tetramisole was found to catalyze the kinetic resolution of monofunctional secondary alcohols via enantioselective silylation. Optimization of this new methodology allows for selectivity factors up to 25 utilizing commercially available reagents and mild reaction conditions.

Nonenzymatic kinetic resolutions are a powerful technique[1] for generating highly enantiomerically enriched chiral compounds. The most common method for the kinetic resolution of secondary alcohols is by acylation,[2] but recently, silylation based kinetic resolutions have become a new and active area of research.[3] Considerable attention has been given to this methodology since silyl groups have a broad tolerance for other functional groups and have many advantages over other protecting groups (orthogonal deprotection to other protecting groups, ease and high yields of protection and deprotection, and easily tunable reactivity).[4] Of the substrates targeted for silylation-based kinetic resolutions, a practical level of selectivity for monofunctional, bicyclic secondary alcohols, such as **1**, has remained elusive and suprisingly difficult until now. This alcohol class contains useful chiral building blocks and important core structures in biologically active compounds[5] such as dopamine agonists, selective norepinephrine reuptake inhibitors, and anti-HIV agents. Although these compounds are most commonly synthesized by the asymmetric reduction of prochiral carbonyl compounds,[6] the work described herein is the first kinetic resolution of monofunctional secondary alcohols via silylation achieving useful levels of enantioselectivity. Our method employs mild conditions and utilizes commercially available reagents, thereby circumventing the need to synthesize catalysts or novel chiral silylating agents.

Great progress has been made in existing silylation based kinetic resolutions, but the substrates have been mostly

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(6) For reviews on asymmetric reductions see: (a) *Modern Reduction Methods*; Wiley-VCH: Weinheim, 2008. (b) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. (c) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (d) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

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10.1021/ol2012617
Published on Web 06/29/2011

limited to compounds exhibiting multivalency such as syn-diols,[7] 1,2,3- triols,[8] pyridyl substituted alcohols,[9] and hydroxy ketones.[10] Monofunctional alcohols have proven to be a difficult class of substrates because they eliminate the possibility of two-point binding with the catalyst, which is what the previous systems have required to achieve good selectivity. The sole report of an organocatalyzed silylation of monofunctional secondary alcohols comes from the Ishikawa group but resulted in low enantioselectivity.[11]

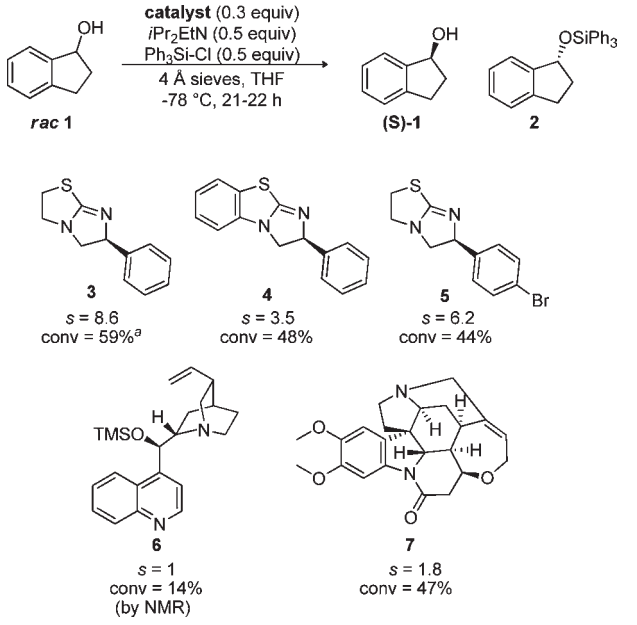
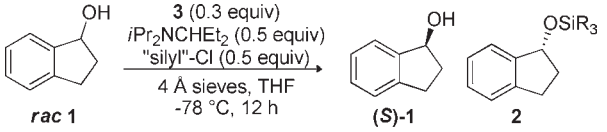


Figure 1. Catalyst screening for the silylation based kinetic resolution of **1**.[15] Reactions were carried out at a substrate concentration of 0.3 M on a 0.3 mmol scale.[16] [a]Reaction was run with 0.6 equiv of Ph_3Si-Cl, 0.6 equiv of iPr_2EtN, and 25 mol % **3** on a 0.5 mmol scale.

Our approach in silylation based kinetic resolutions of alcohols employs a nucleophilic chiral catalyst to selectively silylate one enantiomer over another. We investigated a number of catalysts with different structural motifs to see how this affected reactivity and selectivity (Figure 1). The silylation reactions were run with 1-indanol (**1**) and triphenylsilyl chloride (Ph_3Si-Cl) to give enriched alcohol and silylated product **2**. It was discovered that the commercially available chiral isothiourea (−)-tetramisole (**3**),[2f] originally employed by Birman as an acylation catalyst, gave the best selectivity factor[12] of the catalysts studied, whereas derivatives such as benzotetramisole (**4**)[2f,13] and (−)-*p*-bromotetramisole (**5**) showed less selectivity.[14] In the absence of catalyst, the background reaction was minimal resulting in an 8% conversion after 45 h. By comparison, the same substrate in the presence of **3** reaches full conversion in less than an hour (Table 2, entry 1). Nucleophilic tertiary amine catalysts such as cinchona alkaloid based systems (**6**) or (−)-brucine (**7**) were not found to be selective catalysts for this reaction.

Our choice of triphenylsilyl chloride proved important in obtaining high selectivity and conversion in the kinetic resolution. Alkyl substituted silyl groups such as triethylsilyl chloride (Table 1, entry 1) gave little selectivity while the most sterically hindered silyl chlorides such as *t*-butyldimethylsilyl chloride and triisopropylsilyl chloride gave no observable conversion by ^1H NMR (entries 5 and 6). The silyl groups, which gave both practical conversion and a higher selectivity factor, were those possessing phenyl substituents (entries 2−4). We observed that the selectivity increased when the silicon protecting group contained more phenyl groups, with triphenylsilyl chloride giving the highest selectivity factor of the silyl chlorides screened.

Table 1. Effect of the Substituents on the Silyl Group[a]



entry	"silyl"	conv (%)[b]	s^b
1	Et_3Si-	48	4.0
2	Me_2PhSi-	50	3.4
3	Ph_2MeSi-	46	5.2
4[c]	Ph_3Si-	59	8.6
5[d]	$tBuMe_2Si-$	<5	
6[d]	iPr_3Si-	<5	

[a] Reactions were carried out at a substrate concentration of 0.3 M on a 0.3 mmol scale. [b] See refs 15 and 16. [c] Reaction was run with 0.6 equiv of Ph_3Si-Cl, 0.6 equiv of iPr_2EtN, and 25 mol % **3** on a 0.5 mmol scale. [d] Conversion for this entry was determined via recovered starting material after 48 h.

We also showed that solvent polarity plays a role in reaction selectivity. Polar, coordinating solvents such as THF gave the highest selectivity factor, while other solvents such as dichloromethane and toluene resulted in lower selectivity factors (s = 2.8 to 3.6). Diethyl ether inhibited the formation of product, presumably through

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

(9) (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) Karatas, B.; Rendler, S.; Frohlich, R.; Oestreich, M. *Org. Biomol. Chem.* **2008**, *6*, 1435. (e) Weickgenannt, A.; Mewald, M.; Muesmann, T. W. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2223.

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

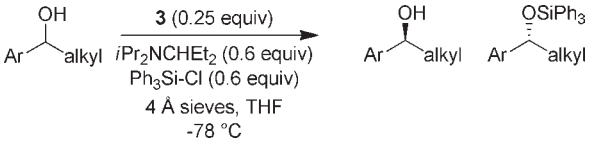
(11) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243.

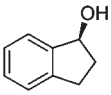
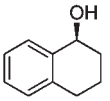
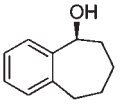
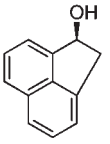
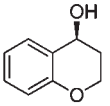
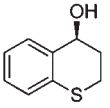
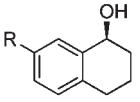
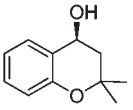
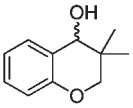
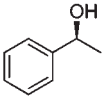
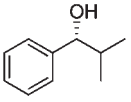
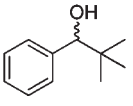
(12) Selectivity factor (s) = (rate of fast reacting enantiomer)/(rate of slow reacting enantiomer).

(13) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859.

(14) Molecular sieves were added to prevent the hydrolysis of Ph_3Si-Cl and help with reproducibility.

Table 2. Substrate Scope of Silylation-Based Kinetic Resolution (Reactions were carried out at a substrate concentration of 0.3 M on a 0.5 mmol scale)



entry	*sec*-alcohol	*t* (h)	conv (%)[a]	er of recovered alcohol	*s*[a]
1[b]		1	60	92:8	**8.6**
2		8	52	89:11	**14**
3		12	59	82:18	**4.9**
4		8	56	80:20	**5.1**
5		14	55	95:5	**22**
6		8	52	94:6	**25**
7	 a. R = -OMe b. R = -F	14	a. 55 b. 55	93: 7 90:10	**16** **11**
8		8	53	91:9	**16**
9		24	<5	--	--
10		25	41	63:37	**2.8**
11		48	29	63:37	**5.6**
12[c]		48	<5	--	--

[a] See ref 15 and 16. [b] Reaction performed with iPr$_2$EtN. [c] Reaction performed with 30 mol % catalyst.

precipitation of the catalyst/Ph_3Si-Cl intermediate. Selectivity was achieved in DMF (s = 6.9 at −40 °C), which is known to activate silicon for alcohol protection.[4] The origin of this selectivity is still under investigation.

Both chiral and achiral amine bases were examined to determine the dependence of the selectivity of the reaction upon the base. From these experiments, we determined that non-nucleophilic, sterically hindered bases such as *N*, *N*-diisopropyl-3-pentylamine (iPr$_2$NCHEt$_2$) gave the best selectivity factors. Hünig's base (iPr$_2$EtN) offered little difference in selectivity when used with substrate **1**, but it did give inferior results for several other substrates; therefore, the more sterically hindered iPr$_2$NCHEt$_2$ was used for subsequent studies.

Our kinetic resolution of **1** is an impressive achievement, since **1** is historically one of the most challenging alcohols to enrich via kinetic resolutions. While enzymatic processes (mainly lipases) have been successful at resolving the two enantiomers of **1** with high selectivity,[17] chemists have had a more difficult time achieving only moderate selectivities with small molecule catalysts. The literature reports selectivity factors for nonenzymatic acylation based kinetic resolutions ranging between 2.5 and 6.[18] To the best of our knowledge, our selectivity factor of 8.6 with the triphenylsilyl chloride reagent is the highest for the organocatalyzed kinetic resolution of **1**. Even under preparative scale conditions, **1** was enriched with only a minor reduction in the selectivity factor.[19]

The reaction conditions developed for the enantioselective silylation of **1** also proved efficient at resolving several other secondary bicyclic benzylic alcohols.[20] There was an increase in selectivity when the substrate's alkyl side was expanded to a six member ring as in the case of 1-tetralol (Table 2, entry 2), however when this ring was further expanded to a seven member ring (entry 3), a decrease in selectivity was observed. Expanding the pi-system in entry 4 decreased the selectivity as well, likely due to the five membered ring in the substrate

(15) Conversions and selectivity factors were calculated from the ee of the product and the ee of the left over starting material. See ref 1a.

(16) Selectivity factors are an average of two runs. Conversion and er correspond to a single run.

(17) (a) Bouzemi, N.; Debbeche, H.; Aribi-Zouioueche, L.; Fiaud, J.-C. *Tetrahedron Lett*. **2004**, *45*, 627. (b) Bouzemi, N.; Aribi-Zouioueche, L.; Fiaud, J.-C. *Tetrahedron: Asymmetry* **2006**, *17*, 797. (c) Wu, X.-M.; Xin, J.-Y.; Sun, W.; Xia, C.-G. *Chem. Biodiv*. **2007**, *4*, 183. (d) Ou, L.; Ludwig, D.; Pan, J.; Xu, J. H. *Org. Process Res. Dev*. **2008**, *12*, 192.

(18) (a) Clapham, B.; Cho, C.-W.; Janda, K. D. *J. Org. Chem*. **2001**, *66*, 868. (b) Spivey, A. C.; Leese, D. P.; Zhu, F.; Davey, S. G.; Jarvest, R. L. *Tetrahedron* **2004**, *60*, 4513–455. (c) Shiigi, H.; Mori, H.; Tanaka, T.; Demizu, Y.; Onomura, O. *Tetrahedron Lett*. **2008**, *49*, 5247.

(19) Kinetic resolution of 1.5 g of **1**: s = 6.8 with 52% conversion and recovered alcohol er was 81:19.

(20) Typical procedure: To an oven-dried 1-dram vial fitted with a stir bar and 4 Å sieves were added, alcohol substrate (0.5 mmol), **3** (0.125 mmol) and dry THF (1.6 mL). The solution was then treated with iPr$_2$NCHEt$_2$ (0.3 mmol) and stirred at −78 °C for 30−45 min. Once cooled, Ph_3Si-Cl (0.3 mmol, 0.357 M in THF) was added via syringe and the resulting solution was left to stir at −78 °C. The reaction was quenched with 250 μL MeOH, poured into saturated NH_4Cl and extracted with diethyl ether. The combined ethereal layers were dried over silica gel, filtered, evaporated, and purified by column chromatography (1:1 hexanes:CH_2Cl_2 to 2% MeOH in CH_2Cl_2) to provide the product and unreacted starting material.

having a more planar structure. However, when oxygen or sulfur was included in the saturated ring (entries 5–6), the reaction proceeded in a highly selective fashion. When we changed the electronics of the aryl ring on tetralol with either a methoxy or fluoro substituent (entry 7a and b) only minor adjustments in the selectivity factor were observed. The absolute stereochemistry of entry 7b was confirmed by comparison of specific rotation of literature versus experimental.[21]

The reaction's sensitivity to steric hindrance on the saturated ring is shown in entries 8 and 9 when 4-chromanol was substituted with methyl groups in the 2 and 3 positions respectively. When the methyl groups are in the 2 position (Table 2, entry 8), a lower selectivity factor was achieved, while the methyl groups adjacent to the alcohol prevent the reaction from proceeding at all (entry 9). Overall, the alcohols discussed thus far required longer reaction times respective to **1** to achieve similarly high conversions, however, the transformations requiring the longest reaction times reached near total conversion in less than one day.

While the success with cyclic alcohols is impressive, acyclic secondary alcohols have proven to be more difficult, resulting in poor selectivity and reaction times requiring up to two days for complete conversion. Low to moderate selectivity factors were obtained with 1-phenylethanol and 2-methyl-1-phenylpropanol (Table 2, entry 10 and 11) and even after 48 h, full conversion had not been reached. Entry 12 (2,2-dimethyl-1-phenylpropanol) proved to be too sterically hindered to react resulting in no observable conversion. These as well as the above examples show the sensitivity of the system to the steric environment adjacent to the alcohol. The major structural difference between 1-phenylethanol and **1** is the ability of the phenyl group to rotate, and presumably because of the large entropic cost, a large difference between their reactivities and selectivities is seen. This suggests the presence of a narrow reaction pocket that only unhindered cyclic alcohols can enter.

This work demonstrates that the silylation method is amenable to difficult and biologically important substrate targets. The results presented herein show previously unachieved levels of selectivity for monofunctional bicyclic alcohols via silylation based kinetic resolutions. Along with achieving selectivity factors of up to 25, the reactions were carried out under mild conditions, with a commercially available, low molecular weight catalyst (**3**) and triphenylsilyl chloride, resulting in high conversion with reaction times as short as one hour. We are currently working to elucidate the mechanism of how our chiral system distinguishes between the enantiomers. The enantioselectivity in this reaction is currently believed to originate from the known chiral propeller conformation of triphenyl substituted silyl groups.[22] Future endeavors will involve the determination of the mechanism as well as expanding the scope of substrates that can be resolved.

Acknowledgment. We gratefully acknowledge support from the University of South Carolina and the National Science Foundation CAREER Award CHE-1055616. This paper is dedicated to the memory of Dr. Marc S. Maynor (University of Texas at Austin).

Supporting Information Available. Experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (a) Aroney, M. J.; Le Fevre, R. J. W.; Ritchie, G. L. D.; Ross, V. *J. Chem. Soc. B* **1966**, 188. (b) Gust, D.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 1535. (c) Mislow, K. *Acc. Chem. Res.* **1976**, *9*, 26. (d) Barbieri, G. *J. Organomet. Chem.* **1979**, *172*, 285. (e) Allen, G. W.; Aroney, M. J.; Hambley, T. W. *J. Mol. Struct.* **1990**, *216*, 227. (f) Shankar, R.; Joshi, A.; Upreti, S. *Polyhedron* **2006**, *25*, 2183.