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Diastereoselective and Enantioselective Silylation of 2-Arylcyclohexanols

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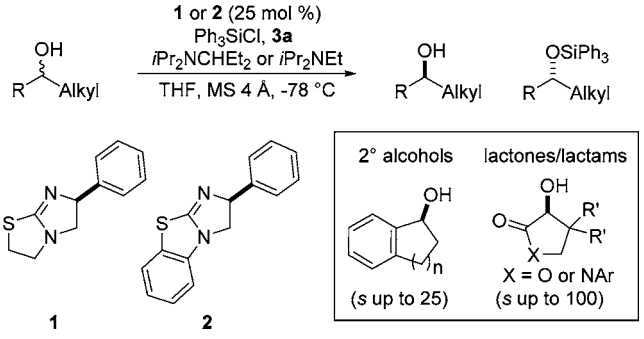
Supporting Information

ABSTRACT: The silylation-based kinetic resolution of *trans* 2-arylcyclohexanols was accomplished by employing a triaryl silyl chloride as the derivatizing reagent with a commercially available isothiourea catalyst. The methodology is selective for the *trans* diastereomer over the *cis*, which provides an opportunity to selectively derivatize one stereoisomer out of a mixture of four. By employing this technology, a facile, convenient method to form a highly enantiomerically enriched silylated alcohol was accomplished through a one-pot reduction−silylation sequence that started with a 2-aryl-substituted ketone.

The formation of enantiopure secondary alcohols is an important endeavor due to their prevalence in the synthetic community as building blocks. Specifically, enantiomerically pure 2-arylcyclohexanols are widely used as chiral auxiliaries in a variety of asymmetric reactions.[1] While these compounds can be synthesized asymmetrically,[2] a viable economical approach is to enrich them through kinetic resolutions:[3] enzymatically[4] or nonenzymatically.[5] The nonenzymatic, small molecule approach usually offers the advantage of facile access to both enantiomers of the resolution catalyst. Even though a number of these methods are highly selective toward resolving 2-arylcyclohexanols, many of them are selective for or react with both diastereomers of the alcohol, *cis* and *trans*.[5a,d,g,k−m] Two common methods to form these alcohols are through nucleophilic opening of epoxides and reduction of 2-arylcyclohexanones.[6] While *trans*-substituted 2-arylcyclohexanols are selectively formed from the epoxide opening, the ketone reduction generates a mixture of diastereomers. When the reduction method is used, this means additional purification steps are needed to separate the diastereomers before the kinetic resolution can be performed. Herein we report the selective silylation-based kinetic resolution of *trans*-2-arylcyclohexanols, with selectivity factors up to the 50s employing a commercially available catalyst. The method is selective for the *trans* compound over the *cis* and can selectively resolve the *trans*-substituted compound out of a mixture of diastereomers (*cis* and *trans*) in order to isolate the silylated product in excellent enantiomeric ratios.

Silylation-based kinetic resolutions have been growing in interest over the last 10 years,[7] with a variety of substrates being resolved through either nucleophilic activation of silyl chlorides[8] or dehydrogenative silylation.[9] Regarding the silyl chloride activation method, our group has developed a silylation-based kinetic resolution for the enrichment of cyclic secondary alcohols[10] and α-hydroxy lactones and lactams[11] with selectivity factors up to 100 (Scheme 1). The method employs either the

Scheme 1. Previous Silylation-Based Kinetic Resolutions Performed by Our Group



isothiourea catalyst tetramisole (**1**) or benzotetramisole (**2**) first reported by Birman[12] and triphenylsilyl chloride (**3a**) as the silyl source for the selective silylation of one enantiomer over another.

The kinetic resolution of *trans* 2-phenylcyclohexanol (**4**) was attempted using conditions similar to those in Scheme 1. When catalyst **1** was employed, very little selectivity was obtained (Table 1, entry 1), but changing the catalyst to **2** improved the selectivity factor to 6 (Table 1, entry 2). We have previously noted that the choice of silyl group can dramatically affect the selectivity of the kinetic resolution, with three phenyl groups on silicon being particularly important.[10] Most recently, we discovered that electron-donating alkyl groups in the para position of the phenyl groups on triphenylsilyl chloride resulted in improved selectivity.[13] When tris(4-isopropylphenyl)silyl chloride (**3b**) was investigated, an improvement in selectivity was again observed (Table 1, entry 3) with an increase in silyl chloride equivalents and reaction time to improve conversion.

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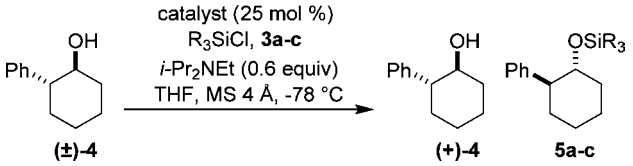
Table 1. Optimization of Catalyst and Silyl Chloride for the Silylation-Based Kinetic Resolution of 2-Phenylcyclohexanol



entry[a]	catalyst	3, R	R_3SiCl (equiv)	time (h)	conv[b] (%)	s^b
1	**1**	**3a**, Ph	0.6	24	52	2
2	**2**	**3a**, Ph	0.6	24	59	6
3	**2**	**3b**, *p*-*i*-Pr-Ph	0.65	48	51	10
4[d]	**2**	**3c**, *p*-*t*-Bu-Ph	0.65	72	<5[c]	

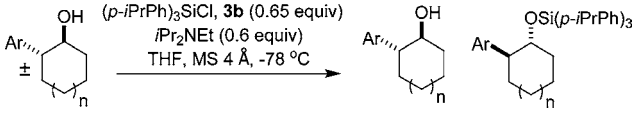
[a]Reactions were run at a concentration of 0.42 M with respect to alcohol. [b]See ref 15. [c]Conversion was determined by ^{1}H NMR. [d]Reactions were run at a concentration of 0.28 M with respect to alcohol.

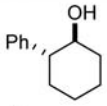
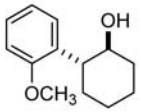
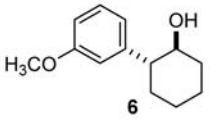
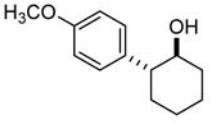
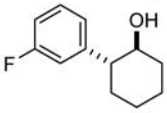
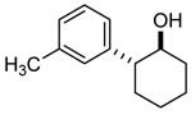
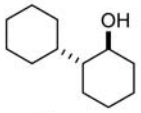
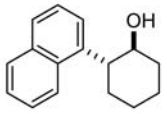
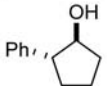
Interestingly, the previously more selective, sterically hindered tris(4-*tert*-butylphenyl)silyl chloride (**3c**) was unreactive under the reaction conditions (Table 1, entry 4), even with increased reaction time relative to that used for entry 3 in Table 1. In the absence of catalyst there is no background reaction after 24 h, even when the less sterically hindered silyl chloride **3a** is used.

With this information in hand, kinetic resolutions were performed on a number of *trans*-2-arylcyclohexanol substrates employing the more selective isopropyl-substituted silyl chloride (Table 2). When the aryl group of the alcohol was substituted with a methoxy, the selectivity generally improved compared to just a phenyl (Table 2, entry 2−4 vs entry 1), but the selectivity was dependent on the position of the methoxy on the aryl group (ortho, meta, or para). The ortho-substituted compound (Table 2, entry 2) had a lower conversion probably due to the increased steric effect, with a modest selectivity factor of 13. The *m*- (**6**) and *p*-methoxy-substituted compounds (Table 2, entries 3 and 4) had excellent selectivity factors of 53 and 28, respectively. The *m*-fluoro-substituted aryl compound had significantly higher selectivity over just a phenyl group (Table 2, entry 5 vs entry 1), but when an electron-donating *m*-methyl-substituted aryl group was employed, it was only modestly more selective than a phenyl group (Table 2, entry 6, $s = 14$). The aryl π system proved to be important for selectivity, as shown by the very small selectivity factor of the saturated cyclohexyl-substituted substrate (Table 2, entry 7). The increased π surface area of a 1-naphthyl aryl group proved too bulky, with only modest conversion (11%) and selectivity (Table 2, entry 8). Cyclohexanol rings are needed for selectivity, as shown by the inability of the method to resolve 2-phenylcyclopentanol (Table 2, entry 9). The importance of the isopropyl-substituted silyl chloride for maintaining high selectivity was demonstrated when the *m*-methoxy-substituted compound **6** was resolved with triphenylsilyl chloride (**3a**), resulting in a much lower selectivity factor ($s = 13$, conv = 45%) as compared to entry 3 in Table 2 ($s = 53$). Finally, the methodology can be scaled up to gram scale without any loss in selectivity,[14] and the silyl ether product **5b** was efficiently desilylated with fluoride to obtain the alcohol in 86% yield.

As for *cis* 2-arylcyclohexanols, those substrates failed to even silylate under the kinetic resolution reaction conditions. Both the phenyl and *m*-methoxyphenyl *cis*-substituted compounds (**7** and **8**, respectively) were employed, but no conversion was observed (Scheme 2). This is likely attributed to the position of the alcohol in the cyclohexane chair conformation, axial versus equatorial.

Table 2. Substrate Scope of the Silylation-Based Kinetic Resolution of *trans*-2-Arylcyclohexanols



entry[a]	recovered alcohol	er of recovered alcohol	conv (%)[b]	s^b
1		83:17	51	10
2		66:34	28	13
3	 **6**	95:5	50	53
4		95:5	52	28
5		85:15	45	27
6		64:36	26	14
7		60:40	40	2
8		54:46	11	5
9		51:49	54	1.1

[a]Reactions were run for 48 h at a concentration of 0.42 M with respect to alcohol on a 0.4 mmol scale. [b]See ref 15.

Employing *A* values, it is simple to figure out the lowest energy conformation of *cis*- and *trans*-2-phenylcyclohexanols **4** and **7** and the percentage of each compound found at that conformation. Due to the larger *A* value of a phenyl substituent over an alcohol (2.8 and 0.95 kcal/mol, respectively),[16] the phenyl group controls the overall conformation of **4** and **7** by placing the phenyl group in the lower energy equatorial position (Scheme 2). This results in >99% of **4** in the conformation where the alcohol is equatorial and 99% of **7** where the alcohol is axial at −78 °C. The position of the alcohol, axial versus equatorial, seems to dictate the reactivity of the alcohol toward silylation in this methodology. This is further validated by employing *cis*- and *trans*-4-*tert*-butylcyclohexanols (Scheme 2). These compounds lack any substituents in the 2-position, eliminating any effect the

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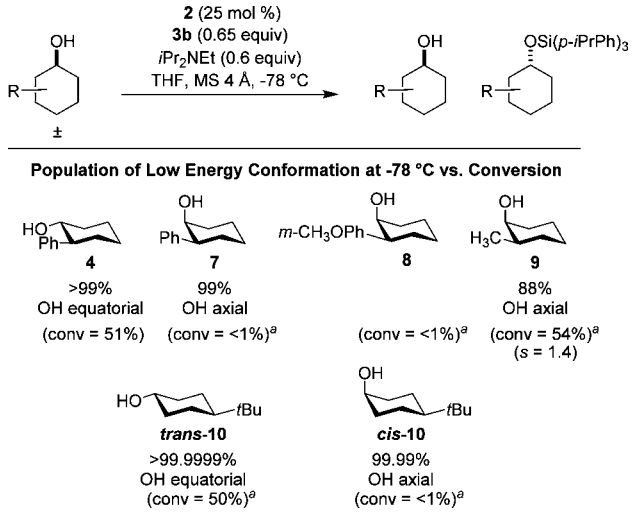
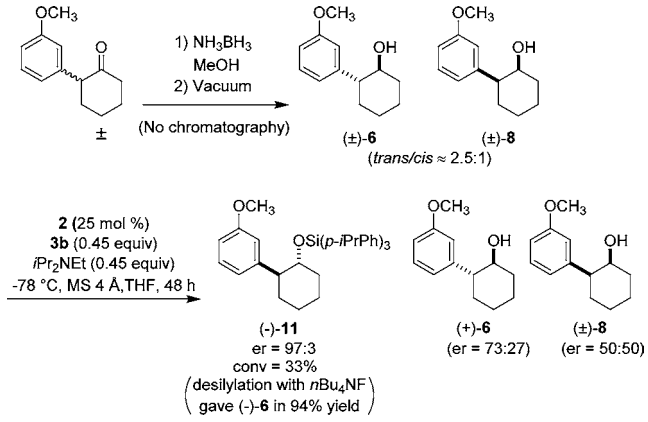
Scheme 2. Substrate Reactivity toward Silylation Based on the OH Conformation (Axial vs Equatorial) and the Population of That Conformation at −78 °C



[a]Conversion determined via ^{1}H NMR.

Scheme 3. One-Pot, Chromatography-Free Reduction Followed by a Kinetic Resolution To Selectively Silylate One Stereoisomer out of a Mixture of Four



phenyl group of *cis*-2-phenylcyclohexanol may have played. Since the *A* value of a *tert*-butyl group is 4.7 kcal/mol,[16] at low temperatures these compounds have a nearly quantitative bias toward one conformation (>99.99%) with the hydroxyl group in either the axial (*cis*) or equatorial (*trans*) position. This reduces the possibility of the Curtin−Hammett principle playing a role by eliminating the presence of one conformation. When the compound was subjected to the same reaction conditions as above, again the hydroxyl group in the equatorial position becomes silylated and the hydroxyl group in the axial position is unreactive toward silylation.

The reactivity of other *cis*-2-substituted cyclohexanols toward silylation can be determined by again employing *A* values to calculate the population of the two main chair conformations. Substituents with small *A* values result in the presence of both conformations, with the alcohol in both the axial and the more reactive equatorial position. The methyl group has an *A* value of 1.74 kcal/mol, resulting in *cis*-2-methylcyclohexanol (**9**) having approximately a 12% population of the conformation with the alcohol equatorial and 88% of the methyl axial (at −78 °C) (Scheme 2). As expected, there was significant conversion (54%) of **9** to the silylated ether due to the increased concentration of the more reactive conformation. Even though the substrate could be silylated, the methodology was not selective for this substrate (s = 1.4).

The selectivity of *trans* compounds being reactive and *cis* compounds being completely unreactive provides the opportunity to selectively resolve *trans* enantiomers in the presence of *cis* enantiomers. This allows for one compound to be silylated selectively over the three other stereoisomers (Scheme 3). Additionally, we wanted to start with a ketone in a one-pot reduction−silylation procedure. The reduction can be accomplished through an ammonia−borane ketone reduction in methanol.[17] This reduction is essentially traceless after the removal of solvents, due to the volatility of the $B(OMe)_3$ byproduct. Therefore, after the reduction of 2-(3-methoxyphenyl)cyclohexanone, the solvent was removed, and the mixture of *trans* and *cis* alcohols **6** and **8** (dr = 2.5:1) was subjected to the kinetic resolution without chromatography or further purification. In order to obtain the product with a high enantiomeric ratio, the reaction needed to be stopped before full conversion was achieved, which was accomplished through limiting the amount of silyl chloride added (0.45 equiv). The resulting one-pot process maintained the selectivity of previous kinetic resolution runs (s = 50), and the resulting silylated product (−)-**11** was obtained with a high enantiomeric ratio of 97:3. This provides a valuable tool for the facile formation and separation of 2-substituted cyclohexanol diastereomers from the starting ketone by eliminating the need for a workup or chromatography between reactions.

In conclusion, we have developed a procedure to effectively resolve *trans*-2-arylcyclohexanols via a kinetic resolution employing a silylation methodology. The system obtains high selectivity when the aryl group is derivatized with a fluoro or a methoxy substituent. Compared to other methods, ours has the advantage of selectively resolving the *trans* enantiomer from a mixture of the *cis*/*trans* diastereomers. This affords the opportunity to selectively remove one compound from a mixture of four stereoisomers. Because of this *cis*/*trans* selectivity, we were able to determine that the alcohol needs to be in the equatorial position to be silylated, with alcohols locked in the axial position being completely unreactive. We are currently performing studies to help elucidate the mechanism of this reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra, and HPLC traces. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00919.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231. (b) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

(2) For representative examples, see: (a) Brown, H. C.; Vara Prasad, J. V. N.; Gupta, A. K.; Bakshi, R. K. *J. Org. Chem.* **1987**, *52*, 310. (b) Gonzalez, J.; Aurigemma, C.; Truesdale, L. *Org. Synth.* **2002**, *79*, 93. (c) Alexakis, A.; Tomassini, A.; Leconte, S. *Tetrahedron* **2004**, *60*, 9479. (d) Vrancken, E.; Alexakis, A.; Mangeney, P. *Eur. J. Org. Chem.* **2005**, 1354. (e) Cho, B. T.; Shin, S. H. *Bull. Korean Chem. Soc.* **2006**, *27*, 1283.

(3) (a) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Ernest, L., Wilen, S. H., Eds.; John Wiley and Sons: New York, 1988; Vol. *18*, p 249. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407. (d) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974. (e) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613.

(4) (a) Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663. (b) Laumen, K.; Seemayer, R.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1990**, 49. (c) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1. (d) Basavaiah, D.; Rao, P. D. *Tetrahedron: Asymmetry* **1994**, *5*, 223.

(5) (a) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543. (b) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, 265. (c) Sekar, G.; Nishiyama, H. *J. Am. Chem. Soc.* **2001**, *123*, 3603. (d) Miyake, Y.; Iwata, T.; Chung, K.-G.; Nishibayashi, Y.; Uemura, S. *Chem. Commun.* **2001**, 2584. (e) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496. (f) Jeong, K.-S.; Kim, S.-H.; Park, H.-J.; Chang, K.-J.; Kim, K. S. *Chem. Lett.* **2002**, 1114. (g) Matsugi, M.; Hagimoto, Y.; Nojima, M.; Kita, Y. *Org. Process Res. Dev.* **2003**, *7*, 583. (h) Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379. (i) Dálaigh, C. Ó.; Hynes, S. J.; O'Brien, J. E.; McCabe, T.; Maher, D. J.; Watsonb, G. W.; Connon, S. J. *Org. Biomol. Chem.* **2006**, 4. (j) Ebner, D. C.; Trend, R. M.; Genet, C.; McGrath, M. J.; O'Brien, P.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6367. (k) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115. (l) Tomizawa, M.; Shibuya, M.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1829. (m) Harada, S.; Kuwano, S.; Yamaoka, Y.; Yamada, K.-i.; Takasu, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10227.

(6) (a) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *20*, 1503. (b) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1. (c) Cho, B. T.; Kang, S. K.; Kim, M. S.; Ryub, S. R.; An, D. K. *Tetrahedron* **2006**, *62*, 8164.

(7) (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.

(8) (a) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243. (b) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67. (c) Zhao, Y.; Mitra, A. W.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8471. (d) You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 547. (e) Rodrigo, J. M.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2011**, *13*, 3778. (f) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8167. (g) Worthy, A. D.; Sun, X.; Tan, K. L. *J. Am. Chem. Soc.* **2012**, *134*, 7321. (h) Giustra, Z. X.; Tan, K. L. *Chem. Commun.* **2013**, *49*, 4370. (i) Manville, N.; Alite, H.; Haeffner, F.; Hoveyda, A. H.; Snapper, M. L. *Nat. Chem.* **2013**, *5*, 768. (j) Sun, X.; Worthy, A. D.; Tan, K. L. *J. Org. Chem.* **2013**, *78*, 10494.

(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) Weickgenannt, A.; Mewald, M.; Muesmann, T. W. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2223.

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

(11) Clark, R. W.; Deaton, T. M.; Zhang, Y.; Moore, M. I.; Wiskur, S. L. *Org. Lett.* **2013**, *15*, 6132.

(12) (a) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (b) Birman has demonstrated recoverability and stability of **2**: Bumbu, V. D.; Birman, V. B. *J. Am. Chem. Soc.* **2011**, *133*, 13902.

(13) Akhani, R. K.; Moore, M. I.; Pribyl, J. G.; Wiskur, S. L. *J. Org. Chem.* **2014**, *79*, 2384.

(14) Kinetic resolution of 998 mg of the compound in Table 2, entry 1: $s = 10$ with 52% conversion and recovered alcohol with an er of 85:15.

(15) (a) Conversions and selectivity factors are based on the ee of the recovered starting materials and products. Percent conversion = $ee_s/(ee_s + ee_p) \times 100\%$ and $s = \ln[(1 - C)(1 - ee_s)]/\ln[(1 - C)(1 + ee_s)]$, where ee_s = ee of recovered starting material and ee_p = ee of product. See ref 3a.. (b) Selectivity factors are an average of two runs. Conversions are from a single run.

(16) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons, Inc.: New York, 1994.

(17) Yang, X.; Fox, T.; Berke, H. *Tetrahedron* **2011**, *67*, 7121.

DOI: 10.1021/acs.orglett.5b00919
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