

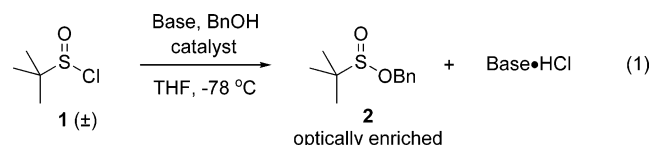
Catalytic Enantioselective Synthesis of Sulfinate Esters through the Dynamic Resolution of *tert*-Butanesulfinyl ChlorideJared W. Evans,[†] Matthew B. Fierman,[‡] Scott J. Miller,^{*,‡} and Jonathan A. Ellman^{*,†}

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Chiral sulfinate esters have been extensively used as the primary source for chiral sulfur compounds such as sulfoxides and sulfonamides.¹ Many diastereoselective methods for the formation of sulfinate esters exist, including highly efficient methods for the addition of chiral alcohols to sulfinyl halides with dynamic kinetic resolution.² In contrast, effective enantioselective methods have not been reported. Enantioselective oxidations of sulfenates,³ activation of sulfinic acids with chiral carbodiimides,⁴ and use of stoichiometric chiral bases have been reported.⁵ However, these enantioselective methods proceed with poor selectivities and typically require the use of stoichiometric chiral reagents. Herein we report the first example of a catalytic enantioselective synthesis of sulfinate esters through dynamic resolution of racemic *tert*-butanesulfinyl chloride (**1**). Under optimal conditions, as little as 0.5 mol % of the chiral catalyst may be used to obtain the desired sulfinate ester product in 99% conversion and with 80% ee.

To achieve a catalytic enantioselective synthesis of sulfinate esters by sulfinyl transfer, we chose to pursue a nucleophilic catalysis approach⁶ in the presence of a stoichiometric amine base that would consume the liberated HCl byproduct of the sulfinyl transfer reaction (eq 1). Therefore, we required reaction conditions where the background rate of catalysis by the stoichiometric base would be minimal. We first examined sulfinyl transfer using benzyl alcohol as the sulfinyl acceptor in the presence of the hindered tertiary amine bases Et₃N, *i*-Pr₂EtN and 1,2,2,5,5-pentamethylpiperidine. However, significant conversion to the benzyl sulfinate **2** was observed even at –78 °C (see Supporting Information).⁷ Proton sponge (1,8-bis(dimethylamino)naphthalene) was next evaluated because of its nonnucleophilic nature.⁸ Addition of 2.5 equiv of proton sponge in THF, ether, or toluene resulted in an undetectable rate after 40 h at –78 °C. In contrast, when the reaction was run in CH₂Cl₂, 27% conversion to the benzyl sulfinate **2** was observed over the same time period.



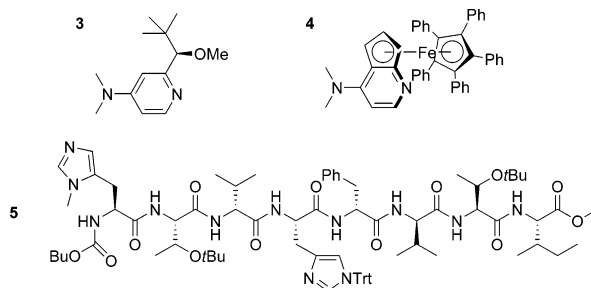
Using the optimized base, proton sponge, we next evaluated three well-studied chiral acyl transfer catalysts **3**–**5**⁹ because of the similarities between sulfinyl and acyl transfer. We first examined the chiral (dimethylamino)pyridine derivative **3** developed by Vedejs because it is expediently synthesized and provides good selectivities when employed as a stoichiometric acyl transfer reagent (Table 1, entries 1–3).¹⁰ Employing 10 mol % of catalyst **3**, we obtained sulfinate ester **2** in high yields in under 40 h, with ether

Table 1. Catalyst Screen for Sulfinyl Transfer (eq 1)

entry	catalyst (mol %)	solvent	time ^a (h)	yield of 2 (%) ^b	ee of 2 (%) ^c
1	3 (10)	PhMe	5	47	41
			40	96	40
2		Ether	5	15	45
			40	94	46
3		THF	5	48	36
			40	>99	37
4	4 (10)	PhMe	40	7	8
5		Ether	20	6	47
6		THF	5	17	56
			40	>99	56
7	5 (2)	PhMe	1	6	44
			20 ^d	>99	47
8		Ether	1	13	46
			20 ^d	>99	46
9		THF	1	56	80
			5	99	80
10	5 (0.5)	THF	40	99	80

^a Unless otherwise indicated, all reactions were performed at –78 °C.^b Yields determined by NMR with comparison to 2,6-dimethoxytoluene as an internal standard. ^c Enantiomeric excess determined by chiral HPLC.^d After 10 h at –78 °C, warming to 0 °C over 10 h was allowed.

providing the highest selectivities (up to 46% ee). It is important to note that, independent of solvent, the level of stereoinduction does not change with the conversion. *Additionally, the observed enantioselectivity at high conversion demonstrates that dynamic resolution occurs under the reaction conditions through rapid epimerization of the sulfinyl stereocenter.*¹¹



We next examined the more electron-rich ferrocene-derived acyl transfer catalyst **4** developed by Fu (entries 4–6).¹² Compared to **3**, catalyst **4** is reported to have increased nucleophilicity and reduced steric congestion, which has enabled its substoichiometric use in acyl transfer, providing resolutions with high selectivities. In the present context,¹³ catalyst **4** proved to be less active than **3** as a sulfinyl transfer catalyst. Reactions run in toluene and ether gave poor selectivity and were prohibitively slow at –78 °C (entries 4 and 5). While sluggish rates were observed in THF (entry 6),

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Table 2. Alanine Scan Library of Peptide **5**

entry	catalyst (residue change)	yield of 2 (%) ^a	ee of 2 (%) ^b
1	6 (L-Ile-1 to L-Ala-1)	>99	72
2	7 (L-Thr-2 to L-Ala-2)	68	64
3	8 (D-Val-3 to D-Ala-3)	>99	70
4	9 (D-Phe-4 to D-Ala-4)	91	81
5	10 (L-His-5 to L-Ala-5)	92	70
6	11 (D-Val-6 to D-Ala-6)	95	80
7	12 (L-Thr-7 to L-Ala-7)	45	32
8	13 (L-Me-His-8 to L-Ala-8)	<2	<2

^a Yields determined by NMR with comparison to 2,6-dimethoxytoluene as an internal standard. ^b Enantiomeric excess determined by chiral HPLC.

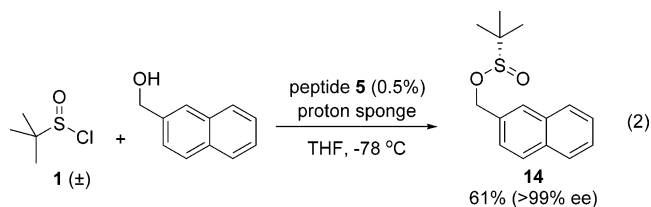
catalyst **4** produced sulfinate ester **2** with increased selectivity over catalyst **3** (up to 56% ee). Again, enantioselectivity did not change with conversion, demonstrating efficient dynamic resolution under the reaction conditions with catalyst **4** as well.

The *N*-methylimidazole-containing peptide **5** has been identified as a highly active and selective acyl transfer catalyst from a directed library of octapeptides.¹⁴ Because of the exceptional activity of **5**, we performed the solvent screen using 2 mol % catalyst loading (entries 7–9). Reactions run in THF provided the greatest rate and selectivity with complete conversion to **2** occurring in less than 5 h with an enantiomeric excess of 80%. Sulfinyl transfer reactions performed in toluene and ether proceeded with significantly diminished rates. Once again, product enantioselectivity did not vary with reaction conversion, demonstrating effective dynamic resolution. Under these optimal reaction conditions, the reaction was repeated at 0.5 mol % catalyst loading (entry 10). After 40 h, product **2** was obtained in 99% yield and 80% ee, demonstrating the exceptional efficiency and potential of this sulfinyl transfer process.

The modular nature of peptide **5** enables rapid analogue synthesis for the potential identification of superior catalysts. To obtain preliminary SAR, an alanine scan was carried out on peptide **5** wherein the eight analogues **6**–**13** were prepared such that alanine was sequentially incorporated at each position of the octapeptide.^{15,16} The library was evaluated with BnOH as nucleophile in THF (Table 2). Clear structure–activity relationships were observed for both yield and selectivity, with the alanine replacements at the *C* and *N* termini having the greatest impact. As expected, replacement of the *N*-terminal *N*-methylated histidine with alanine resulted in a dramatic reduction in rate and selectivity, emphasizing the importance of this residue for sulfinyl transfer (entry 8). Replacement of the *tert*-butyl-protected threonines at residues 2 and 7 also had a significant impact on both the catalytic activity and selectivity of the reaction (entries 2 and 7). In contrast, alanine substitutions in the middle of the peptide had little or no effect on conversion or selectivity (entries 3–6).

Using peptide **5** as the catalyst, a number of alcohols were evaluated as nucleophiles in the sulfinyl transfer reaction, and arylmethyl alcohols were found to react with similar rates and selectivities to benzyl alcohol (see Supporting Information). Indeed, addition of 2-naphthylmethyl alcohol to sulfinyl chloride **1** at 0.5 mol % catalyst loading provided the crystalline sulfinate product **14** (79% ee), which was obtained in >99% ee in a 61% overall yield from **1** after two recrystallizations (eq 2). Addition of phenyllithium to **14** proceeded in 90% yield to give *tert*-butyl phenyl sulfoxide with >99% ee and defines the absolute sense of induction of the sulfinyl transfer reaction (eq 2). Furthermore, this result demonstrates that sulfinyl ester **14** should serve as a versatile intermediate for the preparation of a variety of optically pure *tert*-

butyl sulfoxides and *tert*-butanesulfinamides.



We have developed a new synthetic route to obtain enantiomerically enriched *tert*-butanesulfinate esters in excellent yields through catalytic enantioselective sulfinyl transfer. While the DMAP-based catalysts **3** and **4** provide modest to good enantioselectivities, the *N*-methyl imidazole containing octapeptide **5** is a much more active catalyst and provides higher enantioselectivities. As little as 0.5 mol % of **5** can be used to couple racemic sulfinyl chloride **1** with arylmethyl alcohols in near quantitative yields in up to 81% ee. This method not only provides the first example of the catalytic dynamic resolution of sulfinyl derivatives, but is also the most enantioselective method for the synthesis of sulfinate esters to have been reported to date. We are currently expanding the scope of the method to other sulfinyl chlorides and are seeking more active and selective catalysts on the basis of the information gained from the alanine scan library.

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Supporting Information Available: Experimental procedures, absolute stereochemistry determination of **14**, and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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