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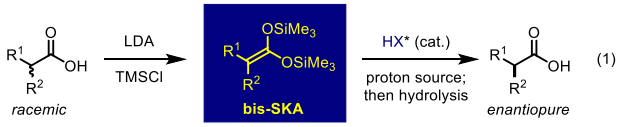
Deracemizing α-Branched Carboxylic Acids by Catalytic Asymmetric Protonation of *bis*-Silyl Ketene Acetals with Water or Methanol

*Francesca Mandrelli, Aurélie Blond, Thomas James, Hyejin Kim and Benjamin List**

Abstract: *We report a highly enantioselective catalytic protonation of bis-silyl ketene acetals. Our method delivers α-branched carboxylic acids, including non-steroidal anti-inflammatory arylpropionic acids such as Ibuprofen, in high enantiomeric purity and high yields. The process can be incorporated in an overall deracemization of α-branched carboxylic acids, involving a double deprotonation and silylation followed by the catalytic asymmetric protonation.*

Carboxylic acids are not only valuable synthetic intermediates, but are themselves ubiquitous structural motifs in biologically active compounds.[1] In particular, enantiomerically pure α-stereogenic carboxylic acids are frequently encountered in a variety of natural products and pharmaceuticals, especially in non-steroidal anti-inflammatory drugs (NSAIDs). Despite their prevalence, multi-step strategies are generally required to access these moieties,[2] as direct catalytic asymmetric α-functionalizations and α-alkylations of free carboxylic acids remain challenging. In continuation of our studies on deracemization[3] reactions of carboxylic acid derivatives,[4] we envisioned that a double deprotonation of α-branched carboxylic acids, followed by an enantioselective protonation of the corresponding *bis*-silyl ketene acetals (*bis*-SKAs) could offer a straightforward approach to the targeted enantiomers (eq. 1). The successful realization of this concept is reported here.



Catalytic enantioselective protonations of silyl enol ethers and silyl ketene acetals have previously been reported.[5] These substrates, however, pose the particular challenge of controlling a substrate's enolate geometry[6] and furthermore often require cryogenic reaction temperatures, slow reagent addition, or a sterically-demanding proton source (PS), such as 2,6-dimethylphenol (DMP), to overcome racemic background reactivity and/or to ensure catalyst stability under the inherently protic reaction conditions (Figure 1).[6a, 6e, 7]

Alternatively, *bis*-SKAs not only offer complementary and direct access to α-stereogenic carboxylic acids, but also intrinsically avoid the added complexity of differing enolate geometry. However, due to their relatively high nucleophilicity and extreme reactivity with any PS, the applicability of *bis*-SKAs has so far required a bulky PS under strictly inert reaction conditions and very low temperatures. The first enantioselective protonation of *bis*-SKAs was reported by Yamamoto *et al.* using a stoichiometric amount of a Lewis acid assisted Brønsted acid (LBA) and a chiral BINOL–tin complex in combination with DMP as a bulky PS (Figure 1).[6a, 6b, 8] In the context of this work, a single example of a catalytic version was also described. Two decades later, Ooi *et al.* reported the use of *p*-spiro diaminodioxaphosphonium barfates as chiral catalysts,[9] expanding the scope of the transformation to α-halo and α-alkoxy alkyl *bis*-SKAs.[10] This method also requires 2,6-dimethylphenol as PS, strict inert conditions, extremely low temperatures, and electronically biased substrates. A general catalytic method that employs a simple proton source and tolerates less-biased *bis*-SKAs (eq. 3) has hitherto not been described.

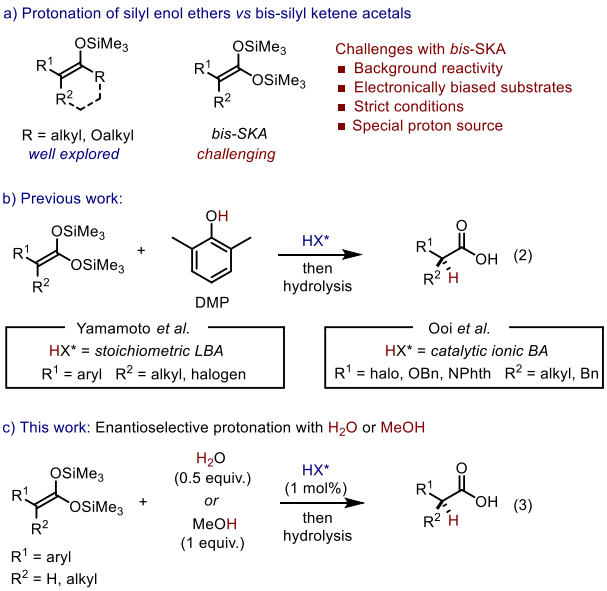


Figure 1. Asymmetric Protonations of *bis*-Silyl Ketene Acetals.

We initiated our studies by investigating the protonation of α-phenyl-α-methyl *bis*-SKA (**1a**) in the presence of chiral Brønsted acid catalysts (see the SI for further information). Remarkably, only chiral disulfonimides (DSIs)[11] showed promising enantiocontrol (Table 1). Using 2 mol% of DSI **2a** in the presence of 1.1 equiv. of MeOH at room temperature led to full conversion of **1a** within 10 min and product **3a** was obtained in promising enantioselectivity (Entry 2, 78:22 er). Further investigation of the substituents in the 3,3'-position of the catalyst revealed that an extended π-surface (**2b**) resulted in increased enantioselectivity (Entry 3, 89:11 er).

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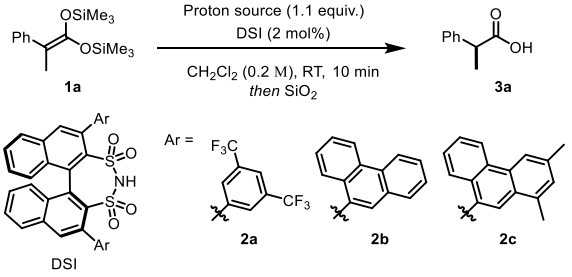
Table 1. Reaction Development.[a]



Entry	Cat.	Proton source	Conv.[b]	er[c]
1	–	MeOH	Full[d]	50:50
2	2a	MeOH	Full	78:22
3	2b	MeOH	Full	89:11
4	2c	MeOH	Full	95.5:4.5
5	2c	2,6-dimethylphenol	Full	95.5:4.5
6	2c	H_2O	Full	95:5

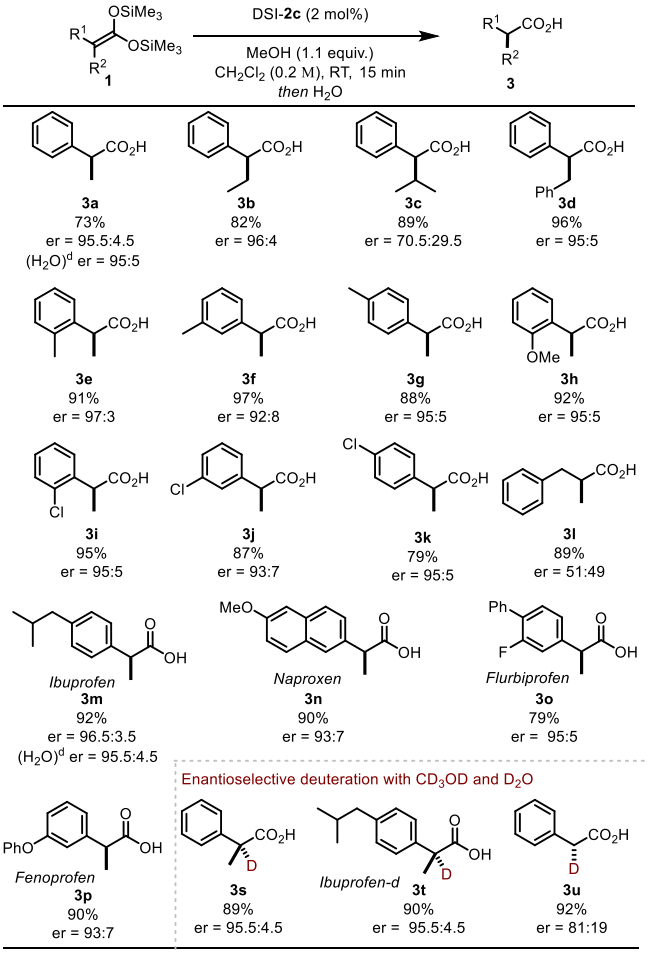
[a] Reactions were performed on a 0.02 mmol scale. [b] Determined by ^{1}H-NMR. [c] Work up: the crude reaction was loaded onto a preparative TLC plate (CH_2Cl_2:MeOH, 98:2) and the er of the product (R_f = 0.5) was directly determined by chiral phase HPLC, see the SI for further information. [d] 6 h.

Ultimately, we identified DSI **2c** as a highly enantioselective catalyst (Entry 4, 95.5:4.5 er). Other PSs such as EtOH, *i*PrOH, *t*BuOH (see Table 3, Entries 4-9) and DMP (Entry 5) were investigated; however, essentially identical enantioselectivities were obtained in all cases. Gratifyingly, even water could be used without compromising the enantioselectivity (Entry 6, 95:5 er).

Encouraged by these promising results, we explored a variety of differentially-substituted *bis*-SKAs, which were obtained quantitatively by an independently developed procedure (for further information, see the SI). Various alkyl substituents were well tolerated in the asymmetric protonation, including a longer alkyl chain (**3b**, 96:4 er) and a benzyl group (**3d**, 95:5 er). However, substitution of the alkyl unit with an isopropyl group (**3c**) resulted in diminished enantioselectivity (70.5:29.5 er), suggesting that the enantioinduction of this catalytic system is extremely sensitive to the size of R^1 and R^2. O*rtho*- (**3e**, 97:3 er, and **3h**, 95:5 er) and *para*-substitution (**3g**, 95:5 er) on the aromatic unit proved to be superior to *meta*-substitution (**3f**, 92:8 er). Electron-rich (**3e**-**3h**), as well as electron-deficient (**3i**-**3k**) aromatic substituents, displayed a similar position-dependent selectivity pattern. NSAID-derived *bis*-SKAs showed an analogous trend, where *para*-substituted starting materials (**3m** and **3o**) gave slightly higher enantioselectivities than *meta*-substituted ones (**3n** and **3p**). As observed in previous DSI-catalyzed transformations, the enantioselectivity of this method is dependent on an α-aromatic-α-alkyl substitution pattern, as α-alkyl- α-alkyl substrates, such as carboxylic acid **3l**, were obtained in essentially racemic form.[11k] Consistent results were obtained also when using water as a PS (**3a**, 95:5 er, and **3m**, 95.5:4.5 er). The robustness of this catalytic system to any PS gave us direct access also to deuteration products (**3s**, 95.5:4.5 er, and **3t**, 95.5:4.5 er) achieving the first organocatalytic enantioselective deuteration of *bis*-SKAs with D_2O or CD_3OD. Moderate enantioselectivity was obtained with a monosubstituted bis-SKA furnishing enantioenriched α-deuterated phenylacetic acid **3u** with an er of 81:19 er.

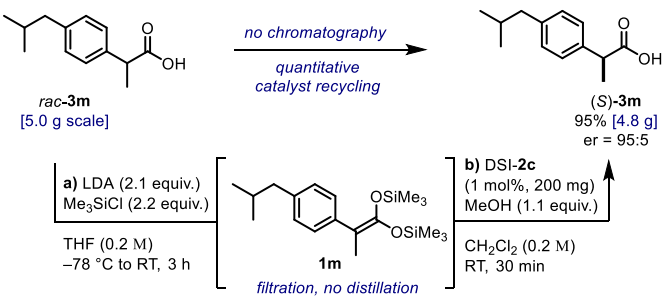
To illustrate the practicality of our method, a late stage deracemization of Ibuprofen (**3m**) was performed on a multigram scale (Scheme 1). Starting from 5.2 grams (25 mmol) of (±)-**3m** in THF, stoichiometric amounts of trimethysilyl chloride (TMSCl)

Table 2. Exploration of the Substrate Scope.[a-c]



[a] Reactions were performed on a 0.2 mmol scale. [b] Isolated yield, upon extraction [c] er was determined by chiral phase HPLC, without further derivatization, see the SI for further information [d] using H_2O (0.55 equiv.) instead of MeOH as proton source.

and freshly prepared lithium diisopropylamide (LDA) were added at –78 °C. The solution was allowed to reach room temperature and upon evaporation, the suspension of product and LiCl was filtered, furnishing ketene acetal **1m** with >95% purity, which was used without further purification. Subsequently, solvent and catalyst (1 mol%) were directly added to *bis*-SKA **1m** and 1.1 equiv. of MeOH were added over 30 min. Upon extraction, the final product was isolated in 95% yield and 95:5 er; furthermore, the catalyst was recycled upon extraction, followed by acidification, in quantitative yield.



Scheme 1. Chromatography-free preparative deracemization of (±)–Ibuprofen (**3m**).

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To gain insight into the reaction mechanism, we studied the effect of the proton source on the conversion and stereochemical outcome (Table 3). In the absence of a proton source, a conversion equal to the catalyst loading was observed (Entries 1 and 2), suggesting that the catalyst is the actual proton source. Turnover was only observed upon adding a stoichiometric amount of proton source (Entries 3 and 4). Notably, enantioselectivities consistently proved to be independent of the proton source (Entries 4-9), suggesting that the stoichiometric PS is not involved in the enantiodetermining step. Further, even a sub-stoichiometric amount of water enables full conversion (Entry 10), as the 0.5 equiv. of silanol, formed during the protodesilylation of the SKA, functions as an efficient proton source, ultimately generating hexamethyldisiloxane.

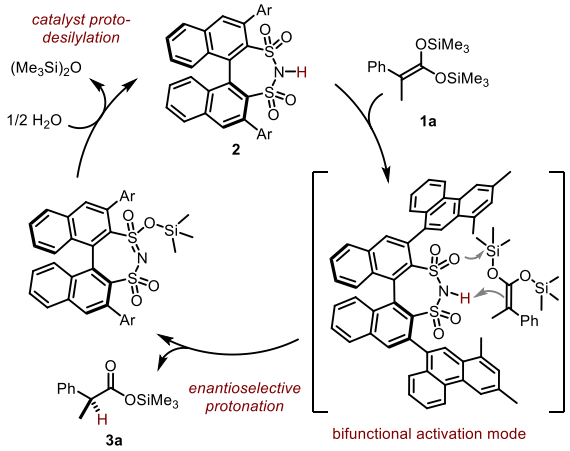
Table 3. Reaction mechanism investigation.[a]

Entry	Cat. (mol%)	Proton source (equiv)	Conv.(%)[b]	er[c]
1	50	-	~50	nd
2	100	-	Full	95.5:4.5
3	50	MeOH (1.0)	Full	95.5:4.5
4	1	MeOH (1.1)	Full	95.5:4.5
5	1	EtOH (1.1)	Full	95.5:4.5
6	1	iPrOH (1.1)	Full	95:5
7	1	tBuOH (1.1)	Full	95:5
8	1	DMP (1.1)	Full	95.5:4.5
9	1	H_2O (1.1)[e]	Full	95:5
10	1	H_2O (0.55) [e]	Full	95:5
11	1	CD_3OD (1.1)	Full	95.5:4.5

[a] Reactions were performed on a 0.02 mmol scale. [b] Determined by ^{1}H-NMR. [c] Determined by chiral phase HPLC, see the SI. [e] Addition of water as stock solution in dichloromethane (2%, V/V).

We speculate that the high efficiency of our catalytic system, compared to that of the racemic background reaction, is a result of a relatively fast protodesilylation event depicted in the proposed transition state (TS) (Figure 2), which likely exploits the bifunctionality of the DSI with its high N–H acidity and concomitant Lewis-basicity of the S=O bond, in combination with the oxophilicity of the silicon group. An analogous protodesilylation event can be envisioned for the re-protonation of **3** by the achiral PS, overall resulting in a fast and efficient enantioselective protonation. In this scenario, the background reaction between **1a** and the achiral PS can be avoided by the high efficiency of the catalytic system without the need of a bulky PS, thereby improving the atom economy of the protonation step.

Figure 2. Proposed catalytic cycle.



In summary, we have developed a deracemization of α-branched aryl carboxylic acids based on the asymmetric Brønsted acid-catalyzed protonation of the corresponding *bis*-silyl ketene acetals in the presence of methanol or water. The operationally simple protocol allows a facile transformation under mild reaction conditions and exclusively furnishes the enantioenriched products in quantitative yields starting from the corresponding racemic acid without the need for additional purification. We suggest that the bifunctional activation mode of the DSI catalyst enables a highly efficient catalytic cycle that in turn circumvents racemic background reactivity with the achiral, stoichiometric PS. The late stage deracemization of NSAIDs on gram scale and the simple direct enantioselective deuteration of bis-silyl ketene acetals using CD_3OD or D_2O as deuterium source demonstrate applicability of the developed system.

Acknowledgements

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Keywords: Brønsted acids · deracemization · bis-silyl ketene acetals · disulfonimide (DSI) · protonation · deuteration · organocatalysis ·

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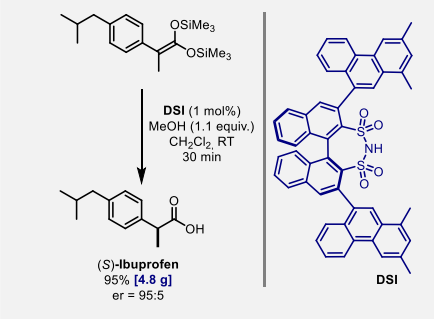

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Deracemizing α-Branched Carboxylic Acids by Catalytic Asymmetric Protonation of bis-Silyl Ketene Acetals with Water or Methanol