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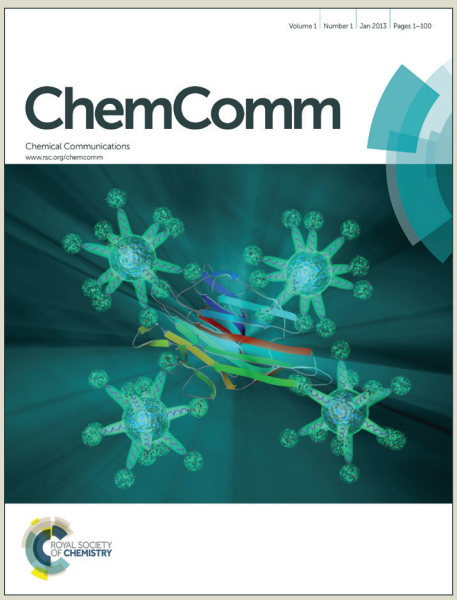

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Enantioselective Protonation of α-Hetero Carboxylic Acid-Derived Ketene Disilyl Acetals under Chiral Ionic Brønsted Acid Catalysis†

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Highly enantioselective protonation of α-halo and alkoxy carboxylic acid-derived ketene disilyl acetals is achieved by using *P*-spiro chiral diaminodioxaphosphonium barfate as a Brønsted acid catalyst, where the enantiofacial discrimination by the catalyst mainly stems from the recognition of the electronic difference between two substituents on the ketene disilyl acetal.

Catalytic enantioselective protonation of prochiral enolates and their equivalents is one of the simplest and most straightforward processes for the construction of a tertiary stereogenic carbon center at the α-position of a carbonyl functionality.[1] An overview of the existing systems reveals the uniqueness of the asymmetric protonation of silyl-masked enolates in terms of geometric integrity of the substrate and non-dependence of their reactivity on the pK_a value of the parent enolate.[2-9] However, protocols that enable a high level of stereocontrol are largely limited to silyl enolates derived from α-tertiary cyclic ketones and α-aryl carboxylic acids. Thus, the development of versatile enantioselective catalysis applicable to other structural classes of silyl enolates is in high demand. In these situations, we recently realized the first catalytic enantioselective protonation of ketene disilyl acetals of α-hetero-substituted carboxylic acids, namely *N*-phthaloyl α-amino acids, by virtue of the prominent proton-transfer ability of *P*-spiro diaminodioxaphosphonium barfate of type **1**·HBArF.[10-13] This chiral ionic Brønsted acid catalyst delivered a proton predominantly from *si*-face of the enolate probably through effective recognition of the terminal substituents, phthaloyl imide and alkyl moieties. As part of our continuous efforts for eliciting the full potential of the catalysis exerted by **1**·HBArF in this mode of stereoselective protonation reactions, we pursued its application to ketene disilyl acetals prepared from other carboxylic acids bearing an α-heteroatom such as halogen atoms with particular interest in the effect of the structural difference between a *planar* phthaloyl imide group and a *spherical* halogen atom on the facial selectivity. Here, we report the preliminary results of our investigations on an enantioselective protonation of α-halo and alkoxy carboxylic acid-derived ketene disilyl acetals under the catalysis of chiral phosphonium barfate **1**·HBArF.[14,15] Highly *si*-face-selective proton delivery was revealed to be a general trend for a variety of hetero-substituted ketene disilyl acetals, thereby demonstrating the importance of the electronic bias of the terminal substituents rather than their steric nature in the present enantiofacial discrimination.

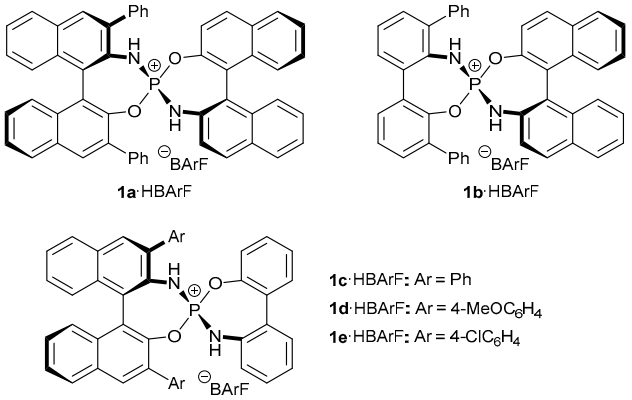


Figure 1. *P*-Spiro chiral diaminodioxaphosphonium barfates **1** (BArF = [3,5-$(CF_3)_2C_6H_3]_4$B)

We chose α-bromo hydrocinnamic acid-derived ketene disilyl acetal **2a** as a model substrate and subjected it to protonation with 2,6-dimethylphenol (stoichiometric proton source) in the presence of 2 mol% each of chiral phosphonium barfate **1**·HBArF and 2,6-di-*tert*-butylpyridine in toluene at –40 °C. Our aim of this inaugural exploration, considering the structural feature of **1**·HBArF consisting of tetraaryl and biaryl subunits, was to objectively evaluate the necessity of incorporating a chiral binaphthyl core into both these components for obtaining a synthetically satisfactory level of enantioselectivity (Table 1). When the reaction was implemented with **1a**·HBArF comprising two binaphthyl-based subunits as a Brønsted acid catalyst, the parent α-bromo hydrocinnamic acid (**3a**) was obtained quantitatively, and the enantiomeric excess was determined to be 89% ee after derivatization to the corresponding methyl ester by treatment with trimethylsilyldiazomethane (entry 1). The observed high

enantioselectivity reflects the ability of the catalyst to discriminate the enantiofaces of prochiral **2a** though the recognition of the steric or electronic difference between the bromide and alkyl substituents. While replacement of the binaphthyl moiety of the tetraaryl component with an achiral biphenyl structure (**1b**·HBArF) impaired the enantioselectivity, a simple biphenyl was found to be superior in serving as biaryl subunit (entries 2 and 3). We then modified the peripheral aryls of the tetraaryl subunit for examining the effect on the selectivity; this revealed that the introduction of 4-substituted phenyl groups slightly decreased the stereoselectivity irrespective of their electronic properties (entries 4 and 5).

Table 1 Optimization of the Catalyst Structure[a]

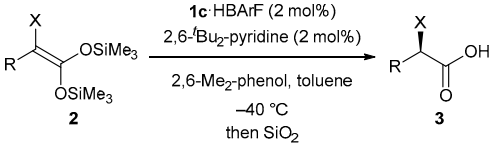
entry	**1**	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	26	99	89
2	**1b**	24	99	75
3	**1c**	21	99	93
4	**1d**	26	99	92
5	**1e**	63	99	83

[a] Reactions were conducted with 0.1 mmol of **2a**, 0.11 mmol of 2,6-Me_2-phenol, 2 mol% of 2,6-^{t}Bu_2-pyridine, and 2 mol% of **1**·HBArF in toluene at –40 °C. [b] Isolated yields were indicated. [c] Enantiomeric excesses of **3a** were determined by chiral stationary phase HPLC as its methyl ester, which was obtained by treatment of **3a** with $Me_3SiCH=N_2$ in benzene/MeOH at rt. Absolute stereochemistry of **3a** was determined to be *R* by comparison of specific rotation with the literature value.[16]

Having identified the catalyst structure suitable for effecting the present asymmetric protonation reaction, we surveyed the substrate generality (Table 2). Under the catalysis of **1c**·HBArF, enantiofaces of a series of bromo-substituted ketene disilyl acetals with linear alkyl chains were precisely discriminated and the parent α-bromo alkanoic acids were isolated with high enantioselectivities (entries 1-3). The steric demand of the alkyl substituent afforded a subtle effect on the degree of facial selectivity, as seen in the reaction with the substrate having an isobutyl group (entry 4). It was of interest that the asymmetric protonation of other α-halo carboxylic acid-derived ketene disilyl acetals also proceeded generally with good to high enantioselectivities, indicating that the identity of the halogen atom had a marginal effect on the stereochemical outcome (entries 5-10). Furthermore, the present system tolerated the incorporation of not only simply spherical halogen atoms but also alkoxy groups as hetero substituents on ketene disilyl acetals, thus offering facile access to enantioenriched *O*-protected lactic acid and mandelic acid derivatives (entries 11-14).

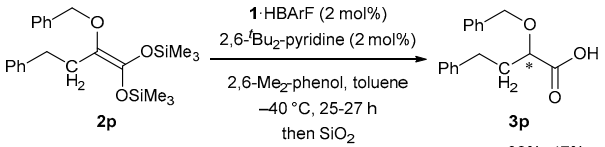
The observed insensitivity of enantioselectivity to the size of a hetero substituent prompted us to clarify the most important factor for precise enantiofacial discrimination at the proton transfer stage. Judging from the scope of this **1c**·HBArF-catalyzed protocol, electronic bias of the terminal substituents plays a more crucial role than their steric features. Therefore, pseudo-symmetric ketene disilyl acetal **2p** with minimal steric difference between the terminal substituents was prepared for assessing the validity of our assumption (Scheme 1). Actual exposure of **2p** to the optimized conditions led to the quantitative formation of the corresponding α-benzyloxy carboxylic acid **3p** with 47% ee. Moreover, the enantiomeric excess of **3p** was significantly enhanced when using **1a**·HBArF as the catalyst. These results clearly show that chiral phosphonium ion **1**·H is indeed capable of appreciating the electronic propensity of the two terminal substituents on **2**.

Table 2 Substrate Generality[a]



entry	X, R (**2**)	time (h)	yield (%)[b]	ee (%)[c]	**3**
1	Br, Me (**2b**)	24	87	89	**3b**[d]
2	Br, Et (**2c**)	23	92	92	**3c**
3	Br, $Me(CH_2)_5$ (**2d**)	22	93	93	**3d**
4	Br, Me_2CHCH_2 (**2e**)	24	90	85	**3e**
5	I, Bn (**2f**)	26	92	93	**3f**[d]
6	I, $Me(CH_2)_5$ (**2g**)	25	99	90	**3g**
7	Cl, Bn (**2h**)	24	86	87	**3h**[d]
8	Cl, $Me(CH_2)_5$ (**2i**)	26	92	90	**3i**
9	F, Bn (**2j**)	27	93	88	**3j**[d]
10	F, $Me(CH_2)_5$ (**2k**)	22	90	92	**3k**[d]
11	BnO, Me (**2l**)	24	86	95	**3l**[d]
12	BnO, Ph (**2m**)	20	99	89	**3m**[d]
13[e]	BnO, 4-$MeOC_6H_4$ (**2n**)	26	93	89	**3n**
14	2-$NaphCH_2O$, Ph (**2o**)	27	92	91	**3o**

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2**, 0.11 mmol of 2,6-Me_2-phenol, 2 mol% of 2,6-^{t}Bu_2-pyridine, and 2 mol% of **1c**·HBArF in toluene at –40 °C. [b] Isolated yields were reported. [c] Enantiomeric excesses of **3** were determined by chiral stationary phase HPLC after converting into the corresponding esters, see ESI† for further details. [d] Absolute configurations were determined to be *R* by comparison of optical rotations with literature data, see ESI† for details. Stereochemistries of other carboxylic acids were assigned by analogy. [e] Reaction temperature was –20 °C.



1c·HBArF: 92%, 47% ee
1a·HBArF: 99%, 90% ee

Scheme 1. Enantioselective Protonation of Pseudo-Symmetric Ketene Disilyl Acetal **2p**

In conclusion, we have achieved a catalytic, highly enantioselective protonation of α-halo and alkoxy carboxylic acid-derived ketene disilyl acetals for the first time based on the utilization of the prominent proton-transfer and stereocontrol abilities of appropriately modified *P*-spiro diaminodioxaphosphonium barfates **1**·HBArF. The origin of the stereoselectivity most likely resides in the recognition of the difference in the electronic attributes of the terminal substituents of the ketene disilyl acetal by the chiral phosphonium ion. We believe that the present study underscores the synthetic potential of this class of chiral ionic Brønsted acid catalysts.

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Notes and references

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of **2** and **3**. See DOI: 10.1039/c3cc00000x/

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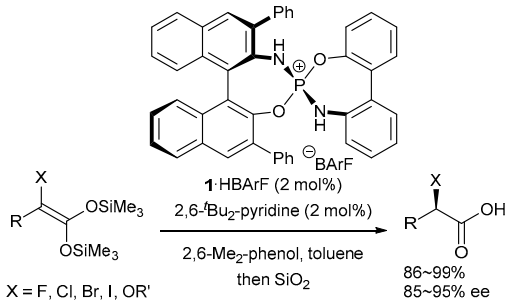
Graphical Abstracts



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