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Catalytic Asymmetric Protonation of Silyl Ketene Imines

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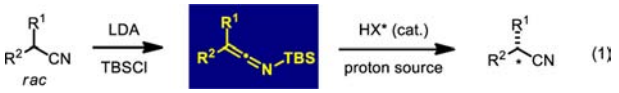
Supporting Information

ABSTRACT: An efficient catalytic and highly enantioselective protonation of silyl ketene imines is described. The reaction is catalyzed by the chiral phosphoric acids **TRIP** or **STRIP** in the presence of a stoichiometric amount of methanol as the proton source and silyl acceptor. A variety of substituted racemic silyl ketene imines have been transformed into highly enantioenriched nitriles.

The nitrile functional group is a pharmacophore in biologically active compounds[1] and a versatile precursor of other functionalities such as carboxylic acids, ketones, aldehydes, and amines.[2] Enantiopure α-alkyl-α-arylnitriles are particularly important as the corresponding carboxylic acids have extensively been used as nonsteroidal anti-inflammatory drugs.[3] While few catalytic asymmetric syntheses of α-branched nitriles have been reported, including olefin hydrocyanations,[4] conjugate cyanations,[5] and Negishsi cross-couplings,[6] a mild, organocatalytic approach may constitute an attractive and complementary alternative. Herein we describe an efficient catalytic and enantioselective protonation of silyl ketene imines (SKIs), which are readily available from racemic nitriles. Our method offers a straightforward entry to enantioenriched secondary nitriles under mild reaction conditions (eq 1).



(1)

The asymmetric catalytic protonation of cyclic ketone-derived enol silanes has been well investigated.[7] However, analogous protonations of enolsilanes derived of acyclic ketones and carboxylic acid derivatives remain challenging.[8,9] We hypothesized that SKIs, which are easily obtained from the corresponding branched nitriles via deprotonation and silylation, and known to easily racemize,[10a] may undergo an asymmetric protonation generating the corresponding enantiopure nitriles via dynamic kinetic resolution. Asymmetric protonations of SKIs had previously been entirely unknown.

SKIs are currently being established as highly useful carbon nucleophiles that have been employed in the construction of challenging all-carbon quaternary stereogenic centers.[10] While the synthetic potential of SKIs is well appreciated,[11] their use in asymmetric catalysis has not been extensively studied. Fu et al. described a catalytic asymmetric acylation of SKIs using a chiral DMAP-type catalyst.[12] Their implementation in chiral Lewis base catalyzed asymmetric aldol reactions with aldehydes has been reported by the Denmark group.[13] Recently, chiral silicon Lewis acid mediated asymmetric Mannich reactions of SKIs with acylhydrazones have been described by Leighton et al.[14]

We have recently introduced chiral disulfonimides (DSI) as highly active and enantioselective pre-Lewis acid catalysts of silicon-transfer-based carbon−carbon-bond forming reactions.[15] In the context of these studies, we also became interested in exploring SKIs as nucleophiles. We quickly realized that, in the presence of our DSI catalysts and diverse electrophiles, often a small amount of the SKI underwent decomposition to the parent nitrile. Remarkably, the obtained material was enantioenriched implying participation of the chiral catalyst. On the basis of this observation, we envisioned that an enantioselective protonation of racemic SKIs could possibly be occurring. Since asymmetric protonations of SKIs had not been reported before and in light of the high synthetic value of enantioenriched α-branched nitriles, we decided to further investigate this remarkable transformation.

We began our studies by investigating the protonation of SKI **1a** in the presence of a variety of chiral Brønsted acid catalysts and methanol as a proton source (Table 1).[16] A catalytic amount of DSI-catalyst **2** (5 mol %) indeed promoted the reaction in the presence of 1.2 equiv of methanol. Complete conversion of imine **1a** in a mixture of pentane and toluene at room temperature was obtained in 2 h, but a very low enantiomeric ratio (60:40 er) was observed (entry 1). We also investigated alternative chiral acids including several BINOL-derived phosphoric acids (**3**,**4**) and the spirocyclic variation **STRIP** (**5**).[17−19] The H8-BINOL phosphate **3** and BINOL phosphates **4a** and **4b** with 3,5-$(CF_3)_2C_6H_3$- and 3,5-$(SF_5)_2C_6H_3$-substituents proved to be highly active, but again, only poor enantioselectivity was obtained (entries 2−4). $SiPh_3$-substituted catalyst **4c** enabled the reaction with a promising enantiomeric ratio (e.r.) of 77:23 (entry 5). A significant improvement was obtained by using commercially available **TRIP** (**4d**) (e.r. = 92:8, entry 6). Even slightly better enantioselectivity (96:4 er) was achieved when using 5 mol % of **STRIP** (**5**, entry 7). Importantly, the catalyst loading could be reduced to only 2.5 mol % with catalyst **5** without erosion of enantioselectivity and yield (entry 8). Decreasing the catalyst loading further to 1 mol % was detrimental (entry 9). Even with **TRIP**, excellent enantioselectivity could be achieved when the reaction temperature was lowered to −78 °C (e.r. = 96:4, entry 10). However, the catalyst loading could not be further reduced with this catalyst (entry 11). SKIs with different silicon protecting groups were also prepared but gave inferior results (entries 12, 13).

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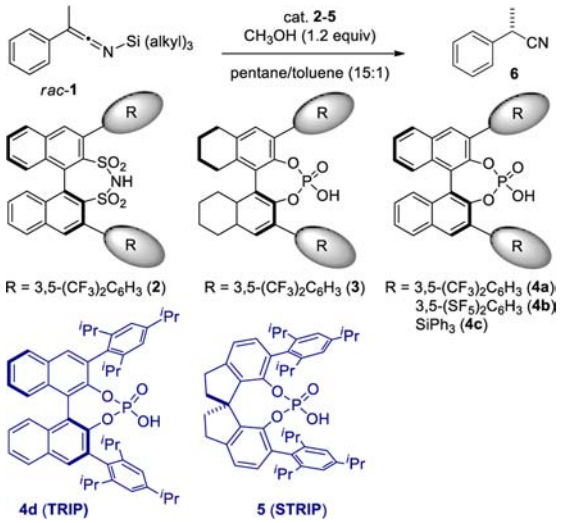
Table 1. Catalyst Identification and Reaction Optimization[a]

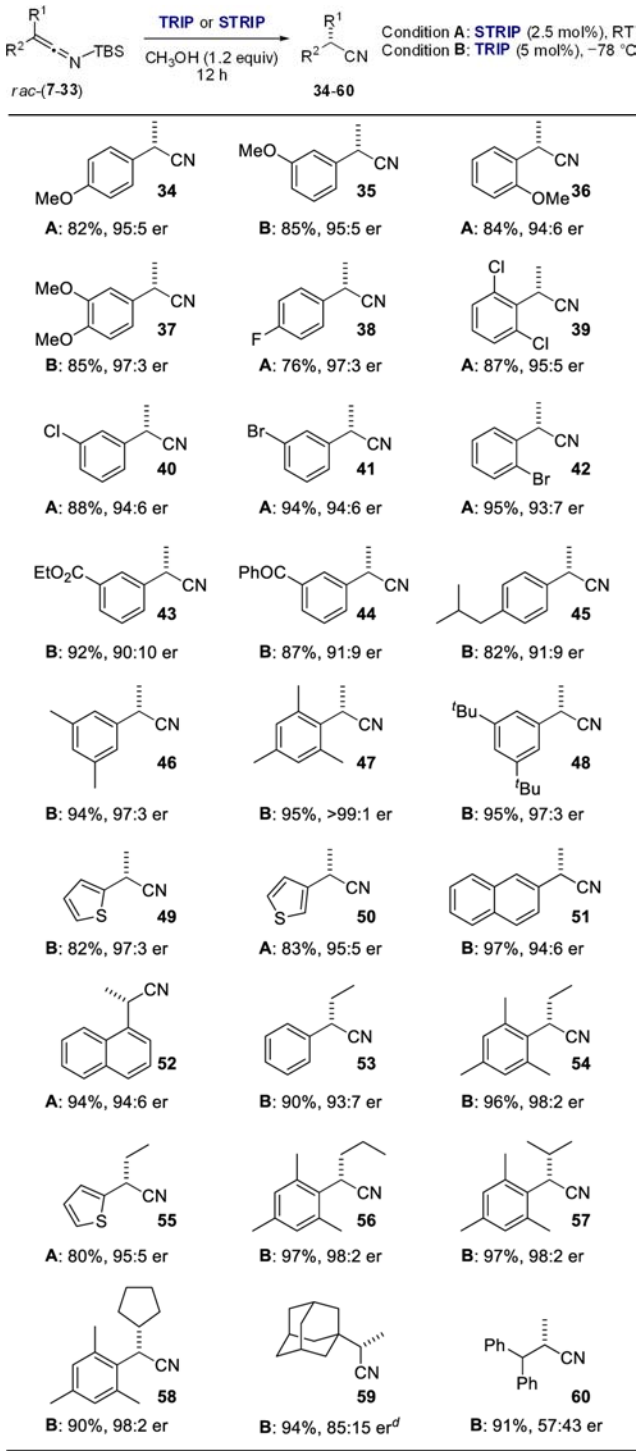


entry	cat (mol%)	Si(alkyl)$_3$	conv(%)[d]	t (h)	er[f]
1	**2** (5.0)	TBS (**1a**)	100	2	60:40
2	**3** (5.0)	TBS	100	6	53:47
3	**4a** (5.0)	TBS	100	6	53:47
4	**4b** (5.0)	TBS	100	6	53:47
5	**4c** (5.0)	TBS	100	6	77:23
6	**TRIP** (5.0)	TBS	100	6	92:8
7[b]	**STRIP** (5.0)	TBS	100(88)[e]	6	96:4
8[b]	**STRIP** (2.5)	TBS	100(87)[e]	12	96:4
9[b]	**STRIP** (1.0)	TBS	100	36	69:31
10[b,c]	**TRIP** (5.0)	TBS	100(87)[e]	12	96:4
11[b,c]	**TRIP** (2.5)	TBS	100	24	64:36
12[b,c]	**TRIP** (5.0)	TES (**1b**)	100	12	70:30
13[b,c]	**TRIP** (5.0)	TIPS (**1c**)	100	12	94:6

[a]Unless otherwise specified, all reactions were carried out at 0.1 mmol scale of SKI **1a** at room temperature in a 15:1 (v/v) mixture of pentane and toluene. [b]Reactions were performed at 0.2 mmol scale of SKIs **1a-c**. [c]Reactions were performed at −78 °C. [d]Determined by ^{1}H NMR analysis. [e]Isolated yield. [f]Enantiomeric ratio (e.r.) determined by HPLC analysis on a chiral stationary phase. TBS = Dimethyl-*tert*-butylsilyl. TIPS = Triisopropylsilyl. TES = Triethylsilyl.

We then directed our attention toward exploring the reaction scope with different substituted SKIs. Several TBS-protected SKIs with varying substituents at both the alkyl and aryl moiety were prepared from the corresponding nitriles using literature procedures (see Supporting Information (SI)).[12,13c] Either one or the other of the two best reaction conditions, with 2.5 mol % of **STRIP** at room temperature (condition **A**) or 5 mol % of **TRIP** at −78 °C (condition **B**), was used. A broad range of SKIs could be converted to the corresponding nitriles **34**−**60** in high yields with good to excellent enantioselectivity (Table 2).[20] Electron-rich SKIs bearing *para*-, *meta*-, and *ortho*-methoxy substituted phenyl moieties delivered the corresponding nitriles **34**−**37** in good yields (82−85%) and enantiomeric ratios (94:6−96:4 er). Electron-deficient SKIs with a fluoro, chloro, and bromo substituent at the phenyl ring were equally well tolerated. Ester and ketone functionalized nitriles **43** and **44** were obtained with slightly lower enantioselectivity.

Table 2. Substrate Scope[a,b,c]



[a]All reactions were carried out at 0.2 mmol scale of SKIs (**7**−**33**) in a 15:1 (v/v) mixture of pentane and toluene (8.0 mL, 0.025 M). [b]Isolated yield. [c]Enantiomertic ratio (e.r.) determined by HPLC on a chiral stationary phase. [d]Enantiomertic ratio determined by GC on a chiral stationary phase.

Gratifyingly, nitriles **45**−**47** with *para*-, *meta*-, and *ortho*-alkyl substituents at the phenyl ring could also be obtained in good yields (88−95%) and with good to excellent enantioselectivity (90:10→99:1 er). A sterically demanding substrate bearing a 3,5-di-*tert*-butyl substituted phenyl moiety gave the desired product **48** in excellent enantioselectivity (97:3 er). Thiophene

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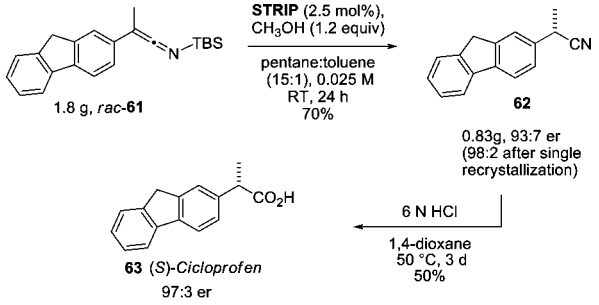
substituted SKIs could also be transformed efficiently to the corresponding highly enantioenriched products **49**–**50**. Naphthyl-substituted SKIs gave products **51**–**52** in slightly lower enantioselectivity.

We further expanded the utility of our reaction toward the synthesis of highly enantioenriched α-alkyl-α-arylnitriles bearing longer *n*-alkyl and α-branched alkyl substituents. Indeed, nitriles **53**–**56** with ethyl and propyl substituents could be prepared with good to excellent enantiocontrol. Remarkably, sterically demanding α-branched alkyl substituted racemic SKIs underwent an efficient protonation and furnished nitriles **57**–**58** in good yields (90–97%) with an excellent enantiomeric ratio of 98:2. α,α-Dialkyl substituted SKIs were also examined in our transformation. Unfortunately, the corresponding nitriles **59**–**60** were formed only in moderate enantioselectivity under the optimized reaction conditions.

Absolute configurations of compounds **6** and **53** [both (*S*)] were determined by comparing the optical rotation with literature data (see the SI), and absolute configurations of all others compounds were assigned by analogy.[21]

To illustrate the practical utility of our reaction, a preparative scale experiment was performed. Accordingly, 1.8 g of SKI **61** was subjected to our catalytic asymmetric protonation protocol and gave 0.83 g of corresponding nitrile **62** in 70% yield with an e.r. of 93:7. A single recrystallization improved the e.r. to 98:2 (Scheme 1). The nitrile **62** was then transformed to the anti-inflammatory drug Cicloprofen **63** in good yield with a high enantiomeric ratio of 97:3.

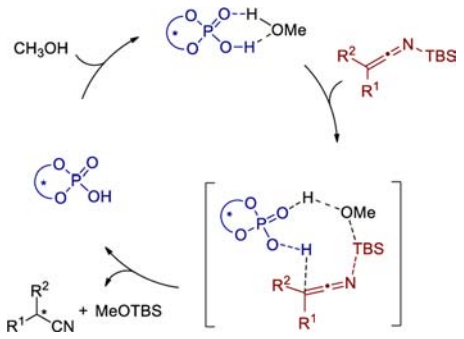
Scheme 1. Gram Scale Experiment and Enantioselective Synthesis of Cicloprofen



In order to obtain an insight into the reaction mechanism, some additional experiments were carried out (see SI). For example, when employing a stoichiometric amount of **TRIP** as the only proton source, a much lower enantioselectivity was observed suggesting a role for MeOH in the enantioselectivity determining event. Also, very sluggish reactivity was observed when the SKI was introduced to the reaction mixture prior to the MeOH. Presumably, the silyl ester of **TRIP** is not the actual catalyst. Based on these observations, we propose a termolecular mechanism, in which a methanol–phosphoric acid complex is initially formed and *C*-protonates the SKI enantioselectively. The simultaneous silyl transfer to methanol further delivers the nitrile product and the corresponding silylether of MeOH, while the catalyst is regenerated (Scheme 2).

In summary, we have described an unprecedented catalytic asymmetric protonation of silyl ketene imines providing an easy access to highly enantioenriched α-branched nitriles. The reaction is catalyzed by either chiral phosphoric acids **STRIP** or commercially available **TRIP**. The use of methanol as the stoichiometric proton source adds to the potential practical value of our method. Several functionalized α-alkyl-α-arylnitriles with varying substituents at both aryl and alkyl chains were obtained in good yields and with excellent enantioselectivity. A gram scale experiment has been performed to illustrate practical aspects, and a mechanism has been suggested.

Scheme 2. Proposed Catalytic Cycle



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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