The Silicon–Hydrogen Exchange Reaction: Catalytic Kinetic Resolution of 2-Substituted Cyclic Ketones

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We have recently reported the strong and confined, chiral SO2 imidodiphosphorimidate (IDPi) catalysts, which enable access to the opposite enol silane enantiomer (Scheme 1a). Alternatively, racemic enol silanes can be formally hydrolyzed using the exact same catalyst, enabling access to the opposite enol silane enantiomer (Scheme 1b).

We have also been successful at expanding the scope of such hydrolytic-type kinetic resolutions to racemic enol silanes derived from 2-substituted ketones. However, we have never applied our approach to a deprotosilylative kinetic resolution of α-branched ketones. We expected this reaction design to be somewhat challenging since Yamamoto and co-workers have previously shown that Lewis acid assisted Brønsted acids, in the absence of a stoichiometric silyl group acceptor, readily catalyze the isomerization of the kinetic enol silane to its corresponding thermodynamic, achiral isomer.1 This reactivity has also been observed by Takasu and co-workers who have used Tf2NH as catalyst for the same isomerization.2

Scheme 1 Asymmetric catalytic silicon–hydrogen exchange reactions.  
Applied in (a) a desymmetrization of achiral ketones, (b) a protodesilylative kinetic resolution of racemic enol silanes, and (c) a deprotosilylative kinetic resolution of racemic, 2-substituted ketones (this work).

Silicon-mediated organic synthesis has become an important subject that is gaining more attention in recent years.1 In this context, silicon–hydrogen exchange reactions interconvert silylated (C-SiR3 or O-SiR3) and hydrogenated (C-H or O-H) compounds, exhibiting promising potential in asymmetric synthesis.2 Catalyzed by chiral acids, such transformations can be used to access highly valuable enantiopure enol silanes. For example, we have recently shown that symmetric ketones can be desymmetrized using strong and confined imidodiphosphorimidate (IDPi) catalysts (Scheme 1a). Alternatively, racemic enol silanes can be formally hydrolyzed using the exact same catalyst, enabling access to the opposite enol silane enantiomer (Scheme 1b).

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Abstract We have recently reported the strong and confined, chiral acid-catalyzed asymmetric ‘silicon–hydrogen exchange reaction’. One aspect of this transformation is that it enables access to enantiopure enol silanes in a tautomerizing α-bond metathesis, via deprotosilylation of ketones with allyl silanes as the silicon source. However, until today, this reaction has not been applied to racemic, 2-substituted, cyclic ketones. We show here that these important substrates readily undergo a highly enantioselective kinetic resolution furnishing the corresponding thermodynamic, achiral isomer.3 This reactivity has also been observed by Takasu and co-workers who have used Tf2NH as catalyst for the same isomerization.4

Key words: asymmetric catalysis, organocatalysis, enol silanes
Remarkably, we have now found that conditions can be found that allow for a highly enantioselective kinetic resolution to occur in depro otosilylative reactions of 2-substituted cyclic ketones with tert-but yldimethyl(2-methylallyl)silane (Scheme 1c). Our method provides an alternative entry to enantioenriched enol silanes, which are of high value in several fundamental applications.5–7

Our studies commenced with the identification of a proper acid catalyst for the asymmetric silicon–hydrogen exchange reaction of 2-phenylcyclohexan-1-one (1a) and methallylsilane 2. As reported in our previous work, while moderately acidic Brønsted acids, such as chiral phosphoric acids (CPA)9 imidodiphosphates (IDP),10 and disulfonimides (DSI)11 were ineffective, the desired enol silane products were obtained under the catalysis of the much more acidic IDPi catalysts (see the Supporting Information, Table S1).12,13 The thermodynamically favored enol silane 4a was observed to be the major product (3a:4a = 1:2) when the reaction was performed at 25 °C in toluene-d8 using IDPi 5a (Scheme 2). Replacement of the Tf substituent with a C6F5SO2 group gave catalyst 5b, which led to an even higher 3a:4a ratio of 1:5. We also investigated different aryl substituents at the 3,3′-positions of the binaphthyl backbone and, to our delight, the kinetically favored product 3a could indeed be obtained as the major regioisomer when catalyst IDPi 5c, bearing a 3-Ph-C6H4 substituent, was employed. Further endeavors focused on modifying the inner core of the catalyst. For example, IDPi 5d possessing a C6F5SO2 group enabled formation of enol silane 3a with good regioselectivity and a promising enantioselectivity of 88:12. With our newly developed catalyst 5e bearing a 2-C10F7-inner core substituent, the e.r. of the desired enol silane 3a could be further improved to 93:7 with a conversion of roughly 50%. Ultimately, beneficial effects on both regioselectivity and enantioselectivity were observed by decreasing the temperature to 0 °C, furnishing 3a in 56:1 r.r. and 96:4 e.r.. Gratifyingly, ketone 1a can be recovered in 94:6 e.r. with high selectivity (s).

Under these optimized reaction conditions, we next explored the substrate scope of the silicon–hydrogen exchange reaction with several racemic 2-substituted ketones. In most cases, the reactions proceeded cleanly and the desired enol silane regioisomers were obtained in high selectivities along with the recovered ketones. As summarized in Scheme 3, product 3a can be obtained in 49.5% yield and 96:4 e.r. with ketone 1a recovered in 47.6% yield and 94:6 e.r. on a 0.1 mmol scale. Substrates with strong electron-donating groups (Me, OMe) and a strong electron-withdrawing group (F) at the para position of the phenyl ring were well tolerated under the reaction conditions, affording the corresponding enol silane products 3b–3d in 49–50.5% yields with 93:7–95:5 e.r., and ketones 1b–1d in 47.5–49% yields with 92:8–95:5 e.r., respectively. It is noteworthy that the catalytic system is very well compatible with the silicon–hydrogen exchange reaction of a 7-membered ketone, furnishing the enol silane product 3e in

![Scheme 2](image-url)

**Scheme 2** Reaction development. Reactions were conducted with rac-1a (0.05 mmol), methallyl-TBS agent 2 (2.0 equiv), and catalyst 5a–5e (1.0 mol%) in toluene (0.1 M) at indicated temperature. * Conversions were determined by GC analysis, calibrating with 1,3,5-trimethoxybenzene as internal standard. The regioisomeric ratio (r.r. = 3a:4a) was determined by 1H NMR analysis. The enantiomeric ratio (e.r.) was determined by HPLC analysis. s = \ln[(1 - conv.)(1 - ees)] / ln(1 - conv.)(1 + ees). * Reactions in toluene-d8 monitored by 1H NMR.
The newly established catalytic system complements our previously reported methods. We are currently exploring this remarkably general approach to obtain a variety of functionalized molecules and toward developing catalysts that can realize a dynamic kinetic asymmetric silicon–hydrogen exchange reaction.

45.4% yield with 98:2 e.r. and the recovered ketone 1e in 42.3% yield with 96.5:3.5 e.r.. In this case, a remarkably high selectivity of 211 was obtained.

Toward a deeper understanding of the reaction, two comparison experiments were carried out using two enantiomerically pure substrates (Scheme 4). Only 6% conversion was observed after 56 hours at 0 °C from the reaction of ketone (S)-1a, which furnished enol silane (S)-3a and ketone (S)-1a without loss of enantiopurity but with moderate regioselectivity (3a:4a = 5.3:1) (eq. 1). In stark contrast, the reaction of ketone (R)-1a proceeded much faster, providing enol silane (R)-3a as the only regiosomer and ketone (R)-1a was recovered with 99:1 e.r. (eq. 2). Interestingly, when the reaction of rac-1a was performed at room temperature, the e.r. of enol silane 3a gradually decreased, and ketone 1a remained nearly racemic throughout the reaction (see the Supporting Information, Figure S11). These control experiments indicate that racemization of the ketone hardly occurs at 0 °C, but takes place at room temperature, suggesting potential for a dynamic kinetic resolution upon identification of a suitable acid catalyst.

We have developed access to enantiopure enol silanes from 2-substituted ketones, via silicon–hydrogen exchange reaction using a strongly acidic and confined IDPi catalyst. The newly established catalytic system complements our
Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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References and Notes

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(8) Example Synthetic Procedure

Methallyl TBS reagent 2 (46 µL, 0.2 mmol, 2.0 equiv.) was placed in a flame-dried Schlenk flask, equipped with a Teflon-coated magnetic stirring bar. IDPi 5e (0.01 equiv.) and toluene (0.1 M, 1.0 mL) were added at 25 °C and stirred for 30 min. The resultant mixture was cooled to 0 °C for 10 min, and the appropriate ketone 3a–3e (0.1 mmol, 1.0 equiv.) was slowly added. Then the reaction was stirred for indicated time at 0 °C. The reaction was monitored by GC, calibrated with 1,3,5-trimethoxybenzene as internal standard. When the conversion of ketone was around 50%, the reaction was quenched by addition of three drops of triethylamine by pipet. Crude NMR was performed to confirm the conversion of ketone and determine the NMR yield with CH2Br2 as internal standard after all organic volatiles were evaporated in vacuo. The crude residue was purified by preparative TLC to afford the desired enol silane 3a–3e, and r.r. was determined by 1H NMR analysis. e.r. of the enol silane product and recovered ketone were determined by HPLC analysis.

Spectral Information for Compound 3a

1H NMR (501 MHz, CD2Cl2): δ = 7.29–7.23 (m, 2 H), 7.23–7.19 (m, 2 H), 7.18–7.13 (m, 1 H), 5.04 (td, J = 4.0, 1.2 Hz, 1 H), 3.35 (td, J = 6.0, 1.9 Hz, 1 H), 2.24–2.05 (m, 2 H), 2.05–1.96 (m, 1 H), 1.72–1.63 (m, 1 H), 1.63–1.54 (m, 1 H), 1.50 (d, J = 6.4 Hz, 1 H), 0.68 (s, 9 H), 0.08 (s, 3 H), 0.00 (s, 3 H). 13C NMR (126 MHz, CD2Cl2): δ = 150.9, 144.7, 128.4, 125.7, 105.4, 46.3, 33.2, 25.2, 24.1, 19.8, 17.7, 4.9, 5.1. Rf = 0.41 (hexanes). ESI-HRMS: m/z calc for C16H25O2Si [M + H]+: 289.1982; found: 289.1977.

HPLC (OD-3R, MeCN–H2O = 65:35, 1.0 mL/min, 298 K, 220 nm): fR1 = 15.0 min, fR2 = 14.0 min; e.r. = 96:4; r.r. = 56:1. [α]D25 = –66.3 (c = 0.35, CHCl3).


