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

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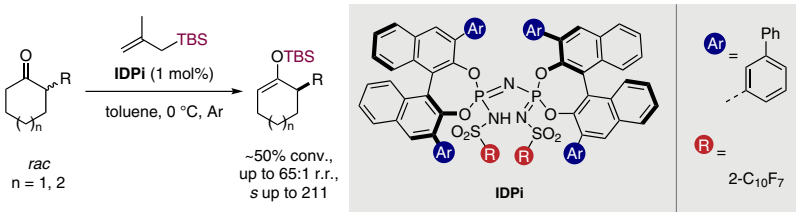

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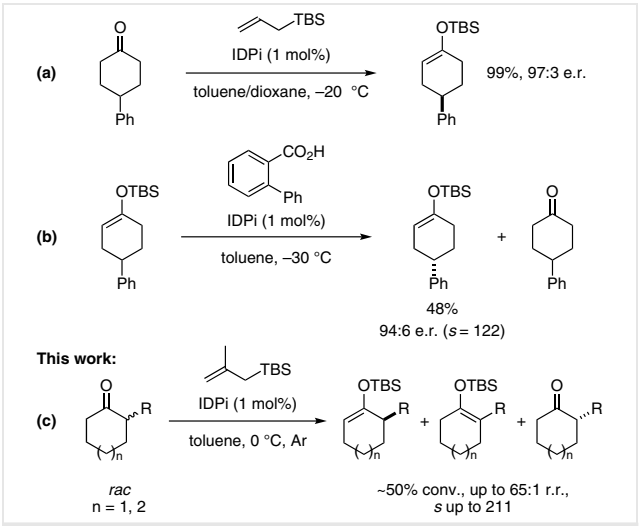
Abstract We have recently reported the strong and confined, chiral acid-catalyzed asymmetric 'silicon–hydrogen exchange reaction'. One aspect of this transformation is that it enables access to enantiopure enol silanes in a tautomerizing σ-bond metathesis, via deprotosilylation of ketones with allyl 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 kinetically preferred enol silanes. Mechanistic studies suggest the fascinating possibility of advancing the process to a dynamic kinetic resolution.

Key words asymmetric catalysis, organocatalysis, enol silanes

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–SiR_3 or O–SiR_3) 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).

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.[3] This reactivity has also been observed by Takasu and co-workers who have used Tf_2NH as catalyst for the same isomerization.[4]

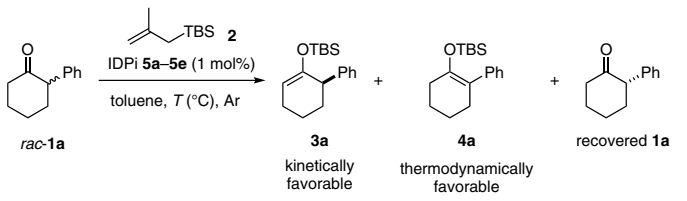


Scheme 1 Asymmetric catalytic silicon–hydrogen exchange reactions. Applied in (a) a desymmetrization of achiral ketones, (b) a protodesilylative kinetic resolution of racemic enol silanes, and (c) a deprotosilylative kinetic resolution of racemic, 2-substituted ketones (this work).

Remarkably, we have now found that conditions can be developed that allow for a highly enantioselective kinetic resolution to occur in deprotosilylative reactions of 2-substituted cyclic ketones with *tert*-butyldimethyl(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]

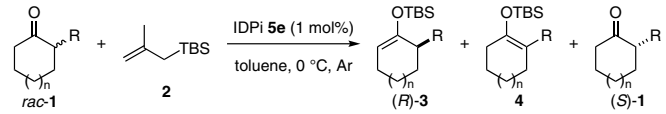
Our studies commenced with the identification of a proper acid catalyst for the asymmetric silicon–hydrogen exchange reaction of 2-phenylcyclohexan-1-one (**1a**) and methallylsilane **2**.[8] As reported in our previous work, while moderately acidic Brønsted acids, such as chiral phosphoric acids (CPA)[9] 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-d_8 using IDPi **5a** (Scheme 2). Replacement of the Tf substituent with a $C_6F_5SO_2$ 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-C_6H_4 substituent, was employed. Further endeavors focused on modifying the inner core of the catalyst. For example, IDPi **5d** possessing a $C_6F_5SO_2$ 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-$C_{10}F_7$ 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*).

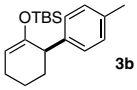
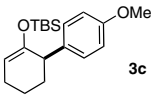
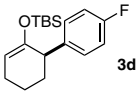
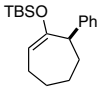
Under these optimized reaction conditions, we next explored the substrate scope of the silicon–hydrogen exchange reaction with several racemic 2-substituted ketones. In most cases, the reactions proceeded cleanly and the desired kinetic enol silane regioisomers were obtained in high selectivities along 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



entry	catalyst	*T* (°C)	t (h)	conv. (%)[a]	r.r.[b]	e.r. (**3a**)[c]	e.r. (**1a**)[c]	*s*[d]
1[e]	**5a**	25	25	92	1:2	50:50	--	--
2	**5b**	25	3.5	42	1:5	58:42	--	--
3[e]	**5c**	25	12	95	53:1	51:49	51:49	--
4	**5d**	25	5	57	12:1	88:12	51:49	--
5	**5e**	25	9	49.6	34:1	93:7	60:40	--
6	**5e**	0	59	49.5	56:1	96:4	94:6	66

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. [a] Conversions were determined by GC analysis, calibrating with 1,3,5-trimethoxybenzene as internal standard. [b] The regioisomeric ratio (r.r. = **3a**:**4a**) was determined by ^{1}H NMR analysis. [c] The enantiomeric ratio (e.r.) was determined by HPLC analysis. [d] $s = \ln[(1 - \text{conv.})(1 - \text{ee}_{\mathbf{1a}})] / \ln[(1 - \text{conv.})(1 + \text{ee}_{\mathbf{1a}})]$. [e] Reactions in toluene-d_8 monitored by ^{1}H NMR.



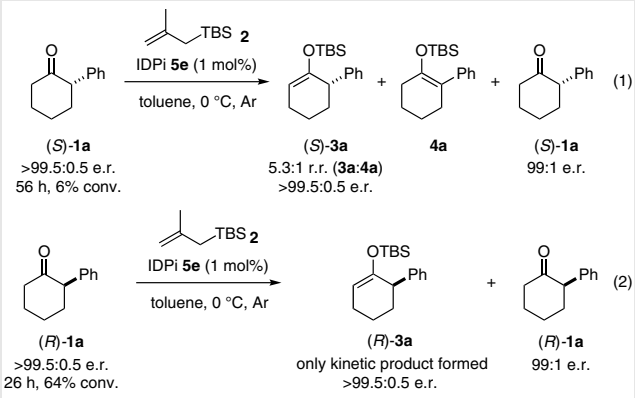
entry	enol silane 3	conv. (%)[a]	yield (%)[b] 3	yield (%)[b] 1	t (h)	r.r.[c] 3 : 4	e.r.[d] 3	e.r.[d] 1	s[e]
1	 3a	49	49.5	47.6	59	56:1	96:4	94:6	66
2	 3b	50	50.5	48.6	59	42:1	94:6	94:6	45
3	 3c	48	49	49	74	50:1	95:5	92:8	56
4	 3d	51	50	47.5	89	65:1	93:7	95:5	42
5[f]	 3e	49	45.4	42.3	63	8:1	98:2	96.5:3.5	211

Scheme 3 Substrate scope of the enol silane synthesis from 2-substituted cyclic ketones **1** and methallyl-TBS agent **2**. Reactions were conducted with *rac*-**1** (0.1 mmol), methallyl-TBS agent **2** (2.0 equiv.), and catalyst **5e** (1.0 mol%) in toluene (0.1 M) at 0 °C. [a] Conv. = $(ee_1) / (ee_1 + ee_3)$. [b] All yields were determined by crude ^{1}H NMR analysis with CH_2Br_2 as internal standard. [c] The regioisomeric ratio (r.r.) was determined by ^{1}H NMR analysis. [d] The enantiomeric ratio (e.r.) was determined by HPLC analysis. [e] $s = \ln[(1 - \text{conv.})(1 - ee_1)] / \ln[(1 - \text{conv.})(1 + ee_1)]$. [f] With 5 mol% catalyst **5e**.

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 regioisomer 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 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.



Scheme 4 Asymmetric catalytic silicon–hydrogen exchange reactions with enantiopure ketones **1a** (0.1 mmol), methallyl-TBS agent **2** (2.0 equiv.), and catalyst **5e** (1.0 mol%) in toluene (0.1 M) at 0 °C. (1) Reactivity comparison reaction of ketone (*S*)-**1a** with **2**, and (2) the reaction of ketone (*R*)-**1a** with **2**.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1670-5829.

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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 **1a**–**1e** (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 CH_2Br_2 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 ^{1}H NMR analysis. e.r. of the enol silane product and recovered ketone were determined by HPLC analysis.
Spectral Information for Compound 3a
^{1}H NMR (501 MHz, CD_2Cl_2): 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 (tq, *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). ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 150.9, 144.7, 128.4, 127.8, 125.7, 105.4, 46.3, 33.2, 25.2, 24.1, 19.8, 17.7, –4.9, –5.1. R_f = 0.41 (hexanes). ESI-HRMS: *m/z* calcd for $C_{18}H_{29}O_1Si_1$ ([M + H]$^+$): 289.1982; found: 289.1977. HPLC (OD-3R, MeCN–H_2O = 65:35, 1.0 mL/min, 298 K, 220 nm): t_{R1} = 15.0 min, t_{R2} = 14.0 min; e.r. = 96:4; r.r. = 56:1. $[\alpha]_D^{25}$ = –66.3 (*c* 0.35, $CHCl_3$).

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