Kinetic Resolution

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Kinetic Resolution of Chiral Secondary Alcohols by Dehydrogenative Coupling with Recyclable Silicon-Stereogenic Silanes**

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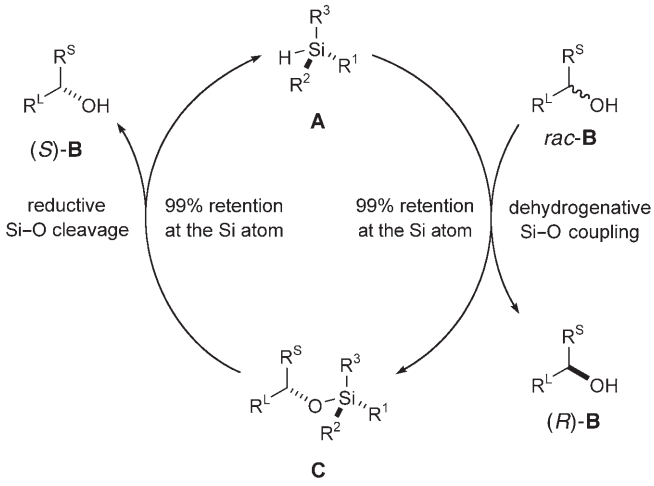
Non-enzymatic kinetic resolution[1] of racemic mixtures is a competitive strategy in asymmetric synthesis for the preparation of chiral building blocks.[2,3] The general approach relies on either a chiral reagent to undergo or a chiral catalyst to promote a stereoselective reaction of one enantiomer over the other. Within the theme of the former scenario, we devised a novel concept based on an unprecedented diastereoselective transition-metal-catalyzed dehydrogenative silicon–oxygen coupling of silicon-stereogenic silanes **A** and racemic alcohols *rac*-**B** (Scheme 1).[4]

We envisioned that if a preferential reaction of **A** with (*S*)-**B** to produce diastereoenriched **C** were viable, the optical antipode (*R*)-**B** would remain in enantioenriched form. Moreover, stereospecific reductive cleavage of the silicon–oxygen bond in **C** would allow complete recovery of the resolving reagent **A**. Importantly, both silicon–oxygen bond formation and cleavage would have to proceed without any erosion of stereochemical information at the silicon atom. Herein, we describe this novel concept of utilizing silicon-stereogenic silanes **A** in a kinetic resolution reaction.



Scheme 1. Kinetic resolution with recyclable silicon-stereogenic silanes ($R^1 \neq R^2 \neq R^3$, R^L = large R, and R^S = small R groups).

We initially sought suitable reaction conditions for silane alcoholysis with a particular emphasis on the stereochemical course at the silicon atom. Several heterogeneous and homogeneous catalysts are available,[5,6] and we selected the copper(I)-catalyzed dehydrogenative coupling introduced by Lorenz and Schubert.[7] Oxygen-sensitive $[\{(Ph_3P)CuH\}_6]$[8] is effectively replaced by a robust precatalyst (CuCl, Ph_3P, NaO*t*Bu) reported by Buchwald and co-workers[9] which also enables simple variation of the phosphine ligand.

We then screened this catalyst in the methanolysis of several asymmetrically substituted silanes[10] **1**–**3** (Figure 1) followed by stereoretentive reduction with aluminum hydrides.[11] To our delight, **1**–**3** were invariably recovered with complete retention of configuration, thereby verifying the stereospecificity of the copper(I)-catalyzed dehydrogenative silicon–oxygen coupling at the asymmetrically substituted silicon atom.[12] These experiments secured the pivotal preservation of the stereochemical integrity at silicon throughout this two-step process.[13]

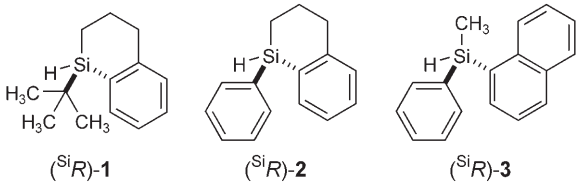


Figure 1. Silanes with silicon-centered chirality.

We then addressed the stereoselectivity of the dehydrogenative silicon–oxygen coupling of racemic alcohols with privileged silane (^{Si}R)-**1**.[14] A selected experiment (*rac*-**4**→(^{Si}S,*S*)-**5**, Scheme 2) showed that unfunctionalized secondary alcohols are essentially ineffective (d.r. ≤ 60:40). These discouraging observations led us to consider the introduction of a pendant donor (Do) in the substrate (Do = CH in **4**, Do = N in **6**), which provides a temporary residence site for the copper catalyst. We reasoned that alcohols capable of two-point binding would create more rigidity around the copper center, which in turn could be beneficial to diastereoselectivity. Consistent with our hypothesis, we were pleased to find that dehydrogenative coupling of *rac*-**6** and (^{Si}R)-**1** proceeded with substantially improved diastereoselectivity and enhanced reaction rate (*rac*-**6**→(^{Si}S,*S*)-**7**, Scheme 2).

The ideal phosphine ligand for this transformation, tri(3,5-xylyl)phosphane (**L1f**), was identified in an extensive screening of mono- and bidentate phosphine and N-heterocyclic carbene ligands (**L1**, **L2**, and **L3**, Table 1). We aimed to elucidate the influence of the ligand on the reaction rate and diastereoselectivity of the dehydrogenative coupling of *rac*-**6**

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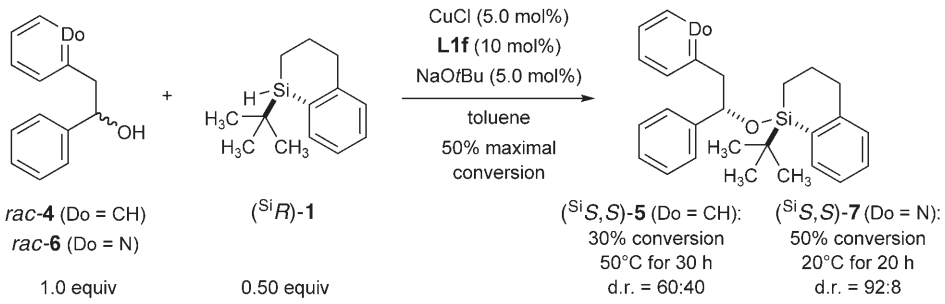
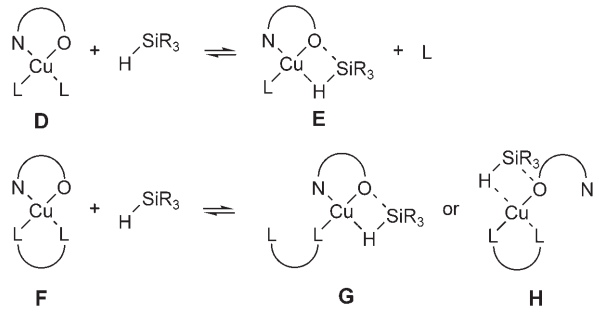


Scheme 2. Control of diastereoselectivity: Beneficial two-point binding. **L1f** = tri(3,5-xylyl)phosphane.

and (^{Si}R)-**1**.[15] A ligand/copper(I) ratio of 2:1 is usually needed to stabilize the catalyst. We began with triphenylphosphane (**L1a**), which gave ($^{Si}S,S$)-**7** under mild conditions with good diastereoselectivity (Table 1, entry 1). The reactivity decreased significantly in the presence of electron-poor phosphines **L1b–d**,[4a] yet the diastereoselectivity remained almost unaffected (Table 1, entries 2–4). Steric hindrance was not tolerated, and 2-tolyl-substituted phosphine **L1e** failed to stabilize the catalyst (Table 1, entry 5). Conversely, 3,5-xylyl-substituted phosphine **L1f** combined high reactivity with excellent diastereoselectivity at complete conversion (Table 1, entry 6). Electron-rich phosphines **L1g** and **L1h** (Table 1, entries 7 and 8), N-hetereocyclic carbene ligands[16] **L2a** and **L2b** (Table 1, entries 9 and 10), and Buchwald biaryl phosphines (not shown) were less effective. Interestingly, bidentate phospines **L3a–d** generated unreactive catalysts and led merely to moderate levels of diastereoselectivity (Table 1, entries 11–14).

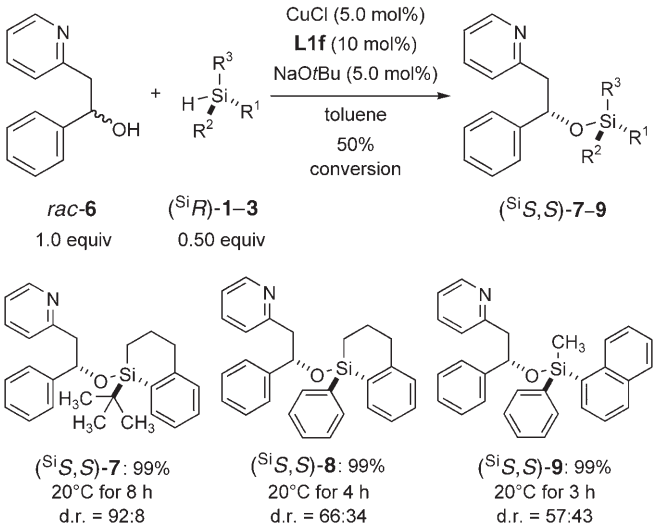
These findings can be roughly rationalized by the model outlined in Scheme 3. In the rate-determining step, one of the ligands L at the copper(I) center is replaced by the weakly



Scheme 3. Model for the postulated rate-determining step.

coordinating silane. This requires ligands with distinctly tuned σ-donor and π-acceptor strength as well as steric demand at electron-rich copper(I). In the case of monodentate ligands, a ligand must dissociate to generate a vacant coordination site (**D**→**E**). In the case of bidentate ligands, one of the chelates must open in an energetically clearly unfavorable step: 1) **F**→**G**, leaving the N,O-chelate intact, or 2) **F**→**H**, without two-point binding. The exact mechanism of the actual silicon–oxygen bond formation is still not completely understood, but is likely to involve—at least in a transition state—a pentacoordinated silicon of unknown configuration. Remarkably, a conceivable pseudorotation[17] and, hence, racemization are not observed, which indicates a concerted σ-bond metathesis.[10c]

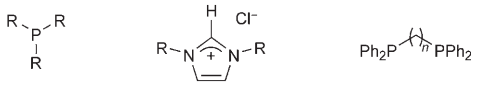
We conducted our investigations with rationally yet empirically designed (^{Si}R)-**1**.[14] A comparison with less sterically encumbered cyclic or even acyclic silanes (^{Si}R)-**2** and (^{Si}R)-**3** impressively demonstrated once again the importance of steric demand and of three truly different substituents at the silicon atom (Scheme 4).[10c] Whereas less-hindered silanes were expectedly more reactive, diastereoselectivity collapsed in the case of cyclic (^{Si}R)-**2** (d.r. = 66:34) and was hardly observed with (^{Si}R)-**3** (d.r. = 57:43).



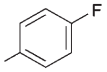
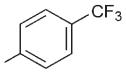
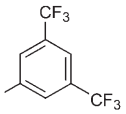
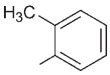
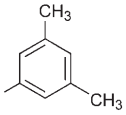
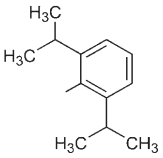
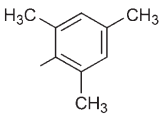
Scheme 4. Probing the steric demand and substitution pattern at the silicon atom.

This preliminary insight set the stage for an investigation of the kinetic resolution itself. As a starting point, we resolved our standard substrate *rac*-**6** by using optically enriched (^{Si}R)-**1** (96% *ee*). Both silyl ether ($^{Si}S,S$)-**7** and alcohol (*R*)-**6**[18] were isolated in quantitative yields, the latter with an encouraging 84% *ee* at 56% conversion (Table 2, entry 1). Importantly, the diastereomeric ratio of ($^{Si}S,S$)-**7** decreases with increasing conversion (d.r. = 92:8 at 50% conversion versus d.r. = 86:14 at 56% conversion). The stereoselectivity factor *s*[1] can only be estimated at larger than 10,[19] as this kinetic resolution involves an enantiomerically impure resolving reagent.[20] Indeed, we were able to verify experimentally this interesting

Table 1: Identification of effective ligands for the conversion **6**→**7**.[a]



L1 **L2** **L3** (n = 1–4)

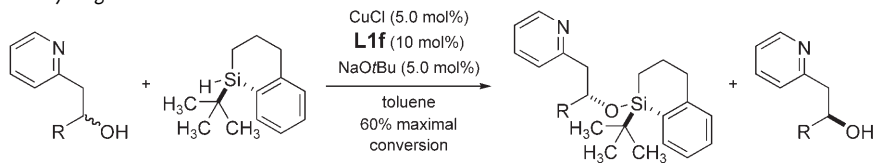
Entry	Ligand L			L/CuCl	T [°C]	t [h]	d.r.[b]	Conv. [%][c]
	L1	R						
1	**L1a**			2:1	20	48	90:10	42
2	**L1b**			2:1	50	48	89:11	37
3	**L1c**			2:1	70	60	83:17	38
4	**L1d**			2:1	70	60	86:14	34[d]
5	**L1e**			2:1	20	–	–	–[e]
6	**L1f**			2:1	20	20	92:8	50
7	**L1g**			1:1[f]	20	24	81:19	33
8	**L1h**			2:1	50	6	75:25	21[e]
	L2	R						
9[g]	**L2a**	 IPr·HCl		1:1	85	2	55:45	10
10[g]	**L2b**	 IMes·HCl		1:1	60	2	76:24	40
	L3[h]		n					
11	**L3a**	(dppm)	1	1:1	45	48	82:18	32
12	**L3b**	(dppe)	2	1:1	45	48	87:13	20
13	**L3c**	(dppp)	3	1:1	45	48	80:20	20
14	**L3d**	(dppb)	4	1:1	45	48	79:21	18

[a] Unless otherwise noted, all reactions were conducted with CuCl (5.0 mol%), **L1** (10 mol%) or **L2**/**L3** (5.0 mol%), NaO*t*Bu (5.0 mol%) with a substrate concentration of 0.1 M in toluene. [b] Determined from the ^{1}H NMR spectra of the crude reaction mixtures by integration of the baseline-separated resonance signals of diastereomeric ($^{Si}S,S$)-**7** at $\delta = 4.93$ ppm and ($^{Si}S,R$)-**7** at $\delta = 5.02$ ppm. [c] Monitored by ^{1}H NMR spectroscopic analysis and determined by integration of the baseline separated resonance signals of **6** at $\delta = 5.16$ ppm and **7** at $\delta = 4.93/5.02$ ppm. [d] Extremely slow conversion. [e] Unstable catalyst. [f] Sterically demanding **L1g** allowed an equimolar ratio of ligand and CuCl. [g] Substoichiometric amounts of NaO*t*Bu (30 mol%) were required. [h] dppm = 1,1-bis(diphenylphosphanyl)methane, dppe = 1,2-bis(diphenylphosphanyl)ethane, dppp = 1,3-bis(diphenylphosphanyl)propane, dppb = 1,4-bis(diphenylphosphanyl)butane.

example of mutual kinetic resolution.[1] For this purpose, we resolved *rac*-**6** with (^{Si}R)-**1** (32% *ee*). The optical purity of (*R*)-**6** (25% *ee*) as well as of (^{Si}R)-**1** (48% *ee*) increased as the reaction proceeded until 50% conversion was reached.[1,20]

An investigation of the substrate scope demonstrated some generality for the class of 2-pyridyl-substituted secondary alcohols (Table 2, entries 2–7). Replacement of a phenyl group (*rac*-**6**) by 1-naphthyl (*rac*-**10**) only had a marginal

Table 2: Copper-catalyzed dehydrogenative kinetic resolution.[a]

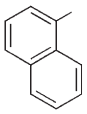
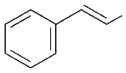
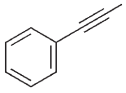


rac-**6**, *rac*-**10**–*rac*-**15** 1.0 equiv

(^{Si}R)-**1** 0.60 equiv

(^{Si}S,*S*)-**7**, (^{Si}S,*S*)-**16**–(^{Si}S,*S*)-**19**, (^{Si}S,*R*)-**20**, (^{Si}S,*S*)-**21**

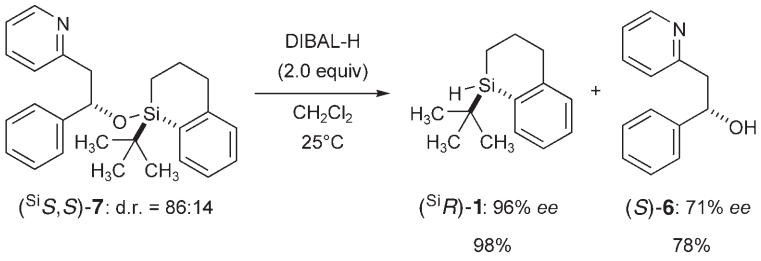
(*R*)-**6**, (*R*)-**10**–(*R*)-**13**, (*S*)-**14**, (*R*)-**15**

Entry	Alcohol	R	Silane (^{Si}R)-**1** *ee* [%][b]	Silyl ether Product[c]	Yield [%][d]	d.r.[e]	Conv. [%][f]	Alcohol Product[c]	Yield [%][d]	*ee* [%][g] ($[\alpha]_D$)[h]
1	*rac*-**6**		96	(^{Si}S,*S*)-**7**	99	86:14	56	(*R*)-**6**	99	84 (+)
2	*rac*-**10**		93	(^{Si}S,*S*)-**16**	97	84:16	58	(*R*)-**10**	99	80 (+)
3	*rac*-**11**		95	(^{Si}S,*S*)-**17**	92	88:12	50	(*R*)-**11**	99	70 (+)
4	*rac*-**12**		93	(^{Si}S,*S*)-**18**	99	87:13	57	(*R*)-**12**	99	74 (−)
5[i]	*rac*-**13**		93	(^{Si}S,*S*)-**19**	99[i]	74:26	64[j]	(*R*)-**13**	84[i]	89 (−)
6	*rac*-**14**		93	(^{Si}S,*R*)-**20**	98	76:24	58	(*S*)-**14**	98	73 (+)
7[k]	*rac*-**15**		94	(^{Si}S,*S*)-**21**	87	94:6[l]	46	(*R*)-**15**	99	68 (−)[l]

[a] Unless otherwise noted, all reactions were conducted with CuCl (5.0 mol%), **L1 f** (10 mol%), NaO*t*Bu (5.0 mol%) with a substrate concentration of 0.1 M in toluene at 25 °C. [b] HPLC analysis using a Daicel Chiralcel OJ-R column (EtOH/H_2O 80:20 at 20 °C) provided baseline separation of enantiomers. [c] Absolute configurations of (^{Si}R)-**1**[10c] and (*R*)-**6**[18] and, therefore, **7** are known. The absolute configurations of enantioenriched alcohols **10**–**15** as well as silyl ethers **16**–**21** were assigned by analogy. [d] Yield of analytically pure product isolated by flash chromatography on silica gel. [e] Determined from the ^{1}H NMR spectra of the crude reaction mixtures by integration of the baseline-separated resonance signals of the diastereomers. [f] Monitored by ^{1}H NMR analysis and determined by integration of the baseline-separated resonance signals of the alcohol and silyl ether. [g] HPLC analysis using a Daicel Chiralcel OD-H column (*n*-heptane/*i*PrOH 90:10 for **6**, **10**, **12**, and **13** and 98:2 for **11** at 20 °C) or Daicel Chiralcel AD-H column (*n*-heptane/*i*PrOH = 98:2 for **14** and **15** at 20 °C) provided baseline separation of enantiomers. [h] $c = 0.22$–0.55 in $CHCl_3$ at 20 °C. [i] Reaction accompanied by partial *Z*-selective alkyne reduction: (^{Si}S,*S*)-**19** contaminated with 7% *Z* alkene and (*R*)-**13** contaminated with 21% *Z* alkene in 57% *ee*. [j] (^{Si}R)-**1**: 0.65 equiv. [k] The reaction was performed with CuCl (10 mol%), **L1 f** (20 mol%), NaO*t*Bu (20 mol%), and (^{Si}R)-**1** (1.2 equiv) at 110 °C. [l] High diastereomeric ratio at conversion below 50% and, therefore, moderate enantiomeric excess.

effect (Table 2, entry 2), whereas the efficiency decreased with less sterically demanding vinyl (*rac*-**11**) and cinnamyl groups (*rac*-**12**) (Table 2, entries 3 and 4). For alkynyl substitution (*rac*-**13**), we probed the efficiency at higher conversion and obtained good enantiomeric purity; however, this reaction was accompanied by partial reduction of the triple bond (Table 2, entry 5). When methyl derivative *rac*-**14** was employed, the kinetic resolution was least efficient (Table 2, entry 6). Dehydrogenative coupling of branched, *t*Bu-substituted alcohol *rac*-**15** was highly diastereoselective, but conversion did not proceed beyond 50%, even at elevated temperatures (Table 2, entry 7).

Finally, our concept would only come full circle with complete recovery of the resolving reagent without racemization at the silicon atom. Reductive cleavage of the silicon–oxygen linkage in (^{Si}S,*S*)-**7** in quantitative yield liberated (^{Si}R)-**1** with an unchanged 96% *ee* (Scheme 5).



Scheme 5. Recycling of the resolving reagent. DIBAL-H = diisobutylaluminum hydride.

In conclusion, we have developed a novel kinetic resolution based on a diastereoselective dehydrogenative coupling of racemic alcohols and asymmetrically substituted silanes. Two-point binding of the substrates emerged as the pivotal feature for stereoselectivity. The efficiency of this strategy was exemplified by resolving a family of 2-pyridyl-substituted alcohols. Apart from the recyclability of the silicon-stereogenic silane, this two-step reaction sequence

involves the simple separation of compounds with substantially different polarity. Further optimization and extension of substrate scope are currently underway in our laboratories.

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