Kinetic Resolution

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Catalytic Asymmetric Si–O Coupling of Simple Achiral Silanes and Chiral Donor-Functionalized Alcohols**

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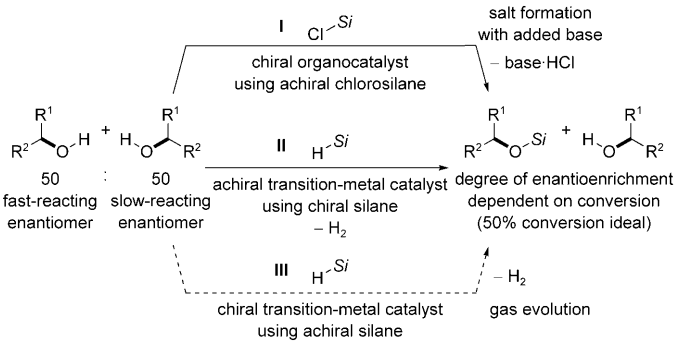
Kinetic resolution[1] of alcohols is usually based on acylation although the indispensable role of silicon-based protective groups[2] in synthetic organic chemistry might actually call for the related silylation to render a conventional alcohol protection step asymmetric.[3] An innovative report by Ishikawa et al. had remained unnoticed[4] until Hoveyda et al. perfected asymmetric silylation through desymmetrization[5] and kinetic resolution.[6] Analogous to the acylation of alcohols,[7] these protocols rely on a nucleophilic organocatalyst and a chlorosilane as the electrophilic silicon source; stoichiometric amounts of a base are necessary to absorb the hydrochloric acid produced in the course of the reaction (**I**; Scheme 1).



Scheme 1. Kinetic resolution by formation of an Si–O bond. $R^1 \neq R^2$ = aryl or alkyl, *Si* = triorganosilyl group.

Parallel to this significant progress, we had devised a conceptually distinct approach to stereoselective Si–O bond formation employing silicon-stereogenic silanes (**II**; Scheme 1).[8–10] In this reagent-controlled kinetic resolution, the direct coupling of an alcohol and a silane is catalyzed by a copper(I) hydride complex ("Cu–H"),[11,12] and enantiomer discrimination originates in the stereochemical information at the asymmetrically substituted silicon atom (transition state **TS1**; Figure 1).

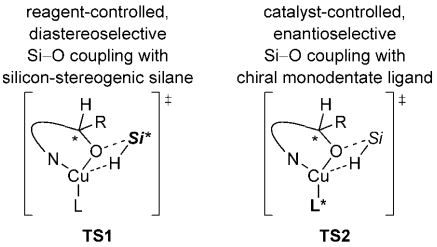


Figure 1. Origin of stereoinduction in reagent- and catalyst-controlled, Cu–H-catalyzed dehydrogenative Si–O couplings. *Si** = asymmetrically substituted silicon atom, L = monodentate ligand, L* = chiral monodentate ligand, N = sp^2-hybridized nitrogen donor, R = aryl or alkyl group.

Naturally, our next goal was to develop a catalyst-controlled asymmetric dehydrogenative Si–O coupling with achiral silanes and chiral ligands (**III**; Scheme 1).[13,14] We had, however, learned in our previous work that achiral monodentate phosphine ligands are generally far superior to related bidentate ligands.[8,9] A quantum-chemical investigation[9] indicated that asymmetric induction in the planned enantioselective Cu–H catalysis will have to arise from a single monodentate chiral ligand (transition state **TS2**; Figure 1).[15] While such a stereochemical situation is not totally unprecedented in transition-metal catalysis,[16–19] it still is a demanding task, for which prominent ligand classes are available:[20] MOP-type phosphine ligands[21] and ligands having the general formula O_2P–X in which a chiral backbone is connected to the oxygen atom[22] [phosphoramidites (O_2P–N),[23] phosphites (O_2P–O), and phosphonites (O_2P–C)]. Herein, we introduce a novel method for kinetic resolution based on an enantioselective dehydrogenative Si–O coupling catalyzed by a chiral Cu–H complex. All data strongly support a mechanism in which only one monodentate enantiopure ligand is responsible for the chiral discrimination.

Our investigation commenced with an extensive survey of chiral monodentate ligands (Table 1) and achiral triorganosilanes (Table 2). For this, we selected proven donor-functionalized alcohol *rac*-**1** from our preceding work,[8–10] but the copper/base/solvent combination (CuCl/NaO*t*Bu/toluene) previously used[8,9] failed to secure adequate turnover. Considerable experimentation then led to the CuCl/Cs_2CO_3/THF system, in which the use of Cs_2CO_3 is essential to suppress the

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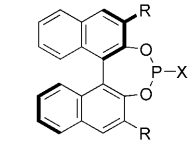
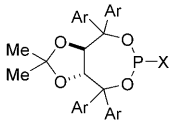
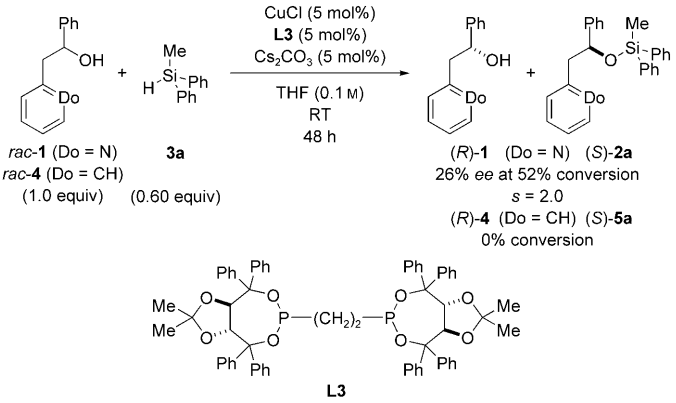
undesired base-catalyzed Si–O coupling otherwise observed in THF.[24] As the initial results obtained with a MeO-MOP ligand[25] were disappointing, we mainly focussed on phosphoramidites and phosphonites. We included different binol-**L1** and taddol-based[26] ligands **L2** in our systematic screening,



L1: binol-based ligands (R = H or Me) moderate performance for X = NR'_2 (*s* = 1.1-5.6) poor performance for X = aryl or alkyl (*s* = 1.1-1.5)



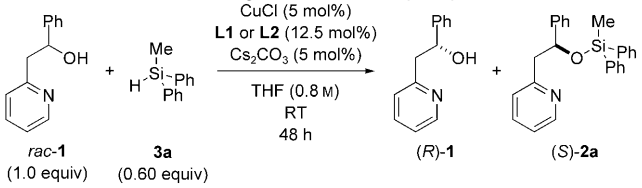
L2: taddol-based ligands (Ar = aryl groups) poor performance for X = NR'_2 (*s* = 1.1-1.5) good performance for X = aryl or alkyl (Table 1)



Scheme 2. Interplay of two-point binding of ligand and substrate.

and selected data are summarized in Table 1. To our surprise, phosphoramidites[23] derived from both binol and taddol were largely unproductive. In contrast, taddol-derived phosphonites **L2**[22a] were particularly promising (Table 1, entries 1–6), and **L2g** ($s = 14$) emerged as the ideal ligand thus far (Table 1, entry 7). We note that all test reactions were optimized for the selectivity factor *s*[27] rather than for conversion and enantiomeric excess.[28]

Table 1: Ligand identification and screening of taddol-based phosphonites.



Entry.	Ligand	X	Ar	Conv. [%][a]	*ee* [%][b]	*s*[c]
1	**L2a**	C_6H_5	C_6H_5	47	41	4.0
2	**L2b**	2,4,6-$Me_3C_6H_2$	C_6H_5	33	6	1.4
3	**L2c**	*n*Bu	C_6H_5	51	38	3.0
4	**L2d**	*t*Bu	C_6H_5	30	32	9.4
5	**L2e**	*t*Bu	3,5-$Me_2C_6H_3$	32	35	9.5
6	**L2f**	*t*Bu	4-*t*BuC_6H_4	51	57	5.9
7	**L2g**	*t*Bu	2-$C_{10}H_7$	55	84	14

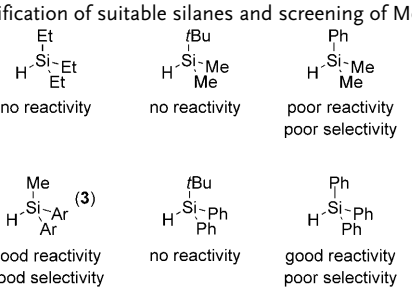
[a] Conversion monitored and determined by ^{1}H NMR spectroscopy as well as GLC analysis using an internal standard. [b] Enantiomeric excess determined by HPLC analysis on chiral Daicel Chiralpak columns. [c] Selectivity factor calculated from $s = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$ where $ee = ee/100$ and $C =$ conversion/100.[27]

Control experiments with novel bidentate phosphonite **L3** and *rac*-**1** as well as its nonfunctionalized counterpart *rac*-**4** gave further indication of the single-point binding of the ligand (Scheme 2): In reactions with *rac*-**1** and **L3**, discrimination of enantiomers ($s = 2.0$) is in the range of that obtained with monodentate **L2c** ($s = 3.0$), indicating that **L3** is not chelating in the stereochemistry-determining step to make room for silane coordination (*rac*-**1**→(*S*)-**2a**). Conversely, no conversion is evident in the absence of a donor tethered to the alcohol (*rac*-**4**→(*S*)-**5a**), which in turn suggests that the donor in *rac*-**1** is crucial in the σ-bond metathesis. Moreover, the selectivity factor emerged as independent of the copper-to-ligand ratio; both 1:2 and 1:1 were equally effective, yet turnover was lower with the latter, likely owing to insufficient stabilization of the copper(I) hydride complex.[15] Excess ligand inhibits the reaction.

The screening of literally dozens of acyclic and cyclic silanes showed that the dehydrogenative Si–O coupling is very sensitive towards the substitution pattern at the silicon atom (Table 2 and the Supporting Information). Silanes bearing a *tert*-butyl group were completely inert; trialkylsilanes were also not acceptable. Reactivity increased with the number of aryl groups ($Ph_3SiH > MePh_2SiH > Me_2PhSiH$) likely because of higher Lewis acidity[24] in that order. $MePh_2SiH$ combined good reactivity with good selectivity. We therefore explored the steric and electronic possibilities of $MeAr_2SiH$ and designated **3a** as a reference point (Table 2, entry 1). We derived a few general trends: Any steric bulk in proximity to the Si–H bond thwarted turnover (**3b** and **3i**, Table 2, entries 2 and 9). Conversely, only little influence on selectivity was seen with **3c** and **3j** (Table 2, entries 3 and 10). Electronic and presumably steric fine-tuning of the arene through *meta* (both positions) and *para* substitution showed that +I substituents (**3d**, **3e**, and **3f**) and −I substituents (**3g**) are tolerated while +M substitution (**3h**) is not (Table 2, entries 4–7 and 8). With silane **3d**, an excellent selectivity factor of > 20 was obtained.

We finally applied the protocol deemed most successful to this point to several substrates with different donor groups (Table 3, entries 1–4) and varied substituents R at the carbinol carbon atom (Table 3, entries 5–10). As expected, the selectivity factors were dependent on the steric and electronic effects imparted by the substitution pattern of the

Table 2: Identification of suitable silanes and screening of $MeAr_2SiH$.[d,e]



Entry	Silane	Ar	Conv. [%][a]	*ee* [%][b]	*s*[c]
1	**3a**	C_6H_5	55	84	14
2	**3b**	2-MeC_6H_4	0	–	–
3	**3c**	3-MeC_6H_4	48	63	10
4	**3d**	3,5-$Me_2C_6H_3$	51	88	35
5	**3e**	4-MeC_6H_4	42	51	9.5
6	**3f**	4-*t*BuC_6H_4	49	75	18
7	**3g**	4-$CF_3C_6H_4$	60	78	7.2
8	**3h**	4-$MeOC_6H_4$	5	–	–
9	**3i**	1-$C_{10}H_7$	0	–	–
10	**3j**	2-$C_{10}H_7$	43	54	10

For footnotes [a]–[c], see Table 1. [d] For data on the other silanes tested, see the Supporting Information. [e] All reactions were conducted using CuCl (5 mol%), **L2g** (12.5 mol%), and Cs_2CO_3 (5 mol%) with a substrate concentration of 0.8 M in THF at room temperature for 48 h.

alcohol. For example, when the nitrogen donor was flanked by an additional methyl group, this resulted in less efficient enantiomer discrimination (Table 3, entry 2). Both aryl and alkyl residues were accepted as R groups. We had expected the latter to be problematic based on our previous experience.[8–10] Turnover was poor with cyclohexyl-substituted alcohols, while methyl- and trifluoromethyl-bearing carbinols were resolved with excellent selectivities (Table 3, entries 8–10).

In summary, we have accomplished an enantioselective, dehydrogenative Si–O coupling for the first time. Extensive screening of ligands and silanes led to the discovery of a copper(I)/phosphonite/silane combination that affords remarkably high selectivity factors in several cases. A noteworthy aspect is the fact that only a single chiral monodentate ligand is involved in the stereochemistry-determining σ-bond metathesis (cf. **TS2**; Figure 1). We think that this new approach to kinetic resolution through the asymmetric coupling of alcohols and silanes will stimulate further research in this area.

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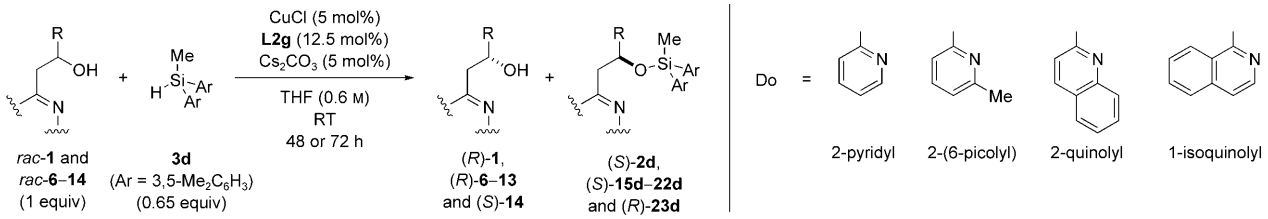
Table 3: Survey of different donors and substituents.



Entry	Alcohol	Donor	R	Silyl ether of fast-reacting enantiomer	yield [%][d]	*ee* [%][b]	Slow-reacting enantiomer	yield [%][d]	*ee* [%][b]	conv. [%][a]	*s*[c]
1[e]	*rac*-**1**	2-pyridyl	Ph	(*S*)-**2d**	49	84	(*R*)-**1**	39	88	51	35
2	*rac*-**6**	2-(6-picolyl)	Ph	(*S*)-**15d**	59	60	(*R*)-**6**	38	87	59	11
3	*rac*-**7**	2-quinolyl	Ph	(*S*)-**16d**	54	72	(*R*)-**7**	43	95	57	22
4	*rac*-**8**	1-isoquinolyl	Ph	(*S*)-**17d**	44	56	(*R*)-**8**	43	76	57	8.2
5	*rac*-**9**	2-pyridyl	1-$C_{10}H_7$	(*S*)-**18d**	49	70	(*R*)-**9**	39	80	53	14
6	*rac*-**10**	2-pyridyl	2-$C_{10}H_7$	(*S*)-**19d**	59	47	(*R*)-**10**	27	87	65	7.3
7	*rac*-**11**	2-pyridyl	4-$MeOC_6H_4$	(*S*)-**20d**	54	71	(*R*)-**11**	40	92	56	19
8	*rac*-**12**	2-pyridyl	Cy	(*S*)-**21d**	25	n.d.[f]	(*R*)-**12**	62	30	25	25
9	*rac*-**13**	2-pyridyl	CF_3	(*S*)-**22d**	43	n.d.[f]	(*R*)-**13**	38	86	53	20
10	*rac*-**14**	2-pyridyl	Me	(*R*)-**23d**	46	70	(*S*)-**14**	40	97	58	23

For footnotes [a]–[c], see Tables 1 and 2. [d] Yield of analytically pure product isolated by flash chromatography on silica gel. [e] This kinetic resolution could also be performed on a larger scale (5.0 mmol). [f] n.d. = not determined.

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