Kinetic Resolution

DOI: 10.1002/anie.200703847

Chiral Recognition with Silicon-Stereogenic Silanes: Remarkable Selectivity Factors in the Kinetic Resolution of Donor-Functionalized Alcohols**

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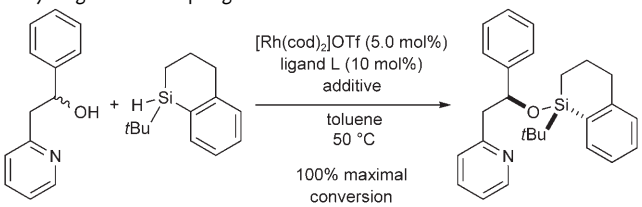
Non-enzymatic kinetic resolution is an important technique in asymmetric synthesis to access optically active materials.[1] A useful parameter for expressing the efficiency of resolution is the selectivity factor *s*, which is the ratio of the rate constants for the reaction of a chiral catalyst or a chiral reagent with the different enantiomers.[2] In order to at the same time obtain high chemical yield, ideally 50% for both the slow- and the fast-reacting enantiomer, and perfect enantioselectivity, selectivity factors must be extremely high ($s > 200$). Such numbers are, however, far from the norm; for example, Vedejs et al. identified an exceptional chiral phosphine-based catalyst for the nucleophilic acylation of benzylic alcohols ($s \approx 350$).[3,4]

As part of our research program on silicon-stereogenic silanes in asymmetric catalysis,[5] in 2005 we introduced a novel reagent-controlled strategy[6] for the kinetic resolution of donor-functionalized alcohols[7] by means of diastereoselective Cu–H-catalyzed[8] dehydrogenative Si–O coupling.[9] In this unique stereoselective alcohol silylation,[10] asymmetry at the silicon atom enables discrimination of enantiomeric alcohols with promising selectivity ($s \approx 10$).[6] We then set out to identify transition-metal–ligand combinations that would catalyze the kinetic resolution with substantially improved selectivity factors and, as a future prospect, that would be capable of alcohol racemization,[11] thereby resulting in dynamic kinetic resolution.[12] Herein, we report on an intriguing rhodium-catalyzed dehydrogenative Si–O coupling, in which a silicon-stereogenic silane kinetically selects one of the two enantiomeric transition-metal–substrate complexes with outstanding preference ($s \approx 900$). This chiral recognition originates from a single stereocenter in a low-molecular-weight (204.38 g mol^{-1}) chiral reagent that is almost a pure hydrocarbon ($C_{13}H_{20}Si$) without any further binding sites.

In light of the above considerations, we decided to use rhodium(I)- and ruthenium(II)-based catalysts, since Corriu and Moreau showed that these species mediate dehydrogenative Si–O coupling of reactive diorganosilanes.[13] However, when using our sterically hindered triorganosilanes,[5] these catalysts were largely unreactive.[14] The Wilkinson catalyst [$RhCl(Ph_3P)_3$] showed promising levels of conversion. Facile variation of the ligand itself and the metal-to-ligand ratio[15] was ensured by employing the cationic precursor rhodium(I) complex [$Rh(cod)_2$]OTf. To test these rhodium–ligand combinations (Table 1), we chose the reaction of the privileged[16] silane *rac*-**1**[17] with donor-functionalized alcohol *rac*-**2**, which had proven to be a good substrate in our earlier study.[6] As the process is diastereoselective by nature, the diastereomeric ratio of silyl ether **3** correlates directly with the selectivity factor of the related kinetic resolution; thus, these catalysts were assessed with racemic silane.

Our screening commenced with three monodentate phosphine ligands (Table 1, entries 1–3). These ligands pro-

Table 1: Ligand screening in the diastereoselective rhodium(I)-catalyzed dehydrogenative coupling.[a]



rac-**2** (1.0 equiv) + *rac*-**1** (1.0 equiv) → ($^{Si}S^*,S^*$)-**3**

Entry	L	*t* [h]	Conv [%][b]	d.r.[c]
1	Ph_3P	24	44	70:30
2	Mes_3P	12	55	80:20
3	tBu_3P	12	54	85:15
4[d]	IMes·HCl	16	100	82:18
5[d]	IPr·HCl	12	100	>99:1
6[d]	IPr·HCl/Mes_3P[e]	4	100	99:1

[a] Unless otherwise noted, all reactions were conducted using [$Rh(cod)_2$]OTf (5.0 mol%) and the indicated ligand (10 mol%) with a substrate concentration of 0.1 M in toluene at 50 °C; when using carbene ligand precursors IMes·HCl and IPr·HCl, slightly less than twice the equimolar amount of KO*t*Bu (relative to the precursor) was added. [b] Monitored by ^{1}H NMR spectroscopy and determined by integration of the baseline-separated resonance signals of **2** at $\delta = 5.16$ ppm and **3** at $\delta = 4.93/5.02$ ppm. [c] Determined by GC analysis using an SE-54 column. [d] The generation of the catalytically active carbene complexes displayed a marked sensitivity towards the temperature of the deprotonation step; maintaining the reaction mixture at room temperature for 1 h prior to substrate addition was critical to success. [e] 1:1 mixture. IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, Mes = 2,4,6-trimethylphenyl, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

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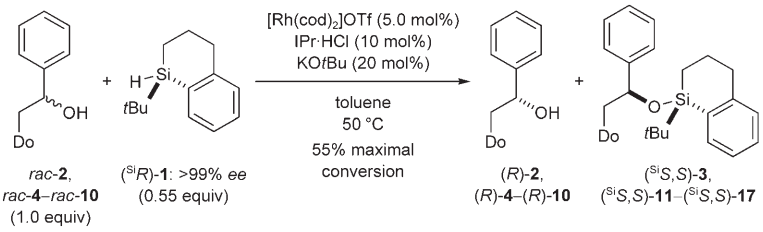
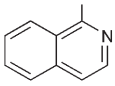
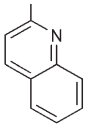
[**] The research was supported by the Deutsche Forschungsgemeinschaft (Oe 249/4-1). M.O. is indebted to the Aventis Foundation (Karl-Winnacker-Stipendium, 2006–2008). The authors thank Barbara Hildmann for skillful technical assistance.

duced unreactive (poor conversion) and unselective (poor diastereomeric ratio) catalysts. Yet these parameters improved with increasing steric bulk and σ-donor strength of the phosphine (tBu$_3$P > Mes$_3$P > Ph$_3$P). Therefore, we turned to N-heterocyclic carbene ligands (prepared from IMes·HCl and IPr·HCl), which generated sufficiently reactive catalysts (Table 1, entries 4 and 5). The latter system afforded **3** with perfect stereocontrol (d.r. > 99:1) as determined by GC analysis. When one of the carbene ligands was replaced by a phosphine, the reaction rate increased, and very high levels of diastereoselectivity were maintained (Table 1, entry 6). We believe that the carbene ligand remains at the rhodium center, while the phosphine dissociates rapidly, thereby providing the necessary vacant site for silane coordination, which stems from a weak interaction.

With this relatively unpretentious catalyst system, we started to perform kinetic resolution of different nitrogen-donor-containing alcohols *rac*-**2** and *rac*-**4** to *rac*-**10**, which have the required array of functional groups, using highly enantioenriched silane (^{Si}R)-**1**[17a] (Table 2). Importantly, the data summarized in Table 2 also includes the diastereomeric ratios of the silyl ethers obtained in the racemic experiment (reaction with *rac*-**1**, column 7), because in this case, diastereoselection is independent of the degree of conversion. Accordingly, the stereoselectivity factor s is the critical parameter in the enantiomeric case (reaction with (^{Si}R)-**1**,

Table 2: Variation of the donor in the kinetic resolution of donor-functionalized secondary alcohols.[a]



Entry	Racemic alcohol	Donor	Silyl ether	Yield [%][b]	d.r.[c]	d.r.[c,d]	Recovered alcohol	Yield [%][b]	*ee* [%][e]	Conv [%][f]	s[g,h]
1[i]	*rac*-**2**		($^{Si}S,S$)-**3**	–[j]	96:4	>99:1	(*R*)-**2**	–[j]	>99	50.8[k]	900
2	*rac*-**4**		($^{Si}S,S$)-**11**	40	94:6	98:2	(*R*)-**4**	38	98	52	>50
3	*rac*-**5**		($^{Si}S,S$)-**12**	–	–	96:4	(*R*)-**5**	–	–	–	–
4	*rac*-**6**		($^{Si}S,S$)-**13**	46	94:6	97:3	(*R*)-**6**	39	96	52	>50
5	*rac*-**7**		($^{Si}S,S$)-**14**	47	95:5	96:4	(*R*)-**7**	42	90	50	>50
6	*rac*-**8**		($^{Si}S,S$)-**15**	50	94:6	98:2	(*R*)-**8**	45	93	51	>50
7	*rac*-**9**		($^{Si}S,S$)-**16**	46	97:3	98:2	(*R*)-**9**	41	90	49	>50
8	*rac*-**10**		($^{Si}S,S$)-**17**	48	95:5	97:3	(*R*)-**10**	39	92	51	>50

[a] Unless otherwise noted, all reactions were conducted using [Rh(cod)$_2$]OTf (5.0 mol%), IPr·HCl (10 mol%), and KOtBu (20 mol%) with a substrate concentration of 0.1 M in toluene at 50°C; Do = donor. [b] Yield of analytically pure product isolated by flash chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy prior to purification by integration of the baseline-separated resonance signals of the diastereomers. [d] The diastereomeric ratio in the racemic series is not biased by conversion. [e] Determined by HPLC analysis using Daicel Chiralcel columns providing baseline separation of enantiomers. [f] Monitored by ^{1}H NMR spectroscopy and determined by integration of the baseline-separated resonance signals. [g] The selectivity factor was calculated by the following equation:[2,18] $s = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$ where $ee = ee/100$ and $C =$ conversion/100; for almost all substrates, s is almost certainly larger than 50. [h] Uncorrected selectivity factor.[20] [i] Final data point in Figure 1. [j] A routine kinetic resolution with yields of isolated product is provided in Table 3, entry 1. [k] Determined by GC analysis (SE-54 column) using decane as an internal standard.

column 12). However, the accuracy of the analytical methods used is not sufficient for its exact calculation[2,18] if $s > 50$.[1,3] Consequently, we carefully determined s in a single example (*rac*-**2**→(*R*)-**2**, Table 2, entry 1) by the linear regression depicted in Figure 1; for this approach, conversion was

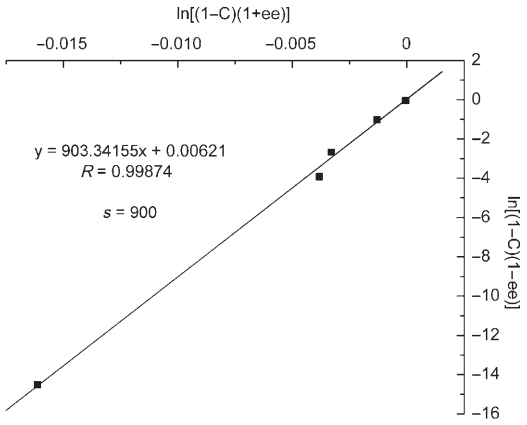


Figure 1. Determination of the selectivity factor by linear regression based on recovered (*R*)-**2** (C = conv/100, ee = *ee*/100, s = 900).

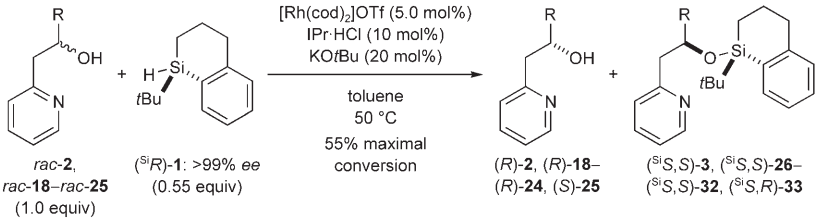
monitored by GC analysis using an internal standard, and enantiomeric excess was measured by HPLC analysis of recovered, slow-reacting (*R*)-**2**. The slope (= selectivity factor) of the linear regression is approximately 900.[19] In order to corroborate this exceptional result, we also determined the enantiomeric excess of the fast-reacting enantiomer (*S*)-**2** after stereospecific reductive cleavage[6,17] of diastereoenriched ($^{Si}S,S$)-**3** (d.r. ≈ 96:4 at 51% conversion). Treatment of ($^{Si}S,S$)-**3** with diisobutylaluminum hydride quantitatively yielded (*S*)-**2** in 93% *ee* along with recovered (^{Si}R)-**1** (> 99% *ee*).[1a,2]

The success with the 2-pyridyl donor ligand prompted us to employ related heteroarenes *rac*-**4** to *rac*-**10**[22] (Table 2). Heteroarenes *rac*-**4** to *rac*-**7**, containing two nitrogen donors, produced invariably high diastereomeric ratios (d.r. = 96:4) in the racemic and excellent selectivity factors ($s > 50$) in the enantioselective experiment (Table 2, entries 2–5); interestingly, the 4-pyrimidyl donor, unlike its 2-pyrimidyl counterpart, failed to undergo the dehydrogenative coupling with sufficient conversion (Table 2, entries 3 and 5). An additional substituent in the proximity of the donor was tolerated; *rac*-**8**, which has a synthetically useful 6-methyl-2-pyridyl unit,[23] reacted with excellent efficiency (Table 2, entry 6). Similarly, 1-isoquinolinyl- and 2-quinolinyl-functionalized alcohols *rac*-**9** and *rac*-**10**, respectively, were resolved with considerable selectivity (Table 2, entries 7 and 8).

After variation of the nitrogen donor, the steric and electronic properties of the substituent R attached to the hydroxylated carbon atom (Table 3) were systematically varied. Naphthyl-substituted alcohols *rac*-**18** and *rac*-**19** compared well with model system *rac*-**2** (Table 3, entries 1–3). Electron-rich anisyl-substituted substrates *rac*-**20** to *rac*-**22** reacted as expected (Table 3, entries 4–6). Conversely, a nitro group at the arene retarded the reaction, thereby preventing sufficient conversion for a resolution; however, the level of diastereoselection in the Si–O coupling of *rac*-**23** was still high (Table 3, entry 7). Alcohol *rac*-**24** with an *ortho*-chloro substituent was prone to racemization at prolonged reaction times (Table 3, entry 8). Kinetic resolution of the arene-substituted alcohols was accomplished with $s > 50$. For comparison, we subjected methyl-substituted *rac*-**25** to the standard procedure. Although this resolution was less efficient, a good enantiomeric excess of 90% at a conversion of 54% (s = 20) was achieved (Table 3, entry 9).

In summary, we developed a rhodium-catalyzed dehydrogenative Si–O coupling using a chiral silane. This reaction proceeds with remarkable levels of diastereoselectivity, and its application to the kinetic resolution of nitrogen-donor-

Table 3: Variation of the substituent in the kinetic resolution of donor-functionalized secondary alcohols.[a]



rac-**2**, *rac*-**18**–*rac*-**25** (1.0 equiv) | (^{Si}R)-**1**: >99% *ee* (0.55 equiv) | (*R*)-**2**, (*R*)-**18**–(*R*)-**24**, (*S*)-**25** | ($^{Si}S,S$)-**3**, ($^{Si}S,S$)-**26**–($^{Si}S,S$)-**32**, ($^{Si}S,R$)-**33**

Entry	Racemic alcohol	R	Silyl ether				Recovered alcohol			Conv [%][f]	s[g]
				Yield [%][b]	d.r.[c]	d.r.[c,d]		Yield [%][b]	*ee* [%][e]		
1	*rac*-**2**	Ph	($^{Si}S,S$)-**3**	50	95:5	99:1	(*R*)-**2**	45	> 99	52	> 50
2	*rac*-**18**	1-naphtyl	($^{Si}S,S$)-**26**	48	96:4	96:4	(*R*)-**18**	45	93	50	> 50
3	*rac*-**19**	2-napthyl	($^{Si}S,S$)-**27**	53	91:9	97:3	(*R*)-**19**	41	> 99	54	> 50
4	*rac*-**20**	2-anisyl	($^{Si}S,S$)-**28**	52	93:7	97:3	(*R*)-**20**	41	> 99	54	> 50
5	*rac*-**21**	3-anisyl	($^{Si}S,S$)-**29**	50	93:7	98:2	(*R*)-**21**	42	98	53	> 50
6	*rac*-**22**	4-anisyl	($^{Si}S,S$)-**30**	52	91:9	98:2	(*R*)-**22**	44	> 99	54	> 50
7	*rac*-**23**	4-nitrophenyl	($^{Si}S,S$)-**31**	–	–	98:2	(*R*)-**23**	–	–	–	–
8	*rac*-**24**	2-chlorophenyl	($^{Si}S,S$)-**32**	41	92:8	96:4	(*R*)-**24**	34	–	48	–
9	*rac*-**25**	Me	($^{Si}S,R$)-**33**	51	85:15	90:10	(*S*)-**25**	41	90	54	20

For footnotes [a]–[g], see Table 2.

functionalized alcohols produced extremely high selectivity factors ($s = 900$, $s > 50$). In contrast to our previously reported Cu–H catalysis, this process might also enable racemization of the slow-reacting alcohol[11] prior to Si–O coupling. Development of a related dynamic kinetic resolution on this basis is currently underway.

Received: August 21, 2007
Revised: September 24, 2007
Published online: November 7, 2007

Keywords: asymmetric catalysis · dehydrogenation · kinetic resolution · rhodium · silicon

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