

A practical concept for the kinetic resolution of a chiral secondary alcohol based on a polymeric silane

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Abstract

The paper describes our preliminary studies on the use of PMHS as a functionalizable polymer and hydride source for the kinetic resolution of secondary alcohols via chiral Cu(I)-catalyzed dehydrogenative silylating process. The chiral phosphine that chelates the Cu metal center has little influence on the selectivity factor of the kinetic resolution. The use of a stereogenic silane appears to be a key requirement to reach enantiodifferentiation in such a process.

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1. Introduction

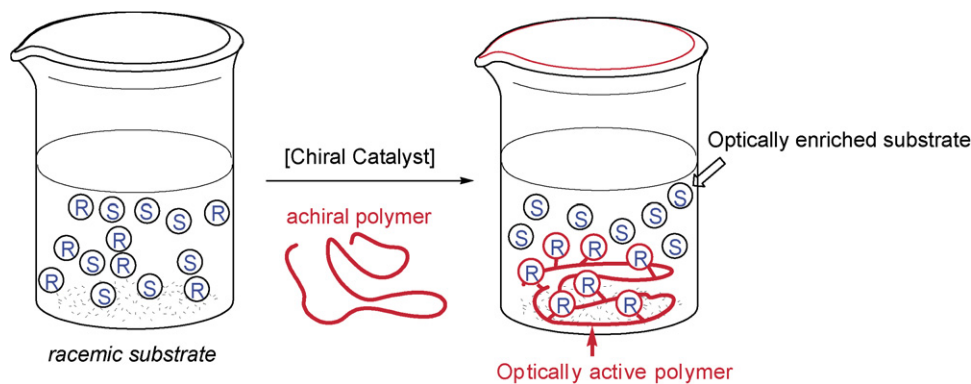
Chiral non-racemic secondary alcohols are important starting materials for the development of biologically active molecules or in the fields of agrochemicals, fragrance and flavour. Three different approaches are commonly used for the obtainment of such molecules and these can be defined as follows: (1) the use of an enantiopure starting material picked in the chiral pool available in nature; (2) their preparation from a prochiral ketone in presence of a chiral metal catalyst; (3) the separation of the enantiomers by chemical or physical means. Efficient asymmetric reactions using various metals, ligands and reducing agents (H_2 , HCO_2H , $iPrOH$, R_3SiH , ...) have been reported and some of them are convenient to use and now commercially available. Alternatively, a popular method to obtain chiral enantiopure secondary alcohols involves the resolution of enantiomers by kinetic resolution. However, as pointed out by Jacobsen and co-workers [1] several conditions must be met to consider kinetic resolution practical. In particular, it requires cheap sources of substrate, catalyst and stoichiometric reagents as well as a highly selective catalyst. Furthermore, the resolved starting material and converted product must be easy to separate [2].

A practical method for an easy and straightforward separation of the product from the substrate would be the development of a kinetic resolution involving the use of functionalizable polymers. The use of an optically active catalyst may preferentially bind one enantiomer of a racemic mixture to a polymeric material present in the reaction mixture. Thus, in principle, at 50% conversion, one enantiomer should be bound to the polymer (optically enriched polymer) while the other one (optically enriched substrate) remains in solution, allowing a straightforward access to both enantiomers in pure form after a simple separation process as illustrated in Scheme 1.

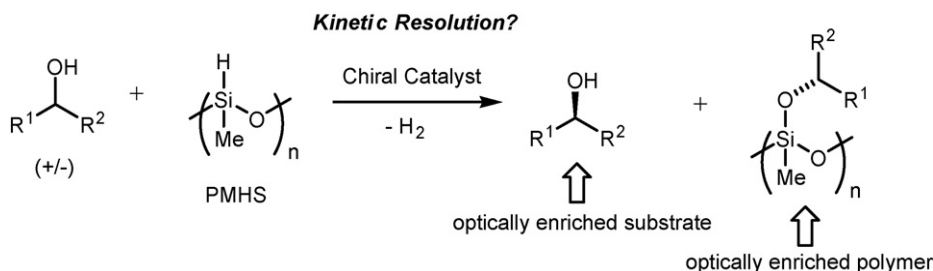
Over the past recent years, metal free and metal-catalyzed asymmetric transformations using cheaper and less toxic metal sources such as copper have received an increased attention. In particular, Ishikawa and co-workers [3] and Hoveyda and co-workers [4] have recently used small chiral organic catalysts for the kinetic resolution of alcohols in a stereoselective silylation process. Remarkably, the suitability of Cu(I) systems for the kinetic resolution of some secondary alcohols has been demonstrated by Oestreich and co-workers [5] via a Cu(I)-catalyzed dehydrogenative coupling in the presence of a silicon-stereogenic silane as a hydride source [6,7]. In order to probe the potential scope of applications of the practical approach proposed above, we have investigated the possibilities of performing the kinetic resolution of secondary alcohols with CuCl/NaOtBu/chiral phosphine catalytic systems [8] via a Cu(I)-catalyzed dehydrogenative silylating coupling using a

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Scheme 1. Schematic description of a kinetic resolution by means of a polymer and a chiral catalyst.



Scheme 2. Kinetic resolution of secondary alcohol by dehydrogenative coupling in the presence of PMHS.

functionalizable silane polymer as an hydride source. For this purpose, polymethylhydrosiloxane (PMHS) appeared as a good candidate for functionalization as it is a safe and an inexpensive polymer coproduct of the silicon industry [9]. In addition, this polymer has been shown by Mimoun to be an effective dehydrogenative silylating agent of alcohols in the presence of a metal hydride (Zn-H) catalyst, allowing an easy access to PMHS-based alkoxy silyl ethers from the corresponding alcohol [10]. Here we report our preliminary studies on the use of PMHS as a functionalizable polymer and hydride source for the kinetic resolution of secondary alcohols via Cu(I)-catalyzed dehydrogenative silylating process (Scheme 2).

2. Results and discussions

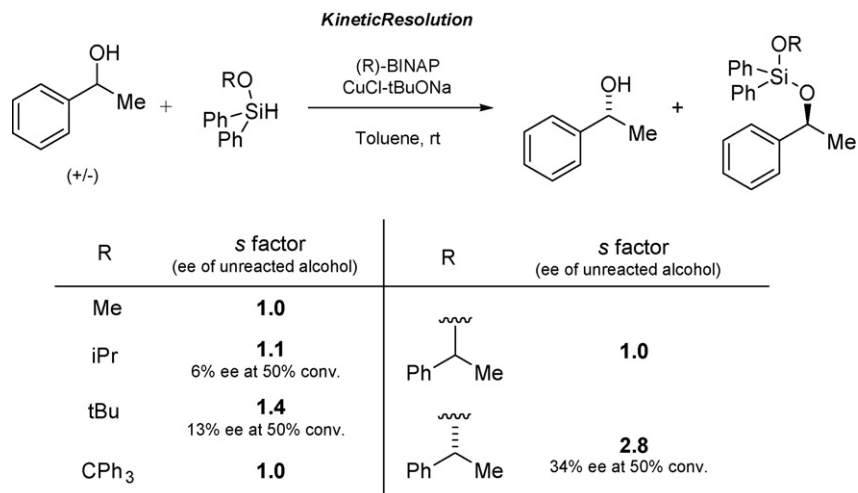
As part of our studies in Cu(I)-mediated asymmetric catalysis, we earlier reported an efficient enantioselective hydrosilylation of aryl ketones catalysed by a chiral BINAP-copper(I) system in the presence of commercially available PhMeSiH₂ as a hydride source [11]. This *in situ* generated catalyst was thus first probed for Cu(I)-catalyzed dehydrogenative reaction of racemic secondary alcohols in the presence of PMHS. We initially conjectured that the chiral environment of the BINAP-Cu chelate may induce a selective Si-O coupling of one enantiomer of the alcohol substrate over the other to yield, at 50% conversion, an PMHS-based alkoxy silyl ether and unreacted alcohol substrate, both being enantiomerically enriched.

In preliminary experiments conducted with Ph₂(RO)SiH, which was generated *in situ* by reaction of Ph₂SiH₂ with one equivalent of the corresponding alcohol ROH, and the opti-

cally active *in situ* catalyst consisting of CuCl, (R)-BINAP and NaOtBu (Scheme 3), the reaction was found to proceed well but no kinetic resolution of a racemic mixture of (±) phenylethanol was observed (*s* = 1). The use of variously R-substituted Ph₂(RO)SiH silanes, all formed *in situ*, provided essentially no significant enantioselection.

Interestingly, the use of the enantiomerically pure silane source Ph₂ [PhCH(CH₃)O]SiH, formed *in situ* by reaction of Ph₂SiH₂ with (R)-phenylethanol provided a selectivity of 2.8 at 50% conversion (34% ee of R enantiomer for the unreacted alcohol) [12]. Our observations may be related to those of Leighton et al. [6] who reported that the environment around the silicon is highly important to reach enantioselection. As demonstrated by Oestreich and co-workers, a key requirement to access to an excellent selectivity in the kinetic resolution step is the use of a chiral silane [5,7]. In our case, the chiral pocket created by the BINAP-Cu chelate does not yield any selectivity (*s* = 1) with (±) phenylethanol. Thus, the presence of an enantiomerically pure chiral center in the silane hydride source appears to be crucial to reach any kinetic resolution in these Cu(I)-catalyzed dehydrogenative reactions.

Encouraged by these results, we carried out this catalysis with various silanes including PMHS. As illustrated in Scheme 4, the active silane RR' (CHMePhO)SiH acting as a hydride source was generated *in situ* by asymmetric hydrosilylation of acetophenone thus providing direct access to various enantiomerically enriched silanes [13]. From the table in Scheme 4, we immediately note that a kinetic resolution takes place when the catalysis is performed with PMHS (*s* = 2.0, 26% ee at 55% conversion). Although the selectivity is rather low, this result directly validates our initial approach on the possibility of functionalizing



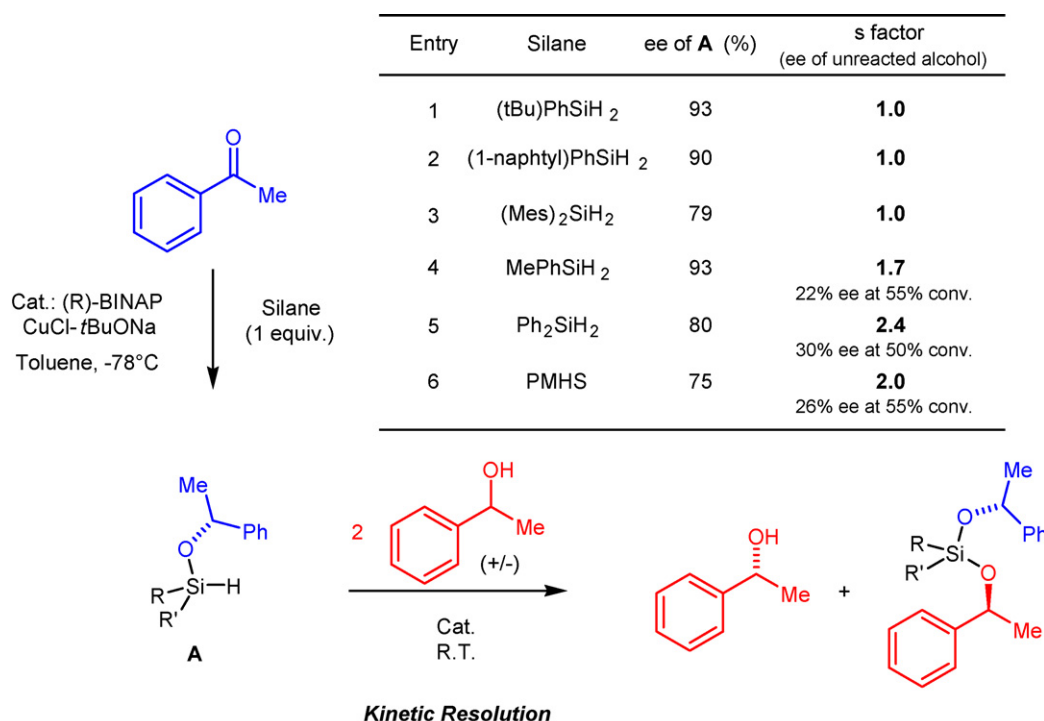
Scheme 3. Kinetic resolution of 1-phenylethanol with Ph₂(RO)SiH generated *in situ* in the presence of 5 mol.% of CuCl/NaOtBu/(R)-BINAP.

a polymer support in an enantioselective manner via kinetic resolution of a racemic mixture.

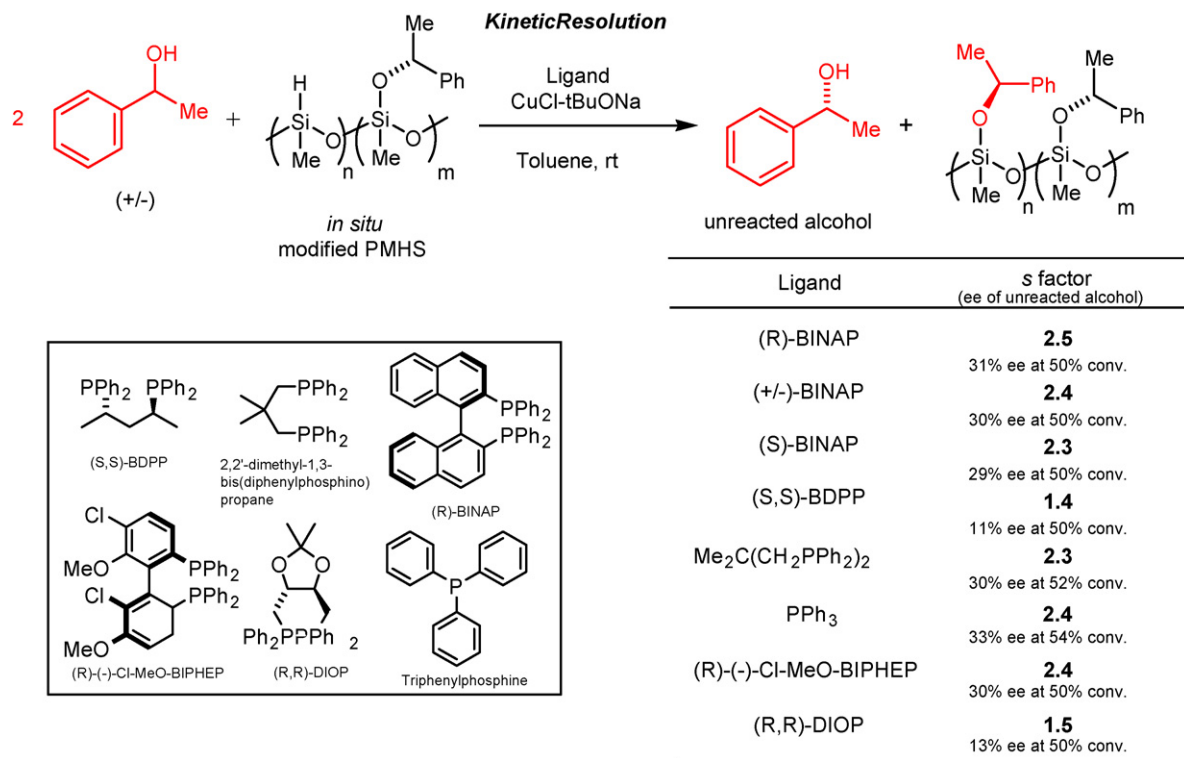
As summarized in Scheme 4, the selectivity appears to be dependent both on the nature of the silane and on the ee of the silane hydride source RR'(CHMePhO)SiH. Thus, significantly encumbered silanes afford no selectivity while loss of enantiopurity in the case Ph₂(CHMePhO)SiH (from 99 to 80% ee in Schemes 3 and 4, respectively) induces a decrease of the selectivity (from 2.8 to 2.4). It is noteworthy that Si–O functionalized and enantiomerically enriched PHMS (75% ee), a chiral polymeric silane, provides a good selectivity ($s = 2.0$, 26% ee at 55% ee) compared to monomeric silanes that were tested although the

latter silanes are more enantiomerically enriched under the studied conditions. These observations show that in our systems the use of a chiral polymer as a hydride source may have a positive impact on the selectivity.

In order to understand the ligand effect, several catalytic runs were carried out using different chiral and achiral phosphines, in the presence of the enantiomerically pure PMHS functionalized with (*R*)-phenylethanol (Scheme 5). As deduced from previous experiments, the chirality of the phosphine has usually little influence on the selectivity factor of the kinetic resolution, with s factors all within a 1.5–2.5 range regardless of the phosphine. This is confirmed by the use of PPh₃



Scheme 4. Kinetic resolution of 1-phenylethanol with RR'(RO)SiH generated *in situ* from the acetophenone and RR'SiH₂ in the presence of 5 mol.% of CuCl/NaOtBu/(R)-BINAP (the ee of A is the enantiomeric excess of the alcohol formed after hydrolysis of A, conducted in a separate experiment).



Scheme 5. Influence of the diphosphine on the kinetic resolution using PMHS-functionalized by (R)-1-phenylethanol.

which gave a selectivity factor of 2.4 (33% ee at 54% conversion).

3. Conclusion

This preliminary work shows that the safe and inexpensive PMHS may be used as hydride source in a Cu(I)-catalyzed dehydrogenative coupling reaction for kinetic resolution of racemic alcohol mixture. Despite the moderate results thus far in terms of selectivity, these results validate our initial approach on the possibility of functionalizing a polymer support in an enantioselective manner via kinetic resolution of a racemic substrate, thereby allowing the preferential attachment to a polymer support of one enantiomer of a racemic mixture. The use of the safe and inexpensive PMHS as polymer support as well as a cheap and less toxic metal source render the catalytic system reported here interesting. Moreover, after a standard kinetic run, the ‘attached’ alcohol may be easily recovered upon hydrolysis of the functionalized polymer and subsequent filtration (for more information, see Section 4). Further studies will focus on the development of new Cu(I)/silane-based catalysts for improvement of selectivity.

4. Experimental

4.1. General procedure for the kinetic resolution presented in Scheme 3 (entry 6)

A Schlenk tube was charged with CuCl (0.025 mmol), NaOtBu (0.025 mmol) and (R)-BINAP (0.025 mmol). Dry

toluene was added under argon (5.0 mL) and the solution was stirred for 20 min at room temperature. After this time, the Ph₂SiH₂ (0.5 mmol) was added dropwise followed by (R)-phenylethanol (0.5 mmol, 99% ee), a small effervescence of hydrogen was observed. The yellow solution was stirred at this temperature until all the alcohol had reacted with the silane (followed by TLC). Then two equivalents (1 mmol) of (±) phenylethanol were added dropwise, an important effervescence of hydrogen was observed. The solution was stirred at room temperature for 4 h and a small aliquot was analysed by ¹H NMR to determine the conversion (50%). After this time the solution was filtered through a chromatography column in order to obtain the unreacted alcohol; GC analysis revealed a 34% ee of (R) enantiomer. The polysilanol was then hydrolysed by using a 1 M NaOH/MeOH solution in order to recover the ‘attached’ alcohol (chiral modifier + transformed alcohol); GC analysis revealed a 31% ee (R, calculated 32% ee). These ee values correspond to a selectivity factor (s) of 2.8 at 50% conversion.

4.2. General procedure for the kinetic resolution presented in Scheme 4

A Schlenk tube was charged with CuCl (0.025 mmol), NaOtBu (0.025 mmol) and (R)-BINAP (0.025 mmol). Dry toluene was added under argon (5.0 mL) and the solution was stirred for 20 min at room temperature. After this time the silane (0.5 mmol) was added dropwise followed by the acetophenone (0.5 mmol). The yellow solution was stirred at -78 °C until all the starting ketone has reacted (followed by TLC). The solution was then heated at room temperature and then two equiva-

lent (1 mmol) of (\pm) phenylethanol was added dropwise, an important effervescence of hydrogen was observed. The same procedure as above was followed.

In a separate experiment, we followed the same procedure as above in order to determine the ee from the reduction of the acetophenone: a Schlenk tube was charged with CuCl (0.025 mmol), NaOtBu (0.025 mmol) and (R)-BINAP (0.025 mmol). Dry toluene was added under argon (5.0 mL) and the solution was stirred for 20 min at room temperature. After this time the silane (0.5 mmol) was added dropwise followed by the acetophenone (0.5 mmol). The yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ until all the starting ketone had reacted. A solution of NaOH in methanol was added (2 mL, 1.0 M) and the resulting solution stirred for 1 h at RT. Subsequent column chromatography provided the desired alcohol in high yield and in a pure form. GC analysis on a chiral column gave the ee and its absolute configuration was determined by comparison of optical rotation with literature values.

4.3. Representative procedure for Scheme 5 (entry 1)

A Schlenk tube was charged with CuCl (0.025 mmol), NaOtBu (0.025 mmol) and the (R)-BINAP (0.025 mmol). Dry toluene was added under argon (5.0 mL) and the solution was stirred for 20 min at room temperature. PMHS (1.0 mmol of “SiH”) was added dropwise followed by the alcohol (*R*)-phenylethanol (ee = 99%) (0.5 mmol), a small effervescence of hydrogen was observed. The yellow solution was stirred at room temperature until all the alcohol has reacted with the silane (followed by TLC). Then two equivalents (1 mmol) of (\pm) phenylethanol were added dropwise, an important effervescence of hydrogen was observed. The solution was stirred at room temperature for 4 h. After this time the solution was filtered through a pad of silica (CH_2Cl_2 as solvent) in order to obtain the recovered alcohol and the polysilanol. A GC analysis gave us 31% ee (the major enantiomer has R as absolute configuration) for the recovered alcohol (0.5 mmol). The polysilanol was then hydrolysed by using a 1 M NaOH/MeOH solution in order to recover the alcohol (chiral modifier + transformed alcohol) in 70% yield (0.71 mmol). A GC analysis gave an ee value of 32% (*R*) (calculated: 33.5% ee). These ee values correspond to a selectivity factor (*s*) of 2.5 at 50% conversion.

Acknowledgments

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 [12] We note that the (*R*)-phenylethanol-functionalized PHMS promote the anchoring of the (*S*) enantiomer. The selectivity factor was found to be dependent on the conversion of the reaction. This result is consistent with the fact that at higher conversion the 'optical purity' of the polymer is lower. Chiral alcohols that do not contain aryl substituents (i.e. (–)-menthol, (+)-diethyl tartrate, ...) were tested without success. π -Stacking interactions between the polymer and the substrate may be at the origin of the kinetic resolution process.
 [13] In some cases, the silicon atom can be stereogenic. For example, when MePhSiH₂ is used as the silane source two diastereomers of A were observed by ¹H NMR with a ratio of ca. 45/55. Based on our preliminary results, it seems that non-prochiral silanes afford a higher *s* factor in the present kinetic resolution reaction (see entries 5 and 6 vs. 4 in scheme 4).