approximately 1000-fold higher than that reported for any other catalytic antibody.[3f, 10] The catalytic efficiency of the antibody for this substrate, $3.3 \times 10^5\ s^{-1}\,M^{-1}$, compares favorably with the efficiency of natural muscle aldolase, $4.9 \times 10^4\ s^{-1}\,M^{-1}$, in the retro-aldolization of its substrate fructose-1,6-bisphosphate.[11]

In conclusion, we have demonstrated that combining transition state analogy and reactive immunization design into a single hapten can result in increases both in the output of catalysts from the immune system as well as their efficiency. This strategy resulted in the characterization of the most proficient antibody catalysts prepared to date. Antibodies 93F3 and 84G3 catalyze a wide array of aldol reactions with *ee* values exceeding 95% in most of the cases studied. A new stereogenic center is formed when acetone is the aldol donor substrate by attack on the *re*-face of the aldehyde, which provides the antipodal complement of ab38C2 in aldol reactions. Both aldol enantiomers may be accessed through aldol and retro-aldol reactions. These catalysts should provide access to a wide variety of enantiomerically enriched synthons with application to natural product syntheses.

Received: April 29, 1999
Revised version: August 4, 1999 [Z13339IE]
German version: *Angew. Chem.* **1999**, *111*, 3957 – 3960

Keywords: aldol reactions · asymmetric synthesis · catalytic antibodies · enantiomeric resolution · retro reactions

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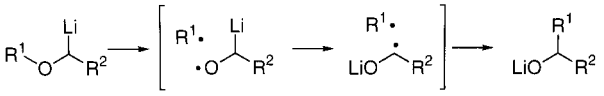
Enantioselective [1,2] Wittig Rearrangement Using an External Chiral Ligand**

Katsuhiko Tomooka,* Kyoko Yamamoto, and Takeshi Nakai*

Since its discovery by Wittig and Löhmann in 1942,[1] the reaction of α-lithiated ethers, now known as the [1,2] Wittig rearrangement, has attracted much interest from both mechanistic and synthetic points of view.[2] This type of carbanion rearrangement is recognized to proceed by means of the radical dissociation – recombination mechanism [Eq. (1)].[2, 3]



(1)

Despite its long history, however, no enantioselective versions of the Wittig rearrangement have been developed yet. Clearly, the radical character provides a great challenge. We now disclose the first enantioselective Wittig rearrangement which relies upon an asymmetric lithiation protocol[4] in which (*S*,*S*)-bis(dihydrooxazol) **3** serves as an external chiral ligand[5, 6] [Eq. (2)]. The most striking feature is that the

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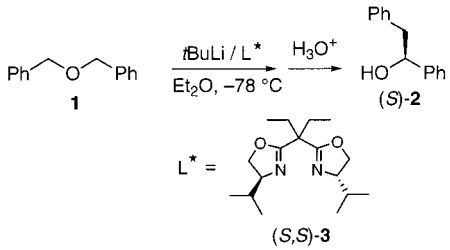
[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and by the Research for the Future Program, administered by the Japan Society of the Promotion of Science.

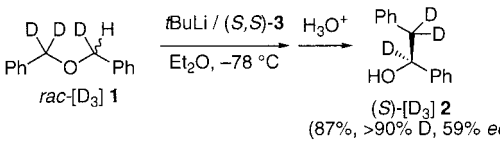


(2)

rearrangement proceeds with essentially the same enantioselectivity even when only a catalytic amount of chiral ligand **3** is used.

We found that the rearrangement of dibenzyl ether (**1**), a historic Wittig substrate,[1] when induced with the premixed complex *t*BuLi/**3** (1.0 equiv each) in diethyl ether at $-78\,^{\circ}C$, afforded alcohol (*S*)-**2** in 55% yield and with 60% *ee*, along with recovered **1** in 43% yield.[7, 8] This is the first example of an enantioselective Wittig rearrangement, though the enantioselectivity is moderate.[9] Significantly enough, when either one more equivalent of *t*BuLi was added after the reaction or the complex *t*BuLi/**3** (2.0/1.0) was initially used, the yield of **2** increased to 90–94% while the same level of enantioselectivity (62% *ee*) was maintained. This means that two equivalents of *t*BuLi are required for the complete reaction. At this point we made two suppositions: 1) The initial lithiation would be effected almost exclusively by the *t*BuLi/**3** complex; *t*BuLi itself, which is known to exist as a dimer in diethyl ether,[10] could not function as an efficient lithiating agent under these conditions.[11] 2) The *t*BuLi dimer could participate in complexing with the resulting **3**-bound lithium alkoxide, thereby taking half out of action to form the *t*BuLi/alkoxide complex[12, 13] while regenerating the active complex *t*BuLi/**3**. These arguments explain how the enantioselective version could proceed even with a catalytic amount of the chiral ligand **3**.

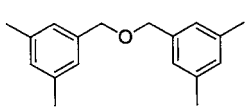
Therefore, the rearrangement of **1** was carried out using 10 mol% of **3** and two equivalents of *t*BuLi under the same conditions. As anticipated, alcohol (*S*)-**2** was obtained in equally high enantioselectivity and chemical yield (60% *ee*, 86%). A similar use of 5 mol% of **3** resulted in 54% *ee* and 81% chemical yield. Scheme 1 depicts a plausible asymmetric catalytic cycle in which the enantioselectivity might be determined at the radical-recombination step involving the chiral ligand-bound anion radical. Indeed, a similar rearrangement of [D_3]**1** (racemate) afforded (*S*)-[D_3]**2** (>90% D content) in 87% yield and with essentially the same enantiomeric excess as previously observed for **1** [Eq. (3)], indicating



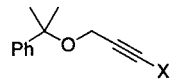
(3)

that the lithiation stereochemistry has nothing to do with the product stereochemistry. The most striking feature of this asymmetric catalysis is that during the course of reaction the chiral ligand **3** switches the lithium species partner at each stage, thereby playing the dual role as a catalyst for the lithiation step and a chiral auxiliary for the rearrangement step. The exact mechanism of the asymmetric induction at the rearrangement step is unclear at present; more detailed work is needed.

Encouraged by this success, we also examined the enantioselective rearrangement of ethers **4**–**6** (TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl) using *t*BuLi/**3** (2.0 equiv each). The results thus obtained are



4: 56% *ee* (65%)



5a, X=TMS: 40% *ee* (52%)
5b, X=TBDPS: 43% *ee* (49%)

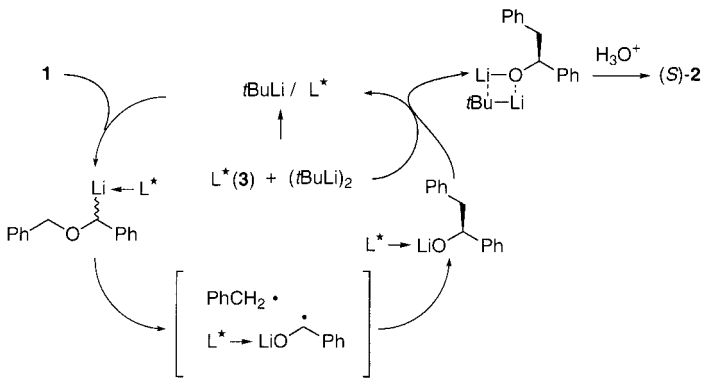
shown below the formula drawings.[14, 15] Of particular interest is the rearrangement of *rac*-**6**, which provides the tertiary alcohol **7** with a relatively high enantioselecitivity [Eq. (4)].

rac-**6a**, X=TMS
rac-**6b**, X=TIPS

7a: 54% *ee* (55%)
7b: 65% *ee* (65%)

(4)

We have described the first example of an enantioselective [1,2] Wittig rearrangement which can proceed even in an asymmetric, catalytic fashion. This is also the first example of an enantioselective, catalytic carbanion-radical rearrangement. Thus, this work opens a new chapter for classic Wittig chemistry as well as for asymmetric reactions of radicals and organolithium species.



Scheme 1. Plausible catalytic cycle of the enantioselective [1,2] Wittig rearrangement.

Experimental Section

To a solution of (*S*,*S*)-**3** (11.2 mg, 0.038 mmol) in diethyl ether (6 mL) at $-78\,^{\circ}C$ was added a commercial solution of *t*BuLi in pentane (0.48 mL of a 1.57 M solution, 0.75 mmol) by means of a syringe, and the mixture was stirred for 15 min. The mixture was maintained at $-78\,^{\circ}C$, and a solution of **1** (75.9 mg, 0.38 mmol) in diethyl ether was added dropwise by means of a syringe. The reaction mixture was stirred at $-78\,^{\circ}C$ for 2 h and then treated with a saturated aqueous solution of ammonium chloride. The resulting mixture was extracted with diethyl ether three times, and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by

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chromatography on silica gel (hexane/diethyl ether 10/1) to give 65.4 mg of (*S*)-alcohol **2** (86% yield, 60% *ee*).

Received: May 3, 1999 [Z13365IE]
German version: *Angew. Chem.* **1999**, *111*, 3955–3957

Keywords: asymmetric catalysis · asymmetric synthesis · rearrangements · Wittig reactions

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[14] The rearrangement of **4** and **6b** with 10 mol% of **3** resulted in 53% *ee* (56%) and 54% *ee* (35%), respectively.
[15] The enantiomeric excesses were determined by ^{1}H NMR analysis of the (*S*)-MTPA esters. The absolute configurations of the major enantiomers obtained from **4** and **5** were not determined. The (*R*) configuration of **7a** was assigned by conversion into the known (*R*)-methyl α-benzylmandelate: $[\alpha]_D^{23} = -13.5$ ($c = 1.20$ in $CHCl_3$) (65% *ee*); value of $[\alpha]_D^{26} = -32.4$ ($c = 3.4$ in $CHCl_3$) in the literature: H. R. Sullivan, J. R. Beck, A. Pohland, *J. Org. Chem.* **1963**, *28*, 2381–2385.

The Design of Leadlike Combinatorial Libraries

Simon J. Teague,* Andrew M. Davis, Paul D. Leeson, and Tudor Oprea

Combinatorial chemistry is now widely applied in the drug-discovery process, for both the identification and optimization of lead compounds (chemical starting points). Initially the key factors in the design of libraries intended for finding lead compounds were considered to be library size and diversity.[1] More recently consideration has been given to designing libraries in which the members have druglike physicochemical properties.[2] Druglike properties are most commonly defined using the "rules of 5": M_r is smaller than 500, the calculated logarithm of the octanol–water partition coefficient (clg *P*) is less than 5, there are less than five hydrogen-bond donor atoms, and the sum of the number of nitrogen and oxygen atoms is less than 10.[3] These guidelines have achieved widespread acceptance as defining the limiting properties of most orally active drugs which are able to be absorbed by passive mechanisms. However, it should be borne in mind that these are empirical rules derived by examination of the properties of existing drugs. Herein we propose that the properties required of library compounds intended to provide leads suitable for further optimization may be rather different.

Our analysis starts from consideration of the common sources of leads for drug discovery (Figure 1). These have been divided broadly into three types. The first are leadlike,

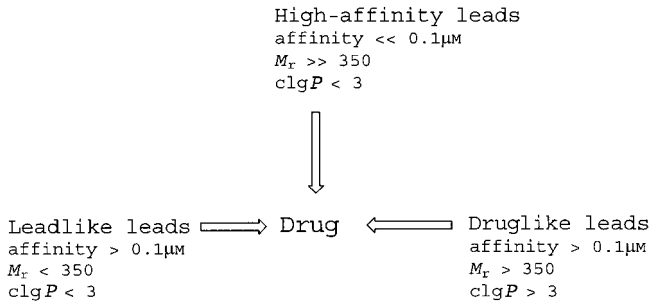

Figure 1. Classification of leads by binding affinity. Lower potency leads are subdivided into leadlike and druglike by reference to their M_r and clg *P* values.

low-affinity (>0.1 μM)[4] compounds which have low molecular weight and clg *P*, typified by some endogenous molecules, for example histamine and GABA. These have been converted into drugs, through the optimization of potency and pharmacokinetic profile, by increasing molecular weight and lipophilicity (Table 1, entries 1–8). The second major source of leads is typified by high affinity and molecular weight. It

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