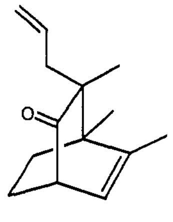
Table I. Bridgehead Substitution of 1-Methoxybicyclo[2.2.2]oct-5-en-2-ones[a]

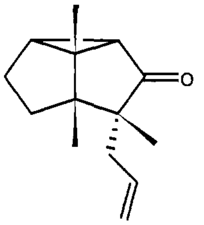
substrate				product		yield[b]
	X	Y	RM		R	(%)
5a	Me	H	MeLi	**1a**	Me	65
5a	Me	H	*n*-BuLi	**1b**	*n*-Bu	68
5a	Me	H	*i*-PrLi[c]	**1c**	*i*-Pr	46
5a	Me	H	*t*-BuLi[d]	**1d**	*t*-Bu	20
5a	Me	H	PhLi	**1e**	Ph	66
5a	Me	H	DIBAH	**1f**	H	44
5b	H	Me	MeLi	**1g**	Me	61
5c	Me	Me	DIBAH	**1h**	H	63
5d	H	H	MeLi	**1i**	Me	46

[a] All synthetic intermediates (**6**, **7**, and **8**) were used without purification. [b] Overall yields from **5**. [c] In situ generated by sonication of a mixture of *i*-PrCl and Li in THF. [d] A mixture of 4-*tert*-butyl-5-methyl-1-methoxybicyclo[3.2.1]oct-2-ones was obtained from **6a** in 47% yield.

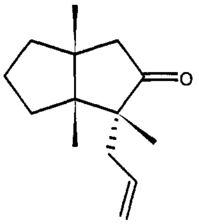
Chart I



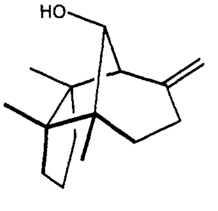
10



11



12



13

suggests that the acid-catalyzed dehydration and the bridge migration are not concerted, and a stable intermediate such as allyl cation **9** may be present. A simple model study of **9** indicates that the C-2 p atomic orbital overlaps preferentially the C-1–C-7 σ bond (the two-carbon bridge) rather than the C-1–C-8 σ bond (the one-carbon bridge).

The minor products, bridgehead hydroxy ketones **7** and the alcohols derived from **7**, were also useful to prepare **1** in a similar manner. In practice, the transformation of **5** to **1** was carried out without chromatographic separation of synthetic intermediates (Table I). The mode of substitution of ketones **1f** and **1h** is contrary to that of Diels–Alder 1,4-adducts derived from the corresponding 1,3-cyclohexadienes and ketene equivalents. Ketones **1b–e** are difficult to prepare selectively by means of simple Diels–Alder strategy.

The ketone **1h** has been employed as the starting material for the formal total synthesis of (±)-gymnomitrol (**13**), a unique tricyclic sesquiterpene.[8,9] Sequential treatment of **1h** with LDA, 3-iodopropene (THF–HMPA), LDA, and iodomethane (THF–HMPA) gave **10** stereoselectively in 72% overall yield.[10] The oxa-di-π-methane rearrangement of **10** proceeded efficiently in acetone to form **11** in 94% yield. Reduction of this cyclopropyl ketone by lithium in liquid ammonia gave the substituted diquinane **12** (75% yield) which had already been converted into (±)-gymnomitrol.[9c]

Thus, it is clear that this bridgehead substitution expands the utility of bridged polycyclic compounds for natural product syntheses.

Acknowledgment. Financial support by the Kurata Foundation is gratefully acknowledged.

Supplementary Material Available: Spectral (IR and ^{1}H NMR) and analytical data (elemental analysis) for **6a**, **6c**, **7a**, **8a**, **1c–h**, and **10–12** (3 pages). Ordering information is given on any current masthead page.

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[8] Isolation: Connolly, J. D.; Harding, A. E.; Thornton, I. M. S. *J. Chem. Soc., Chem. Commun.* **1970**, 1320–1321; *J. Chem. Soc., Perkin Trans. 1* **1974**, 2487–2493.

[9] Synthesis: (a) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765–6767; **1982**, *104*, 2198–2208. (b) Buchi, G.; Chu, P.-S. *Ibid.* **1979**, *101*, 6767–6768; *Tetrahedron* **1981**, *37*, 4509–4513. (c) Welch, S. C.; Chayabunjonglerd, S. *J. Am. Chem. Soc.* **1979**, *101*, 6768–6769. Welch, S. C.; Chayabunjonglerd, S.; Parakasa, R. *J. Org. Chem.* **1980**, *45*, 4086–4093. (d) Han, Y.-K.; Paquette, L. A. *Ibid.* **1979**, *44*, 3731–3733. Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1831–1835. (e) Kodama, M.; Kurihara, T.; Sasaki, J.; Ito, S. *Can. J. Chem.* **1979**, *57*, 3343–3345.

[10] The ^{1}H NMR spectrum of **10** shows a singlet at δ 0.78 due to the *endo*-3-methyl protons which are shielded by the carbon–carbon double bond. Details are listed in the Supplementary Material.

The Role of the Product in Asymmetric C–C Bond Formation: Stoichiometric and Catalytic Enantioselective Autoinduction

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Evidence for aggregation of (alkali) metal enolates, alkoxides, and condensation products in the solid state and in solution has been rapidly accumulating in the past decade.[1] The organic moieties are mono- or bidentate ligands in these clusters prior to their liberation to monomeric products in the hydrolytic workup. Although C–C bond formation via condensation of organometallic reagents with carbonyl compounds is by far the most important synthetic procedure in organic chemistry (especially in the area of asymmetric induction with chiral auxiliary ligands), the stereochemical effect *of the product* acting as a ligand in intermediate complexes has not been systematically investigated.

We studied the effect of enriched (+)-(*R*)-1-phenyl-1-propanol-d_1 (+24.40),[2] **1D**, on the addition of ethyllithium to benzaldehyde:

$$\mathrm{PhCHO}\ \xrightarrow[\text{or: }(+)\text{-}(\mathrm{PhC^*DEtO})_4\mathrm{Ti/ZnEt_2}]{(+)\text{-}\mathrm{PhC^*D(OLi)Et/EtLi}}\ \xrightarrow{\mathrm{H_3O+}}\ \underset{\mathbf{1D}}{\mathrm{PhC^*D(OH)Et}} + \underset{\mathbf{1H}}{\mathrm{PhC^*H(OH)Et}}$$

To a solution of 2 mmol of the alkyllithium in benzene (filtered from LiBr, 5 mL, 0.402 M) was added 1 mmol of **1D** at room temperature (all operations under dry nitrogen). Ethane was evolved in an exothermic reaction. The homogeneous solution was cooled in ice, and 1 mmol of freshly distilled benzaldehyde in 1 mL of dry benzene was added within 5 min with stirring. After 10 min the reaction mixture was subjected to a hydrolytic workup with dilute HCl and ether. The product, a mixture of **1D** and **1H** (94%), was purified by molecular distillation (0.1 mm, 100 °C bath temperature, repeated until constant rotation). The use of deuterated **1D** allowed us to determine the ee of **1H** separately in the mixture. The ratio of **1D** vs **1H** (found 100:86) was determined by integration of the methine proton in **1H** at 5.1

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[1] For a recent review: Seebach, D. *Angew. Chem.* **1988**, 100, 1685.

[2] Prepared via the quinine-catalyzed addition of diethylzinc to benzaldehyde-*d* in 70% ee (according to Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *5*, 135). The optical properties of **1D** and **1H** are identical within experimental error. The relationship between specific rotation and various mixtures of **1D** and racemic **1H** is linear. All rotations measured at c = 100, in toluene, 21 °C, 578 nm.

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ppm relative to the CH_3 group of **1D** + **1H** ($CDCl_3$, 300 ^1H NMR). Subsequently the ee of **1H** was calculated after comparison of the rotation **1D** + **1H** (+18.7°) with a stoichiometrically identical mixture of **1D** wih *racemic* **1H** (+13.1°). The ee of **1H** was established to be 17% in favor of the *same* (+)-isomer (an average of three runs, accuracy 5%). This value was in agreement with the ee of **1H** determined by integration of the enantiomeric methine proton in **1H** using quinine as a shift reagent.[3]

We define the effect of a product ligand acting on the stereochemical course of a reaction as *the principle of enantioselective autoinduction*. The formation of mixed aggregates containing *both* product and starting material fragments influences the stereochemistry of subsequent C–C bond formation.[4,5] A vast majority of asymmetric synthetic reactions proceeding via addition of organometallic reagents to carbonyl compounds, the observation of an autoinductive effect, is pertinent to all these examples.[1,6]

We successfully demonstrated the effect to be operative in a catalytic manner. Recently it was shown that orthotitanates catalyze the widely studied[7] addition of diethylzinc to benzaldehyde.[8,9] We prepared the titanate from **1D** and $TiCl_4$ in ether with triethylamine. One mmol of this compound, a colorless oil, was added to 16 mmol of diethylzinc in toluene (1.1 M solution) at room temperature. Benzaldehyde, 12 mmol, was added, and the homogeneous mixture was left overnight. After hydrolytic workup a 72% yield of **1D** and **1H** was obtained with a ratio of **1D** vs **1H** of 100:512. The ee of **1H** was determined by comparison of the found rotation (+15.5°) with that of a stoichiometrically identical sample of **1D** and racemic **1H** (+4.0°). The optically active alcohol was replicated with an ee of 32% in favor of the same enantiomer completely *without* the assistance of chiral auxiliaries.

Further research is directed toward the realization of more efficient examples as well as to a detailed study of the interplay of enantioselective autoinduction and auxiliary induction with chiral ligands in asymmetric synthesis.

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[3] The double doublet is split into eight lines (1:1 **1D**/**1H**:quinine, $CDCl_3$, 21 °C, 300 MHz ^1H NMR) (+)-isomer at 5.134, 5.120, 5.144, 5.088 and the (−)-isomer 5.124, 5.110, 5.096, 5.082). Rosini, C.; Ucello-Barretta, G.; Pini, D.; Abete, C.; Salvadori, P. *J. Org. Chem.* **1988**, *53*, 4579.

[4] The methyl ether of 1D does not induce an ee of 1H.

[5] Seebach was the first to recognize the potential role of mixed aggregates: Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622, in a paper with a philosophical character. See, also: Jackman, L. M.; Lange, B. C. *J. Org. Chem.* **1983**, *48*, 4789.

[6] Adverse enantioselective autoinduction takes place in the reaction of a lithium–magnesium reagent with benzaldehyde: addition of a second equivalent of the carbonyl compound is detrimental to the optical yield (Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597). Adverse autoinduction overrules auxiliary induction in the second stage of the quinine-catalyzed bishydroxylation of olefins: the second equivalent is produced with a 7% excess of the "wrong" enantiomer (Sharpless, K. B.; Marko, I.; Svendsen, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 737). Capricious results in asymmetric condensations with enolates and metal alkyls with the first, second, third, and fourth equivalent of the carbonyl compound were obtained earlier: Mukayama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K.; *J. Am. Chem. Soc.* **1979**, *101*, 1455. Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695. Mazaleyerat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 789. By using the same method with an optically active deuterated hydroxyester, we have studied enantioselective autoinduction in the aldol condensation of the Li enolate of ethyl acetate and benzaldehyde indepth. Small counterproductive effects were observed. However, precipitation of a tetrameric diastereomeric Li–O complex is a crucial factor in the stereochemistry of this process and probably in several of the reactions listed in Table IX in ref 1 Alberts, A. H.; Wynberg, H. to be published). In the perspective of nonlinear effects in asymmetric induction (ref 7), assuming precipitation-inactivation of aggregated complexes with internal mirror planes, we note that in enantioselective autoinduction (as in auxiliary induction processes with partially resolved chiral ligands) the optical purity of the formed product is *not necessarily limited* by the optical purity of the previously added product.

[7] Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028 and references cited here.

[8] Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657.

[9] The zinc alkoxide, prepared in situ by addition of 0.1 equiv of (+)-**1D** to 10 mmol of diethylzinc, catalyzed this reaction less effectively (3 days, 20 °C, 54% yield) and with an enantioselectivity in favor of the (+)-isomer slightly above experimental error, confirming the results of Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.

Reaction in the Bicontinuous Phase of a Nonaqueous Microemulsion: Amidation of the Olefin $C_8F_{17}CH{=}CH_2$ by γ Radiolysis

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A microemulsion is generally defined as a transparent medium made up of water, oil (saturated or unsaturated hydrocarbon), a surfactant, and a cosurfactant (a short chain amphiphile such as an alcohol or an amine).[1] Depending on the proportions of the constituents, three main types of structure can be distinguished:[1,2] reverse micelles (**W/O**), direct micelles (**O/W**), or bicontinuous structures (Figure 1). In general, reactions carried out in microemulsions take place either in the direct micellar zone or more commonly in the reverse micellar zone.[3] There are few reports of reactions taking place in the bicontinuous phase.[4]

We have demonstrated for the first time the use of microemulsions based on formamide instead of water to produce media for carrying out chemical reactions.[5] Formamide was employed in view of the low solubility of many organic compounds in water. Moreover, formamide can be used as a reactant, with the preparation of microemulsions in which the two main components (oil and formamide) are reactants.

We describe here the amidation of the olefin $C_8F_{17}CH{=}CH_2$ by γ radiolysis in a formamide (**F**) microemulsion containing 1,1,2-trihydroperfluoro-1-decene ($C_8F_{17}CH{=}CH_2$) as oil (**O**), potassium 2,2,3,3-tetrahydroperfluoroundecanoate ($C_8F_{17}C_2H_4CO_2K$) as surfactant (**S**), and 1,1,2,2-tetrahydroperfluorohexanol ($C_4F_9C_2H_4OH$) as cosurfactant (**CoS**). The phase diagram of this system reported in a previous publication[6] was explored after γ radiolysis. Study of self-diffusion by ^1H NMR[7] enabled the structures of the various microemulsions to be determined. The results are shown in Figure 2 and Table I.

Self-Diffusion Measurements. The self-diffusion coefficients (cf. Table I) defined three microemulsion zones similar to those of the corresponding aqueous systems: (a) Microemulsions 1 and 2 have an **O/F** structure similar to that of direct micelles (**O/W**); the olefin in droplets has a much lower self-diffusion coefficient than that of the pure liquid, while formamide, making up the continuous phase, diffuses readily. (b) In contrast, microemulsions 4 and 5 have a **F/O** structure similar to reverse micelles (**W/O**); the formamide in droplets has a low self-diffusion coefficient unlike that of the olefin. (c) In microemulsion 3, the coefficients of self-diffusion of formamide and oil are similar, indicating the presence of a bicontinuous phase, not organized in micelles. This type of structure, well-known in aqueous media,[6] is described here for the first time in nonaqueous microemulsions.

These results show that by judicious choice of surfactant and cosurfactant, it is possible to find systems in formamide micro-

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[1] (a) Daniellson, I.; Lindman, B. *Colloids and Surfaces* **1981**, *3*, 381. (b) Langevin, D. *Acc. Chem. Res.* **1988**, *21* (71), 255.

[2] Lindman, B.; Stilbs, P. *Microemulsions*; Friberg, S., Bothorel, P., Eds.; CRC Press: Boca Raton, FL, 1987; p 119.

[3] Fendler, J. H.; Fendler, E. J. *Catalysis in micellar and macromolecular systems*; Academic Press Inc.: London, 1975.

[4] Candau, F.; Zekhnini, I.; Durand, J. P. *J. Colloid Interface Sci.* **1986**, *114*, 398.

[5] Rico, I.; Lattes, A. *Microemulsions Systems*; Rosano, H., Clausse, M., Eds.; Marcel Dekker: New York, 1987; Vol. 23, p 341 and cited references.

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