in the reactants, the polar media must stabilize the reactants more efficiently than the TS. Consequently, the hydrolysis rate decreases with increasing water density.

In summary, we have demonstrated that the hydrolysis of esters takes place exclusively by ionic mechanisms, whereby hydroxide ions dissociated from SCW catalyze the reaction. This mechanism is dominant in the initial stage of the reaction, since the concentration of the generated carboxylic acid is low. As the concentration of carboxylic acid increases with the progress of the reaction, the mechanism would change to the proton-catalyzed reaction if the concentration of substrates were sufficiently high.[9] Our results clearly indicate that one must consider the involvement of hydroxide ions in other reactions in SCW, because dissociation of water produces the same amount of protons and hydroxide ions.

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[18] Addition of sodium hydroxide (4.8×10^{-7} mol L^{-1}) enhanced the rate of hydrolysis by a factor of about 2.5. However, the lack of data on the dissociation constant of sodium hydroxide in SCW and the difficulties in obtaining an accurate value of k_3 prevented our making detailed kinetic analyses.

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Modular Ligands for Asymmetric Synthesis: Enantioselective Catalytic Cu^{II}-Mediated Condensation Reaction of Ethyl Pyruvate with Danishefsky's Diene**

Peter I. Dalko,* Lionel Moisan, and Janine Cossy*

The search for new catalysts for asymmetric synthesis is an area of significant importance in modern organic synthesis, and a number of spectacular advances have been reported in recent years.[1, 2] However, there is still a need for simple and readily available catalysts, particularly for C–C bond-forming processes.[3] A modular system that allows quick access to a great diversity of ligands from simple components is valuable. Peptide-based ligands have been developed for Ti-catalyzed additions of TMSCN to *meso* epoxides[4] and imines (Strecker amino acid synthesis),[5] and Zr-catalyzed addition of dialkylzincs to imines.[6] Recently, peptide-based phosphane ligands have been shown to promote efficient Cu-catalyzed conjugate addition.[7] Moreover, this class of ligands allows the regio- and enantioselective formation of quaternary carbon centers by using allylic reagents.[8] We report herein a simple and efficient approach that leads to the generation of a great diversity of asymmetric ligands from easily available components.[9]

The catalyst preparation is based on the condensation of 1,2-diamines[10] of type **1** with ketones or aldehydes **2** (Scheme 1), which affords imidazolidines **3** in solution in equilibrium with the open form **4**. The corresponding bisimine **5** and the starting diamine **1** are often present with compounds **3** and **4** in the reaction mixture.[11] We anticipated that chelating metals such as Cu^{II} would shift this equilibrium toward the metallacyclic form **6** by forming a bidentate complex (Scheme 1).[12] Although no precedent for the use of

[*] Dr. P. I. Dalko, Prof. Dr. J. Cossy, L. Moisan
Laboratoire de Recherches Organiques associé au CNRS, ESCPI
10 rue Vauquelin, 75231 Paris Cedex 05
Fax: (+33) 1-40-79-46-60
E-mail: peter.dalko@espci.fr, janine.cossy@espci.fr

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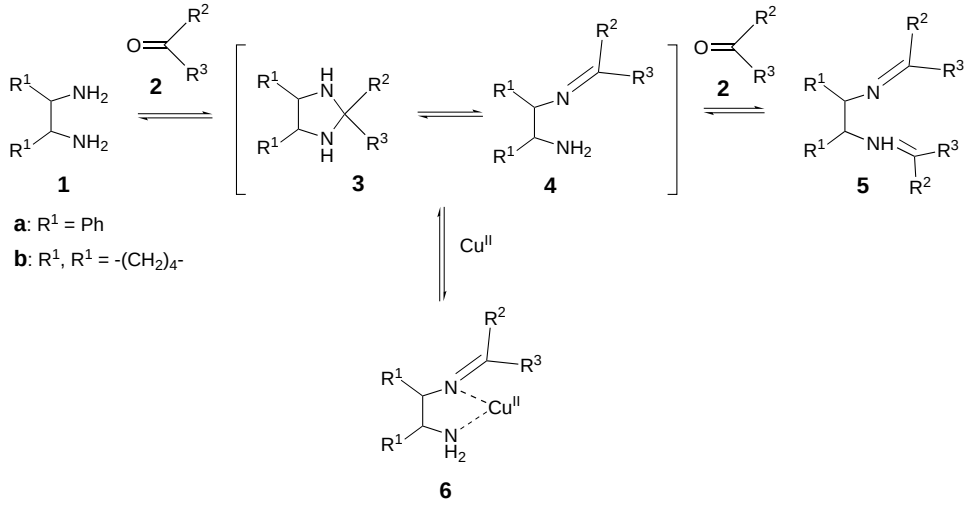
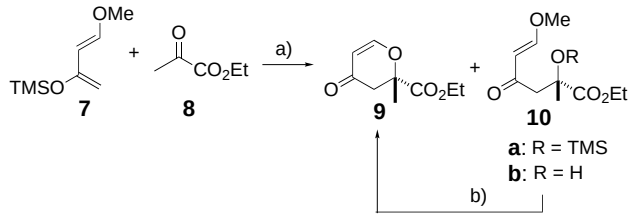


Scheme 1. Condensation reaction between vicinal diamines and carbonyl compounds.

this type of ligand in enantioselective catalytic reactions has been reported, analogous reactions in the literature suggest that these complexes may be active in a number of reactions.[13]

To demonstrate the practical use of the catalyst system, a condensation reaction between *trans*-1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (**7**; Danishefsky's diene) and ethyl pyruvate (**8**) was selected (Scheme 2).[14, 15] In this reaction,



Scheme 2. Reaction between Danishefsky's diene and ethyl pyruvate by using chiral Cu^{II}-derived catalysts. Reagents and conditions: a) $Cu^{II}-L^*_n$ (10%), 4-Å molecular sieves, THF, −72 °C, 72 h; b) CF_3COOH (cat.), room temperature.

dihydropyrone **9** can be formed through two distinct mechanistic pathways, that is, through a traditional hetero-Diels–Alder (HDA) cycloaddition reaction or by a Mukaiyama aldol condensation pathway followed by cyclization.[16] It is generally accepted that the Mukaiyama aldol product **10** can either be isolated, or may undergo a ring-closure reaction to give dihydropyrone **9** under the reaction conditions or by treatment with acid. Herein we show that complexes derived from chiral diamines, carbonyl compounds, and Cu^{II} salts catalyze both reaction pathways and afford the desired adducts with high enantiomeric excesses.

The ligands were prepared by the condensation of amines **1** (Scheme 1) with ketones or aldehydes (see Table 1).[17] The chiral Lewis acid catalysts were obtained by adding a stoichiometric amount of $Cu(OTf)_2$ to the reaction mixture, which was allowed to stand for 16 h at room temperature (premixing).[18] The premixing time significantly influenced the enantioselectivity of the condensation reaction. In general, a lower *ee* value was obtained for dihydropyrone **9** when the premixing time was reduced (see below).

The condensation reaction between **7** and **8** in the presence of the chiral complexes derived from diamines **1a** and **1b** (10 mol%), carbonyl compounds **2a–f**, and copper(II) salt at −72 °C afforded dihydropyrone **9** and the Mukaiyama aldol product **10** (Scheme 2). At this stage, the *ee* value of the primary cycloadduct **9** was determined[19] (Table 1), but unfortunately the *ee* values of **10a** and **10b** could not be determined. The mixture of **9** and **10** was converted into the dihydropyrone **9** by treatment with a catalytic amount of triflic acid, and the *ee* value of the resulting dihydropyrone was measured (Table 1).[20]

Tabelle 1. Condensation of **7** and **8** by using Cu^{II} complexes derived from chiral amine.

Entry	Amine **1**	Ketone **2**	**1/2**	**9** yield [%]	*ee* [%][a]	*ee* [%][b]
1	(−)-**1a**	none		0	–	–
2	(−)-**1a**	cyclohexanone (**2a**)	1:1	72	70	(92)
3	(−)-**1a**	cyclopentanone (**2b**)	1:1	85	91	(92)
4	(−)-**1a**	cyclobutanone (**2c**)	1:1	85	94	(≥98)
5	(−)-**1a**	(−)-menthone (**2d**)	1:1	63	10	(10)
6	(+)-**1a**	(−)-menthone (**2d**)	1:1	61	12	(17)
7	(−)-**1a**	acetone (**2e**)	1:1	67	54	(70)
8	(−)-**1a**	benzaldehyde (**2f**)	1:1	80	5	(18)
9	(−)-**1a**	benzaldehyde (**2f**)	1:2	<2	–	–
10	(−)-**1b**	cyclohexanone (**2a**)	1:1	0	–	–

[a] The *ee* values after treatment with acid. [b] The *ee* values before treatment with acid. Reaction conditions: THF, catalyst (10%), −72 °C, 4 Å molecular sieves, 72 h.

As expected, the diamine–copper(II) triflate complex was inefficient in mediating the reaction (Table 1, entry 1). When ligands derived from diamine (−)-**1a** and cyclohexanone **2a** were used (Table 1, entry 2) the reaction afforded the hetero-Diels–Alder product **9** with high *ee* (92%). However, after treatment with triflic acid, the enantiomeric excess of **9** proved to be lower (*ee* 70%).[20, 21] When the complexation time (premixing) was reduced from the usual 16 h (Table 1, entry 2) to 1 h, **9** was obtained in identical chemical yield, but the *ee* value dropped from 70% to 49%.

Upon decreasing the ring size of the ketone component from five to four carbon atoms, the *ee* value of cycloadduct **9**, before treatment with acid, increase from 92% (Table 1, entry 3) to better than 98% (Table 1, entry 4). Likewise, the *ee* value of **9** after treatment with acid increased from 91% (Table 1, entry 3) to 94% (Table 1, entry 4). Somewhat surprisingly, low enantioselectivity (10%) was observed when (−)-menthone was used in combination either with the (1*R*,2*R*)- or with the (1*S*,2*S*)-diphenylethylene diamine

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(Table 1, entries 5 and 6). This lack of selectivity may be a consequence of the increased steric hindrance in the proximity of the metal center in **6**, which implies less selective reaction paths. Interestingly, acyclic ketones such as acetone **2e** were shown to be less selective than cyclic ketones (Table 1, entry 7). Also, imidazolidines derived from diamine and benzaldehyde **2f** resulted in low enantioselectivity (Table 1, entry 8). Although bis-imines of type **5** were shown earlier to be efficient in promoting enantioselective copper(II)-mediated HDA reactions,[2a] the bis-benzyl imine–copper complex derived from **1a** and **2f** afforded only traces of a nearly racemic product **9** under standard conditions (Table 1, entry 9).[22] Furthermore, ligands derived from **1b** and **2a** promoted neither the formation of the HDA adduct nor the Mukaiyama aldol product (Table 1, entry 10).

The Cu^{II}/ligand stoichiometry was critical to the selectivity and reactivity. This dependence was monitored on the HDA adduct **9**.[23] Whereas a 1:1 ratio of cyclohexylidene ligand derived from (−)-**1a**, **2a**, and $Cu(OTf)_2$ afforded **9** in 92% *ee*, an increase in the Cu^{II}/ligand ratio to 2:1 resulted in only 73% *ee*. On the other hand, when a twofold molar excess of ligand relative to the Cu^{II} salt was used, the catalytic activity of the complex was inhibited.

The vicinal diamine ligands can be replaced by a chiral α-aminoalcohol. Although this reaction was not optimized, a reversal in enantioselectivity of the dihydropyrone **9** (67% yield, 35% *ee*) from that of the Mukaiyama aldol product **10** was observed when (*R*)-phenylglycinol (**11**) was used.

11

The foregoing three-component catalyst systems provide a simple and effective approach for generating a variety of structurally diverse chiral complexes for use in asymmetric synthesis. Important structural features responsible for the catalytic activity are unknown at the present time. The operational simplicity, easy availability, low cost, stability, and diversity of potentially active organometallic structures all contribute to the potential usefulness of these catalysts.

Experimental Section

Diamine **1** (0.09 mmol, 0.1 equiv) and ketone **2** (0.09 mmol, 0.1 equiv) were dissolved in a small amount of dichloromethane (2 mL). After 4 h at room temperature, the solvent was evaporated, and the residue was co-evaporated twice with benzene. $Cu(OTf)_2$ (32.6 mg, 0.09 mmol, 0.1 equiv) and the ligand were introduced in a dry flask with a small amount of ground 4-Å molecular sieves (ca. 100 mg), and THF (1.5 mL) was added to the solid through a cannula. The slurry was stirred under an inert atmosphere of Ar for 16 h at room temperature. The slurry was cooled to −72 °C, ethyl pyruvate (100 μL, 0.9 mmol, 1.0 equiv) and Danishefsky's diene (215 μL, 1.3 mmol, 1.2 equiv) were added in one portion through a syringe, and the mixture was stirred for an additional 72 h at −72 °C. Trifluoroacetic acid (0.1 mL) was then introduced to the mixture, which was allowed to warm to room temperature. After 12 hours, the solution was neutralized with saturated sodium bicarbonate, the organic phase was separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, the solvent was evaporated, and the crude reaction mixture was purified on a short column of silica gel (pentane/ethyl acetate 4:1 eluent). $R_f = 0{,}5$ (silica gel, EtOAc/pentane 1:1); IR (film): $\tilde{\nu} = 1740$, 1680, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.36$ (d, $J = 5.9$ Hz, 1H), 5.42 (d, $J = 5.9$ Hz, 1H), 4.22 (q, $J = 7.0$ Hz, 2H), 3,00 (d, $J = 16.5$ Hz, 1H), 2.68 (d, $J = 16.5$ Hz, 1H), 1.66 (s, 3H), 1.27 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 190.1$, 171.0, 161.9, 107.4, 82.9, 62.4, 44.8, 24.2, 14.1; MS (EI, 70 eV): *m*/*z*: 184 (27), 111 (100), 110 (24), 86 (12), 71 (89), 69 (25).

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[18] Other Cu^{II} salts such as $Cu(SbF_6)_2$, $Cu(BF_4)_2$, $Cu(ClO_4)_2$, $Cu(OAc)_2$, $Cu(PF_4)_2$ showed lower selectivity in this reaction.
[19] The *ee* value of **9** was determined by chiral GC-MS on a Crompack Chirasil-DEX CB column.
[20] No epimerization of **9** was observed after treatment with acid.
[21] The absolute configuration of the newly formed stereogenic center of **9** was found to be *R* in each case when the (1*R*,2*R*)-diphenylethylene diamine ligand was used. The absolute configuration was determined by comparison of the optical rotation of **9** with the literature value.[15c]
[22] The ligand was prepared by condensation of benzaldehyde (2 equiv) with **1a** followed by addition of $Cu(OTf)_2$ (1 equiv).
[23] The reaction was quenched at $-72\,^{\circ}C$ by using trifluoroacetic acid and was allowed to stir at $-10\,^{\circ}C$ for 1 h. This workup procedure allowed the isolation of the HDA and aldol products. No interconversion between the aldol and HDA products was observed under these conditions.

A Thermotropic Mesophase Comprised of Closed Micellar Aggregates of the Normal Type**

Petra Fuchs, Carsten Tschierske,* Klaus Raith, Kumar Das, and Siegmar Diele

The ability of amphiphilic molecules to self-organize in aqueous systems with formation of micelles, vesicles, and lyotropic mesophases is of great importance for numerous applications of surfactants in several fields of science and technology, and it is also a prerequisite for the development of biological structures.[1, 2] In these polymolecular assemblies the hydrophilic parts (together with the solvent molecules) and the lipophilic parts of the amphiphiles are segregated into nanoscopic compartments, whereby changing the degree of curvature of the interfaces between the incompatible nanophases gives rise to a sequence of different mesophase morphologies. Hence, in dependence on the amphiphile structure, its concentration, and the temperature, different lyotropic mesophases can result.[1–3] Arrays of alternating layers yield smectic phases (SmA), regular arrangements of cylinders give rise to hexagonal columnar phases (Col_h), and closed globular or nonglobular micelles can form cubic mesophases (micellar cubic phases, Cub_I). Another type of cubic mesophase, consisting of two mutually interwoven networks of branched cylinders (bicontinuous cubic mesophases, Cub_V), occurs at the transition between smectic and columnar organization (Figure 1). For each of the nonlamellar mesophases two different types are possible. In normal phases (type 1, positive curvature of the polar/apolar interface), the stronger cohesive forces (hydrogen bonds) are located in the continuum surrounding the aggregates. In the reversed (or inverse) phases (type 2, negative interface curvature) they are

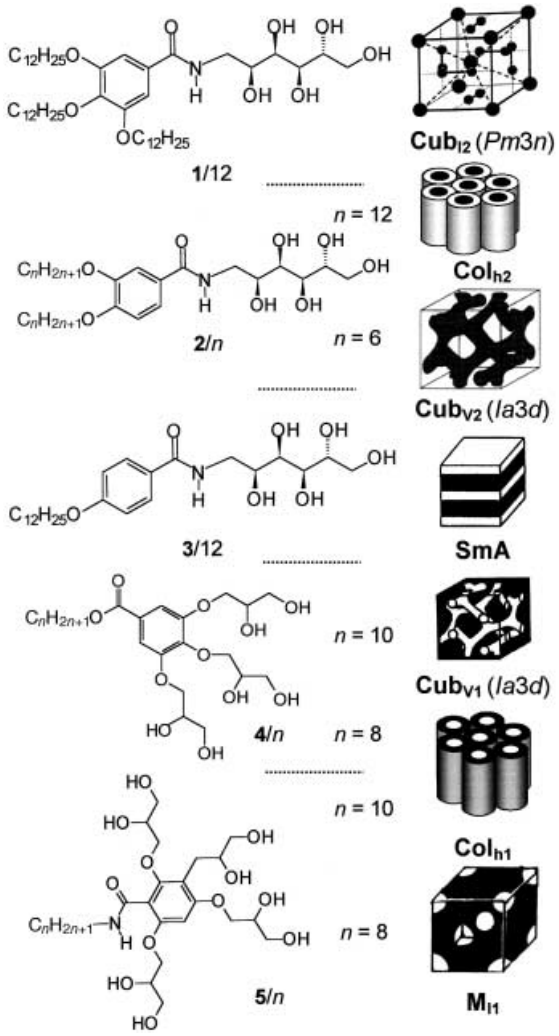

Figure 1. Dependence of the mesophase morphology of different polyhydroxy amphiphiles on the molecular structure. Abbreviations: Cub_{I2} = reversed discontinuous (micellar) cubic mesophase with *Pm3n* lattice; Col_{h2} = reversed hexagonal columnar mesophase; Cub_{V2} = reversed bicontinuous cubic mesophase with *Ia3d* lattice; SmA = smectic A-phase; Cub_{V1} = normal-type bicontinuous cubic mesophase with *Ia3d* lattice; Col_{h1} = normal-type hexagonal columnar mesophase; M_{I1} = mesophase comprised of discrete direct micelles with unknown lattice (the *Im3m* lattice is shown as one of the possible structures).

[*] Prof. Dr. C. Tschierske, Dr. P. Fuchs
Institute of Organic Chemistry
Martin-Luther-University Halle – Wittenberg
Kurt-Mothes-Straße 2, 06120 Halle (Germany)
Fax: (+49) 345-55-27223
E-mail: tschierske@chemie.uni-halle.de
Dr. S. Diele, Dr. K. Das
Institute of Physical Chemistry
Martin-Luther-University Halle – Wittenberg
Mühlpforte 1, 06120 Halle (Germany)
Fax: (+49) 345-55-27157
Dr. K. Raith
Faculty of Pharmacy
Martin-Luther-University Halle – Wittenberg (Germany)
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