26.65° of sample B3 is also consistent with the (101) reflection of quartz, and also with a preferred orientation of silicate crystals. Under the reaction conditions used an oxidation of the Si-library substrate can be excluded, which is supported by the lack of such a reflection in the rest of the library. Examination of the dot areas after the experiment by light microscopy shows no signs of attack of the single crystal–wafer surface after removal of the crystal layers. For detailed characterization of the individual materials formed the interesting reactions identified by X-ray diffraction would have to be repeated and investigated by conventional means in the laboratory.

Our reaction system combined with analyses has an enormous potential for increased efficiency in the development of new materials and the automatization of characterization of samples obtained by combinatorial methods, and it is certainly not limited to the synthesis under hydrothermal conditions. Currently, the lower limit of 50 μm for the focussing of the X-ray beam restricts the miniaturization of the diameter of the microreactors. The material selected for the reactor walls limits reaction temperatures up to 300 °C; much higher temperatures may become possible through the selection of different polymeric materials. An increase in the library dimension to 10 cm diameter as well as a decrease in the drilling distance can readily be realized without technical problems.

Minimization of the manual efforts for the preparation of starting solutions as well as for the filling of the microreactors can be achieved readily with commercially available pipetting robots. Even the direct synthesis in the reactor by the direct use of ultrasound for proper mixing of the tiny probe volumes is realizable. In general, every solid synthesis in liquid phase under pressure and temperature should be possible. Such a reactor should be ideal for the combinatorial screening of new microcrystalline or amorphous solids, especially since the reactor bottom can be exchanged and libraries can be prepared directly on the substrate of choice.

Experimental Section

Our standard experimental conditions for the preparation of this material library have been described in the original literature of Taramasso et al.[7] Since only very small amounts are necessary to fill of the microreactors, the reaction volumes were reduced by a factor of 200 and mixed in 10-mL flasks. The reaction mixtures have been modified as described in Table 1. A1 and F1 each contain the original recipe as described in the patent. The reaction was carried out in a sealed autoclave at a temperature of 200 °C for 36 h. After reaction the mother liquor was separated from the microreactor and the remaining crystals in the microreactor were washed several times with 2 mL of destilled water. The removal of the liquid was achieved by the capillary forces of porous rods directly in the microreactors. The compounds were then dried in the open microreactors at 100 °C. After removal of the teflon and steel mask the Si wafer with the dried-on crystal products were calcined at 600 °C for 36 h. After reaction the mother liquor was separated from the microreactor and the remaining crystals in the microreactor were washed several times with 2 mL of destilled water. The removal of the liquid was achieved by the capillary forces of porous rods directly in the microreactors. The compounds were then dried in the open microreactors at 100 °C. After removal of the teflon and steel mask the Si wafer with the dried-on crystal products were calcined at 600 °C for 10 h.

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COMMUNICATIONS

Chiral C2-Symmetric CuII Complexes as Catalysts for Enantioselective Hetero-Diels–Alder Reactions**

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Previous reports from this laboratory have demonstrated that C2-symmetric CuII–bis(oxazoline) complexes 1–3 (Tf = trifluoromethanesulfanyl) are efficient chiral Lewis acid catalysts for Diels–Alder,[2] pyruvate aldol,[3] and glyoxylate–ene reactions.[4] Each of these processes exhibits behavior consistent with previously proposed chelation models for asymmetric induction. In a further extension of this methodology, we recently reported that α,β-unsaturated acyl phosphonates undergo enantioselective hetero-Diels–Alder

[9] All diffraction data were measured with Cu Kα, radiation (λ = 1.541 Å). Data collection time varied from 5 to 80 min per spot. The distance between the sample and detector was 19.8 cm and the range between 6.2 and 33.2° (2θ). During data collection the sample oscillated by 2° and with an incident angle of the primary X-ray beam of 16°. The spatially corrected raw data have been integrated with a constant 2θ value (Laue cones).
The reaction of ethyl vinyl ether with unsaturated keto ester endo ethers in the presence of complexes 1 and 2 [Eq. (1)]. We now disclose the analogous cycloaddition reactions of β,γ-unsaturated α-keto esters [Eq. (2)], reactions of established utility in the construction of enantiomerically enriched dihydropyrans. A similar study has been recently reported by Jørgensen et al. The present work expands the scope of this process by providing significant operational simplifications including lower catalyst loadings, convenient reaction temperatures that facilitate short reaction times, and a catalyst recycling procedure. An X-ray crystallographic study is also provided in support of a proposed model for asymmetric induction.

Unsaturated keto esters 4a–4f and keto amide 4g undergo highly enantioselective cycloaddition reactions with enol ethers in the presence of complexes 1 and 2 (Table 1). The reaction of ethyl vinyl ether with unsaturated keto ester 4a in the presence of [Cu(2(S,S)-xbox)]OTf [1; 2 mol %, THF, 0 °C; box = bis(oxazoline)] provided cycloadduct 6a in 93% yield, with an endo/exo selectivity of over 20:1, and with 97% ee. The same reaction in the presence of [Cu(OTf)2(OH2)][(S,S)-xbox]]OTf [3] and molecular sieves (3 Å) afforded identical results. Complex 3, a readily prepared blue powder that may be stored indefinitely without special precaution, is an attractive alternative to the hygroscopic anhydro complex 1. While enantioselectivities of greater than 99% may be obtained for these cycloadditions at lower temperatures, we have found that these reactions may be conveniently carried out at 0 °C with little loss in stereoselectivity (95–99% ee).

Consistent with previous observations, complex 3 can be employed as an effective catalyst over a broad range of temperatures and solvents. Adduct 6a was produced stereoselectively from unsaturated ester 4a and ethyl vinyl ether in the presence of 3 at temperatures ranging from −40 °C to 25 °C. An enantioselectivity/solvent profile with substrate 4c and complex 3 (0 °C) demonstrates that excellent results may be obtained in a number of solvents (THF, endo/exo = 24:1, 97% ee; Et2O, endo/exo = 24:1, 97% ee; toluene, endo/exo = 28:1, 98% ee; dioxane, endo/exo = 24:1, 93% ee; CH2Cl2, endo/exo = 19:1, 89% ee).

The reaction tolerates a broad range of substituents R at the unsaturated ester terminus. Alkyl (4d, e), aryl (4a), alkoxy (4d, e), and thioenyl substituents (4f) afford cycloadducts in excellent yields and stereoselectivities (Table 1). In addition, under identical reaction conditions, the Weinreb amide 4g underwent a highly stereoselective reaction (endo/exo = 64:1, 99% ee) to yield 6g. This adduct is particularly versatile in view of the malleability of the amide functionality. To demonstrate the preparative utility of this reaction, 2 mol% of catalyst 3 was used to prepare 6.7 g (98%) of cycloadduct 6a from 5.0 g of heterodiene 4a (endo/exo > 99:1, 99% ee). Cyclic enol ethers are also effective reaction partners. In the presence of 3 and molecular sieves (3 Å), 2,3-dihydropyran reacted with the unsaturated esters 4a and 4b to provide bicyclic unsaturated esters 8a and 8b in good diastereo- and enantioselectivity (Table 1).

The cycloaddition to form 6c was conducted with as little as 0.5 mol% of catalyst 3; there was only a slight decrease in stereoselectivity (endo/exo = 19:1, 96% ee). Preliminary studies indicate that complex 3 can be reused in multiple reaction cycles (Table 2). When the catalyzed cycloaddition is

![Diagram](image_url)
conducted in hexane in the presence of an adsorbent (florisil), conditions under which complex 3 is apparently insoluble, the product solution may be decanted at the end of the reaction and the catalyst reused. A series of five catalyst recycling experiments (Table 2) demonstrates that the catalyst/adsorbent mixture may be reused without significant diminution in yield or selectivity.[16]

The absolute configuration for structures 6a and 6b was unambiguously proven by chemical correlation with lactones 9a and 9b of known configuration [Eq. (3)].[17] The remaining cycloadducts are assigned the indicated configuration by analogy.

The absolute configuration of the cycloadducts is consistent with our previously proposed model for asymmetric induction, in which the CuII complex and vicinal carbonyl functionalities form a well-defined reactive complex 11. Stereoregular behavior has been observed with substrates which can engage in chelation with 1, for example, N-acylimides[24] pyruvate and glyoxylate esters,[16, 4] acyl phosphonates,[15] and now β,γ-unsaturated α-keto esters. In conjunction with the construction of a suitable catalyst–substrate model, the X-ray crystal structure of the bis(aquo) complex 3 was obtained (Figure 1). The crystallographic data for 3 reveal a distorted square pyramidal geometry, in which one of the triflate ligands is weakly bound to the metal center in the apical position (Cu–OTf 2.624 Å) while the other is fully dissociated (Cu–OTf 3.667 Å). The two water molecules occupy the equatorial positions and are distorted by approximately 26° out of the plane of the ligand. Replacement of the water molecules with the chelating substrate generates reactive complexes 10 and 11. Semiempirical calculations (PM3) have been employed to model these catalyst–substrate complexes.

For simplicity, the triflate counterions are omitted from the calculations. The cationic complexes [Cu(tBu-box)(acyl phosphonate)]‡ (10) and [Cu(tBu-box)(β,γ-unsaturated α-keto ester)]‡ (11) generated at the PM3 level are illustrated in Figure 1. In both cases, the heterodiene α-Si face of the heterodiene is blocked by the bulky tert-butyl substituent on the ligand, leaving the α-Re face accessible to the dienophile.

In summary, the stereoselective hetero-Diels–Alder reaction of β,γ-unsaturated α-keto esters and amides with enol ethers catalyzed by C2-symmetric CuII–bis(oxazoline) complexes provides a general and practical entry into enantioenriched dihydropyrans. Application to complex target synthesis will be reported in due course.

### Experimental Section

3: To an oven-dried round-bottom flask containing a magnetic stir bar was added, in an inert-atmosphere glove box, 2,2-bis[2-[4(S)-tert-butyl-1,3-oxazolinyl]propene[15] (163 mg, 0.554 mmol) and copper(ii) trifluoromethanesulfonate (200 mg, 0.554 mmol). The flask was fitted with a serum cap,
removed from the glove box, and charged with THF (20 mL). The reaction mixture was stirred under argon for 1 h, affording a clear green solution to which distilled water (20 mg, 1.11 mmol) was added. The resulting blue solution was concentrated in vacuo to afford a blue solid. Hexane (5 mL) was added, and the solvent was removed in vacuo to provide 3 as a light blue powder (372 mg, 0.538 mmol, 97% yield). Analytical element of CHC(CH3)C produced in the presence of molecular sieves (3 Å).

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[11] The use of bis(aq) complex 3 without molecular sieves severely attenuated reaction, indicating that the anhydrous complex 1 is generated in the presence of molecular sieves (3 Å).

[12] At 40 °C: >99% ee; at –20 °C: 98% ee; at 0 °C: 97% ee; at 25 °C: 94% ee.

[13] For reviews on the synthetic utility of the Weinreb amide, see a) M. Mentzel, 4-methoxymethyl vinyl ether with ethyl chlorooxoacetate: L.-F. Tietze, H. Meier, E. Voss, Synthesis 1998, 274–277. Substrate 4f was prepared from 4e and phenylmethylthio in the presence of catalytic amounts of sodium bisulphate. Substrate 4g was prepared by addition of 1-propenylmagnesium bromide to the bis(Weinreb amide) of oxalic acid: M. P. Sibi, M. Marvin, R. Sharma, J. Org. Chem. 1995, 60, 5016–5023. Details of the synthesis of these substrates will appear in a full account of this work.

[14] The use of bis(aq) complex 3 without molecular sieves severely attenuated reaction, indicating that the anhydrous complex 1 is generated in the presence of molecular sieves (3 Å).

[15] At 40 °C: >99% ee; at –20 °C: 98% ee; at 0 °C: 97% ee; at 25 °C: 94% ee.


[17] The ligand may also be recovered (50%) by aqueous workup (3 M NH4OH) and chromatographic separation of the adduct and ligand. For an example of catalyst recycling in an enantioselective reaction, see K. B. Hansen, J. L. Leighton, N. E. Jacobsen, J. Am. Chem. Soc. 1998, 120, 10924–10925.

[18] Catalytic activity is diminished slightly in subsequent runs. In the absence of florisil or in the presence of other adsorbents (SiO2, Al2O3), lower enantioselectivity and/or reactivity is observed. Attempts to optimize this process and identify the role of the adsorbent are currently being actively studied.