bound to I2-NH_a through hydrogen bonds. The carbonyl groups not involved in the intramolecular hydrogen-bonding pattern form hydrogen bonds with solvent molecules, leading to an intermolecular cross-linkage of the individual knots.[10]

The ^{1}H NMR spectra of **5** show more signals than the spectra of comparable catenanes and macrocycles.[5, 7, 12]

The preferred formation of knot **5** over formation of a topologically isomeric catenane or the non-knotted topologically isomeric macrocycle (with 12 CONH groups each) is attributed to hydrogen bonds between amide groups, as in comparable template syntheses of catenanes and rotaxanes.[12, 13] Instead of the usual macrocyclic tetralactam host (of type **3**) the middle loop of the knot could, however, act as a noncyclic concave template for a CONH guest group.[14]

Molecular trefoil knots, for which we propose the name "knotanes", are topologically chiral, and in some cases Sauvage succeeded in the resolution of racemates.[2] The centrosymmetric unit cell of **5** proves that both enantiomers exist. Orientating attempts to separate the enantiomers of the new knot **5** by means of HPLC using cellulose carbamate column material (retention times $R_t = 8$ and 9 min, eluent: *n*-hexane/ethanol 85/15), which we successfully performed for catenanes, rotaxanes, and pretzelanes with similar structure elements,[15] revealed that more effort is required for a quantitative separation, as for Sauvage's knots.[2]

Sauvage's hope in 1999 that[2] "hopefully, chemical knots will expand to other fields than transition metal chemistry in the future" has come true surprisingly soon. The results obtained should be interesting not only for higher mechanically linked assemblies but also for combinations with knots of the phenanthroline and other types[16, 17]—a treasury for topological stereochemistry and topological chirality.

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Highly Regioselective Oxygenation of C–H Bonds: Diamidomanganese Constructs with Attached Substrates as Catalyst Models**

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The functionalization of the hydrocarbon framework of an organic compound is an exciting challenge of wide-reaching consequences.[1] The regioselective functionalization of C–H bonds of complex organic compounds is of significant synthetic potential.[2] The catalytic or reagent-driven transfer of an oxygen,[3] carbon,[4] or boron atom[5] into C–H bonds

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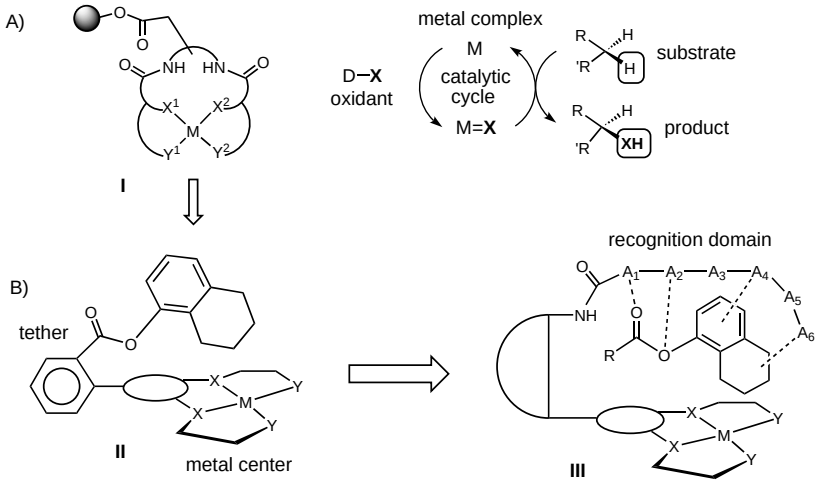
would be of particular preparative value. To achieve such challenging goals, programmable compounds are required that possess the capacity for both recognition and derivatization of organic substrates.[6]

For this we chose the combination of metal-centered catalysis and molecular recognition and have designed systems containing a metal coordination core and a recognition domain supported by a suitable molecular scaffold (**III**, Scheme 1). We began our search for novel metal catalysts



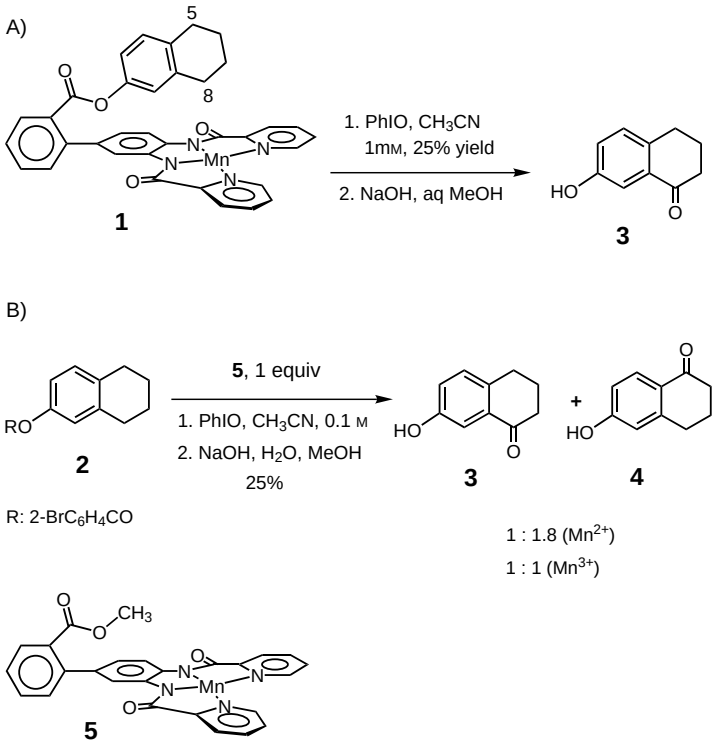
Scheme 1. Development of reagents and catalysts for selective C–H bond functionalization. A) Generation of novel metal complexes suitable for atom group transfer to C–H bonds by screening of solid-bound metal complexes. B) Covalent tether as a mimic of molecular recognition forces.

capable of atom transfer, by screening solid-bound metal complexes.[7] Promising metal complexes emerging from the screening process will ultimately be incorporated into metal complex/receptor constructs of general type **III**. During the initial studies we learned to appreciate the full magnitude of the problem and realized the need for simpler model systems, which would allow the facile evaluation of the characteristics of metal complexes (under conditions mimicking the substrate proximity found in enzymes). As a consequence, we proposed constructs of type **II** consisting of a substrate attached, through a designed tether, to a metal complex.[8] The covalent tether is viewed as a mimic for a noncovalent recognition event. The simplicity and synthetic accessibility of these models were considered as pivotal factors not only for the rapid analysis of products (by substrate functionalization), but also for the deduction of degradative processes occurring within the ligand sphere. Herein we report on the highly selective oxygenation of tetrahydro-2-naphthol and 4-aminomethylcyclohexylmethanol on covalent attachment to a metal complex unit.

The screening of solid-supported diamidomanganese complexes identified several systems capable of C–H bond oxidation in the presence of iodosylbenzene, of which the 1,2-bis(picolinamido)benzene ligand proved to be most efficient.[9] We designed a rigid biphenyl tether for the attachment of a substrate to the ligand (**1** and **5**, Scheme 2).[10] Owing to the well-known lability of benzylic C–H bonds to oxidants, we selected 5,6,7,8-tetrahydro-2-naphthol as the first substrate.[11] The rigidity of construct **1** augured well for the selective presentation of the benzylic C–H bonds at position 8 to the metal center. We predicted that oxidation at position 5 should be suppressed, provided the intramolecular mechanism was operative. This proved to be the case, as treatment of the manganese(II) or manganese(III) complex **1** (the Mn^{III} complex contains AcO^- as counterion) with PhIO under high dilution conditions (1 mM) yielded a single product, which upon basic hydrolysis afforded ketone **3** exclusively. The mass balance amounted to 80% (25% product, 55% starting material).

The intramolecular nature of this reaction was secured by appropriate control experiments (Scheme 2B): 1) The intermolecular reaction of 2-bromobenzoate **2** with PhIO in the presence of one equivalent of complex **5** did not yield the corresponding oxidation product under identical dilution conditions (1 mM). 2) A concentrated solution of **2** and **5** (0.1M) afforded a mixture of ketones **3** and **4**. Interestingly, the Mn^{II} complex **5** provided ketone **4** as the major product, a result similar to the known oxidation of 2-acetoxytetralin with CrO_3.[12] Presumably, the C–H bonds at position 5 are more electron rich, and hence more vulnerable to electrophilic metal oxidants. In contrast, such electronic preferences are completely overridden by restricting the approach of the substrate to the metal center.

We then turned to the oxidation of unactivated aliphatic C–H bonds. In this instance, a substituted cyclohexylmethanol was linked to



Scheme 2. Selective oxidation of tetrahydro-2-naphthol.

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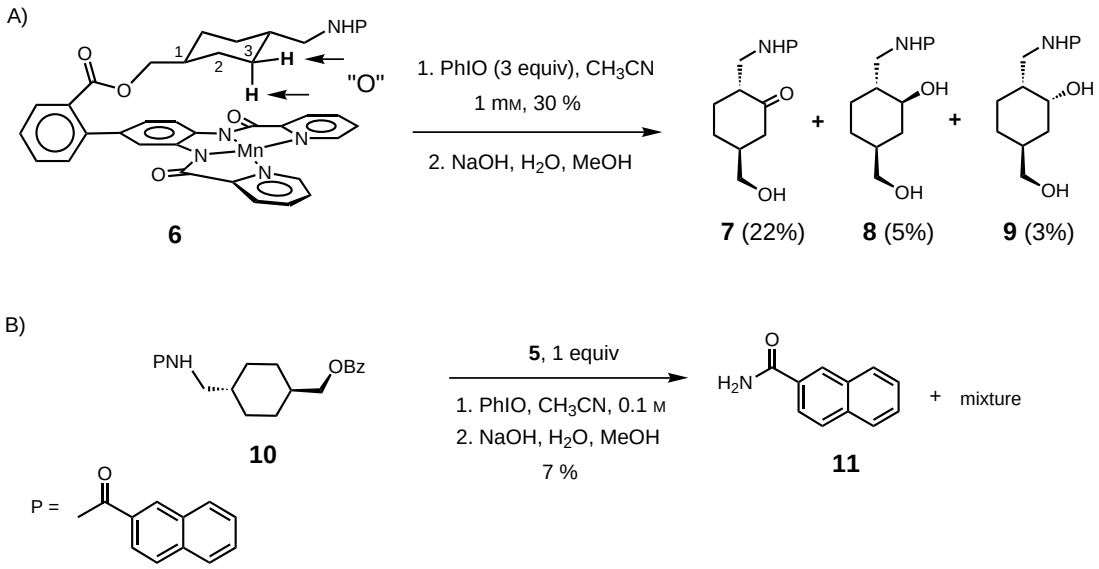

Scheme 3. Highly selective oxidation of unactivated C–H bonds by a diamidomanganese complex.

the biphenylic backbone providing system **6** (Scheme 3). The installation of the naphthoyl group proved necessary for HPLC analysis of reaction mixtures. In analogy to the above case, reaction of a solution of **6** in acetonitrile (1 mM) in the presence of three equivalents of PhIO, followed by hydrolysis, afforded a mixture of ketone **7** (22%), equatorial alcohol **8** (5%), and axial alcohol **9** (3%), and the starting material (50%, determined by HPLC). Again, the intramolecular mechanism of this reaction was confirmed by appropriate dilution as well as intermolecular control experiments. 1) The reaction of benzoate **10** in the presence of one equivalent of complex **5** under identical conditions yielded no detectable oxidation, whereas the same reaction performed at saturation led to formation of naphthylamide **11** and intractable mixtures of side products (Scheme 3B); 90% of starting material **10** was recovered in this case. 2) Cyclohexylmethyl benzoate was not oxidized under identical conditions. Apparently, C–H bonds at α-position to the amide moiety are particularly activated toward oxidation by an electrophilic manganese oxidant (presumably metal–oxo species).[13]

Remarkably, the cyclohexane ring in **6** was oxidized exclusively in position 3, despite the presence of more reactive C–H bonds (C–H bonds adjacent to the amide and ester moiety; two tertiary C–H bonds). Inspection of a molecular model of **6**, founded on the X-ray crystal structure of **12** (Figure 1), shows that all reasonable "productive conformations", in which the cyclohexane ring is located over the metal complex, permit selective proximity of the methylene groups in position 3 to the metal.[14] A crude qualitative analysis explained the experimental results well even in the absence of detailed mechanistic knowledge.

In conclusion, the oxidation of model systems **1** and **6** provided the following information: 1) a free radical mechanism can be ruled out; 2) in the transition state the C–H bond is found in the proximity of the metal–oxo moiety; 3)

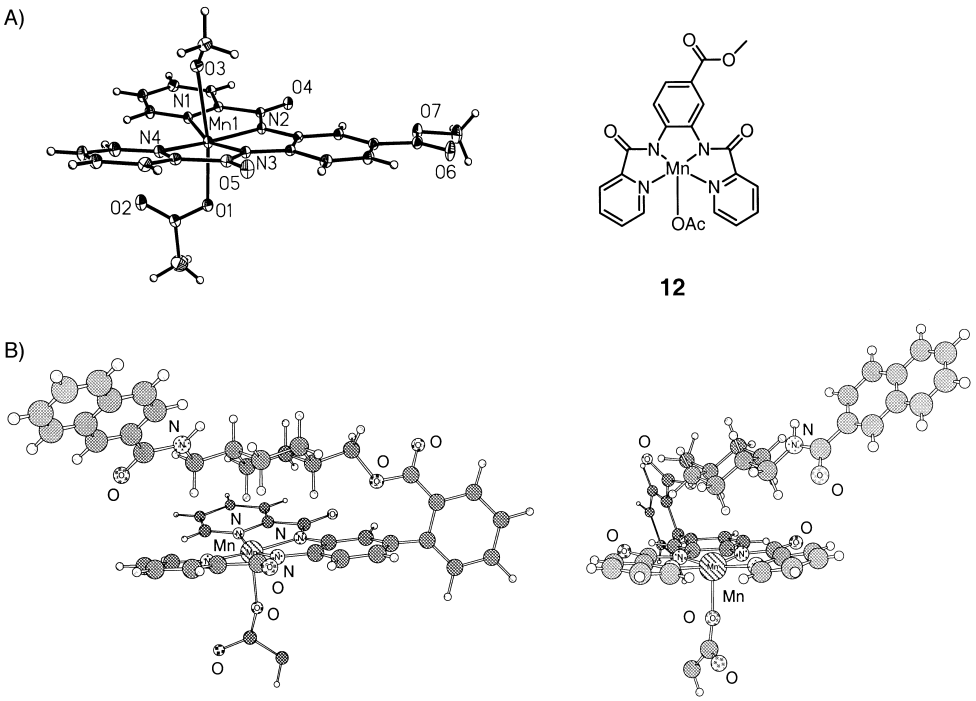

Figure 1. A) ORTEP representation of **12**: The pyridyl and deprotonated amide nitrogen atoms occupy the equatorial sites in the octahedral ligand sphere. B) Molecular model of **6** (side and front view, Chem3D), which indicates the proximity of hydrogen atoms at position 3 of the cyclohexyl ring to the metal center. This is true for all reasonable conformations in which the ring is placed over the metal complex.

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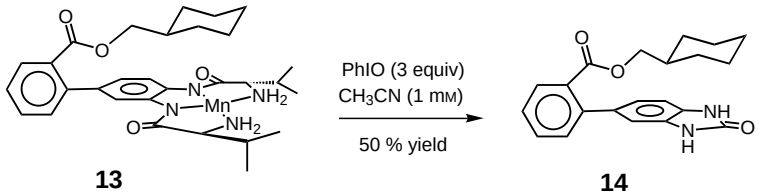
the ligands are stable under the oxidation conditions. For instance, system **5** was not oxidized under the reaction conditions, suggesting that the deactivation of the metal complex is not the result of ligand degradation. In contrast, the bis(valine) complex **13**, when submitted to the same reaction conditions (3 equiv PhIO), led to complete degradation of the ligand segment yielding the cyclic urea derivative **14** as the major product (Scheme 4).[15]



Scheme 4. Complete degradation of the bis(valine)manganese complex **13** in the presence of iodosylbenzene.

The simplicity of covalently assembled models of this type render them suitable probes for the rapid evaluation of novel metal complexes with regard to their capability to functionalize C–H bonds. We are currently studying possibilites for predictable positioning of the substrate to the metal through noncovalent recognition forces in order to attain a truly catalytic oxidation species.

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Solid-Phase Synthesis of Unprotected N-Glycopeptide Building Blocks for SPOT Synthesis of N-linked Glycopeptides

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Several approaches to the chemical synthesis of N-linked glycopeptides have been reported.[1] For the synthesis of glycosylated amino acids, the carbohydrate moiety is usually protected but unprotected glycosylamines have also been used.[2, 3] Using unprotected glycosylamines generally results in low yields[4, 5] and the compounds have to be purified by column chromatography. We present here a new and efficient method for the solid-phase synthesis of unprotected N-glycopeptide building blocks on a continous surface (SPOT synthesis). SPOT synthesis on cellulose[6] is a highly effective

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