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Report

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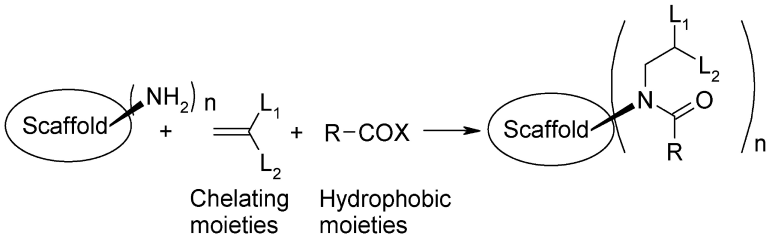

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Modular Liquid-Phase Parallel Synthesis of a Highly Diverse Ligand Library

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The design and synthesis of chelators for specific binding of metal ions, especially those classified as "hard" Lewis acids, are of both pharmacological and environmental interest. Extractions of radioactive actinides,such as plutonium and americium, are potentially useful in radioactive waste remediation.[1] Chelators could also be used medically to carry metal ions, such as Ga^{III}, ^{99m}Tc, or In^{III} [2] for removal of toxic metal (Pu^{IV}, U^{VI}) [3] or for treatment of metabolism disorders (Fe^{III}).[4] The development of an ideal chelating agent must be the result of a subtle balance of manifold parameters. It is an established fact that the efficiency (binding and selectivity) of a ligand depends crucially on an electronic, geometric, and steric interplay between the molecule and the metal center. Moreover, for clinical use, good bioavailability and toxicity properties are essential; they are influenced by the lipophilicity, ionization state, and molecular size of the compound.[5] Because of these numerous interrelated variables, combinatorial approaches are of great interest in this field. Furthermore, the diversity of libraries is here an essential asset because of the difficulty in forecasting structure−activity relationships in biological studies. Although some combinatorial approaches to the synthesis of chelating agents have already been described to date,[6] none of them has led to important structural variations that would allow the optimization of all parameters detailed above.

We report here a modular approach to structurally diverse multidentate ligands with the aim of synthesizing a library that could be screened for diverse applications. Thus, we developed a solution-phase parallel synthesis that allows the incorporation of four sources of diversity. The main feature of the synthesis is the modular assembly of three chemsets, namely amine scaffold **3**, acrylate **A** and acylating agent **4** (Scheme 1). The amine scaffold **3** (dipodal, tripodal, tetrapodal, ...) determines the architecture and the denticity of the ligand. The bifunctionalized acrylate **A**, which is prepared from the two first chemsets **1** and **2**, allows the incorporation of chelating moieties on the scaffold. Reagent chemset **4** allows modulation of another property of the chelates, in this case, its lipophilicity. The key step in the synthesis is the Michael addition of the amine scaffold **3** to the acrylate **A**. Michael additions of primary amines are rarely used for parallel solution-phase synthesis because of their reversibility and side reactions leading to mixtures of polyaddition products.[7] In our experimental conditions, monoadditions proceed very selectively, thus allowing further functionalization of the corresponding secondary amines with the acylating agent **4**. The obtained chemset **5** leads to the final products **6** after a quantitative deprotection step. Chemsets **1**, **2**, **3**, and **4** are shown in Figures 1−4. The combination of these reagents would lead to 288 chelates.

Recently, α-additions of nitrogen nucleophiles (e.g., phthalimides and sulfonamides) to alkynoates have been described for the synthesis of dehydroamino acids.[8] We found that this method could be efficiently extended to pyridone

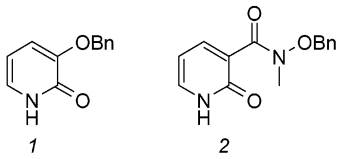

Figure 1. Diversity reagents **1**{*1*−*2*}: nucleophiles for the preparation of acrylate chemset **A**.

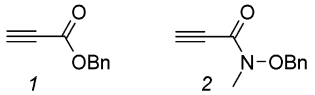

Figure 2. Diversity reagents **2**{*1*−*2*}: alkynes for the preparation of acrylate chemset **A**.

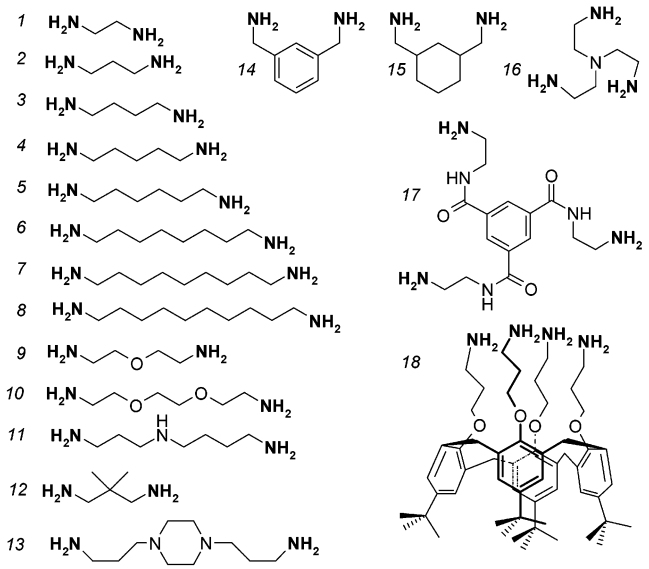

Figure 3. Diversity reagents **3**{*1*−*18*}: polyamine scaffolds for the ligand library. **3**{*17*} and **3**{*18*} were synthesized by known procedures.[9,1a]

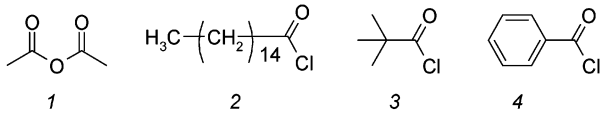

Figure 4. Diversity reagents **4**{*1-4*}: acylating agents for ligand library.

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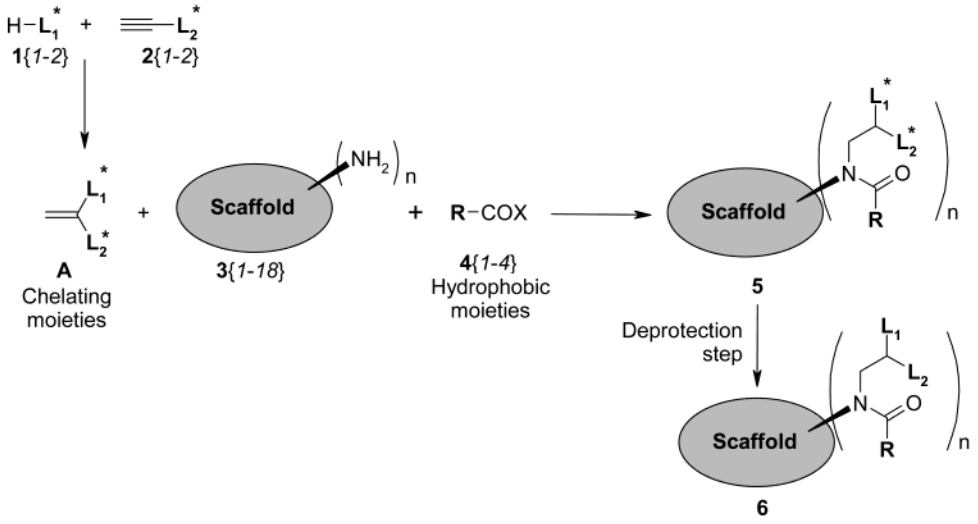
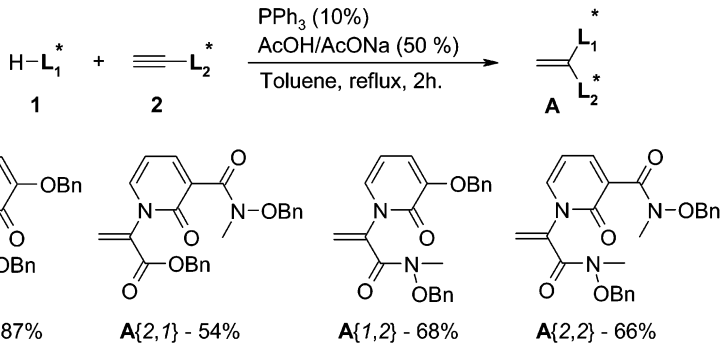
Scheme 1. Modular Synthesis of Multidentate Ligands

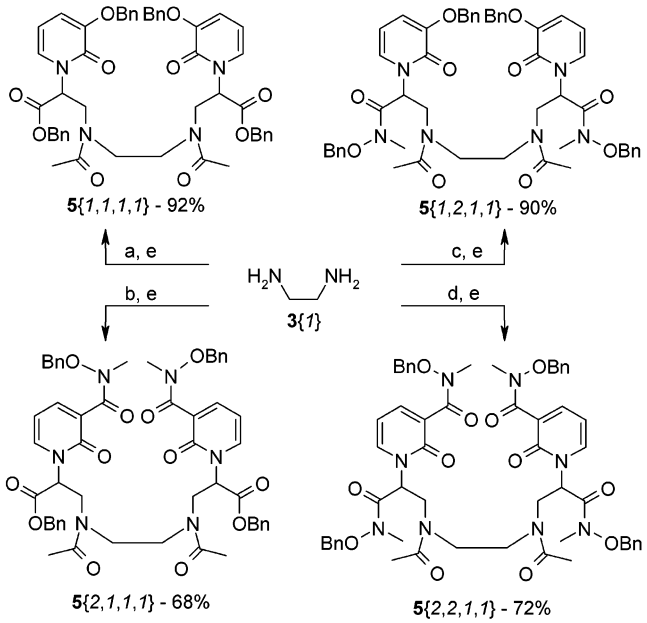


L* and L are respectively protected and unprotected chelating functions. Library size ($2 \times 2 \times 18 \times 4 = 288$).

Scheme 2. Synthesis of Mixed Acrylates **A**



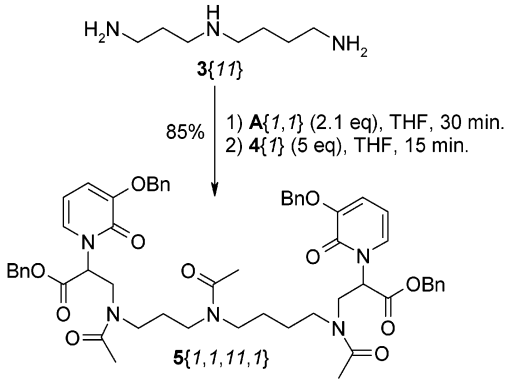
Scheme 3. Reaction of Acrylates **A** with Ethylene Diamine **3**{*1*} and Acetic Anhydride **4**{*1*}



a) **A**{*1,1*} (2.1 equiv), 25 °C, THF, 30 min; (b) **A**{*2,1*} (2.1 equiv), 25 °C, THF, 30 min; (c) **A**{*1,2*} (2.1 equiv), 25 °C, THF, 12 h; (d) **A**{*2,2*} (2.1 equiv), 45 °C, THF, 12h; and (e) **4**{*1*} (5 equiv), 25 °C, THF, 15 min.

nucleophiles. Thus, combination of alkynoate **2** with pyridone derivative **1** led to four acrylates **A**, containing well-known

Scheme 4. Preparation of **5**{*1,1,11,1*}: Chemoselectivity for Primary Amines



"hard" Lewis acid chelating functions, in good yields (Scheme 2).

The reactivity of acrylates **A** on primary amines has been studied using **3**{*1*} as a model scaffold (Scheme 3). The two amino sites of **3**{*1*} undergo very smooth Michael addition to reagents **A**{*1,1*} or **A**{*2,1*} at room temperature. Using 2.1 equiv of these acrylates, the reaction is complete after 30 min, leading cleanly to the product of double monoaddition on **3**{*1*}. Acrylates **A**{*1,2*} and **A**{*2,2*} are less reactive, but reactions still proceed selectively and in good yields. After in situ acetylation with Ac_2O **4**{*1*}, the corresponding adducts are easily amenable to purification using filtration through silica gel.

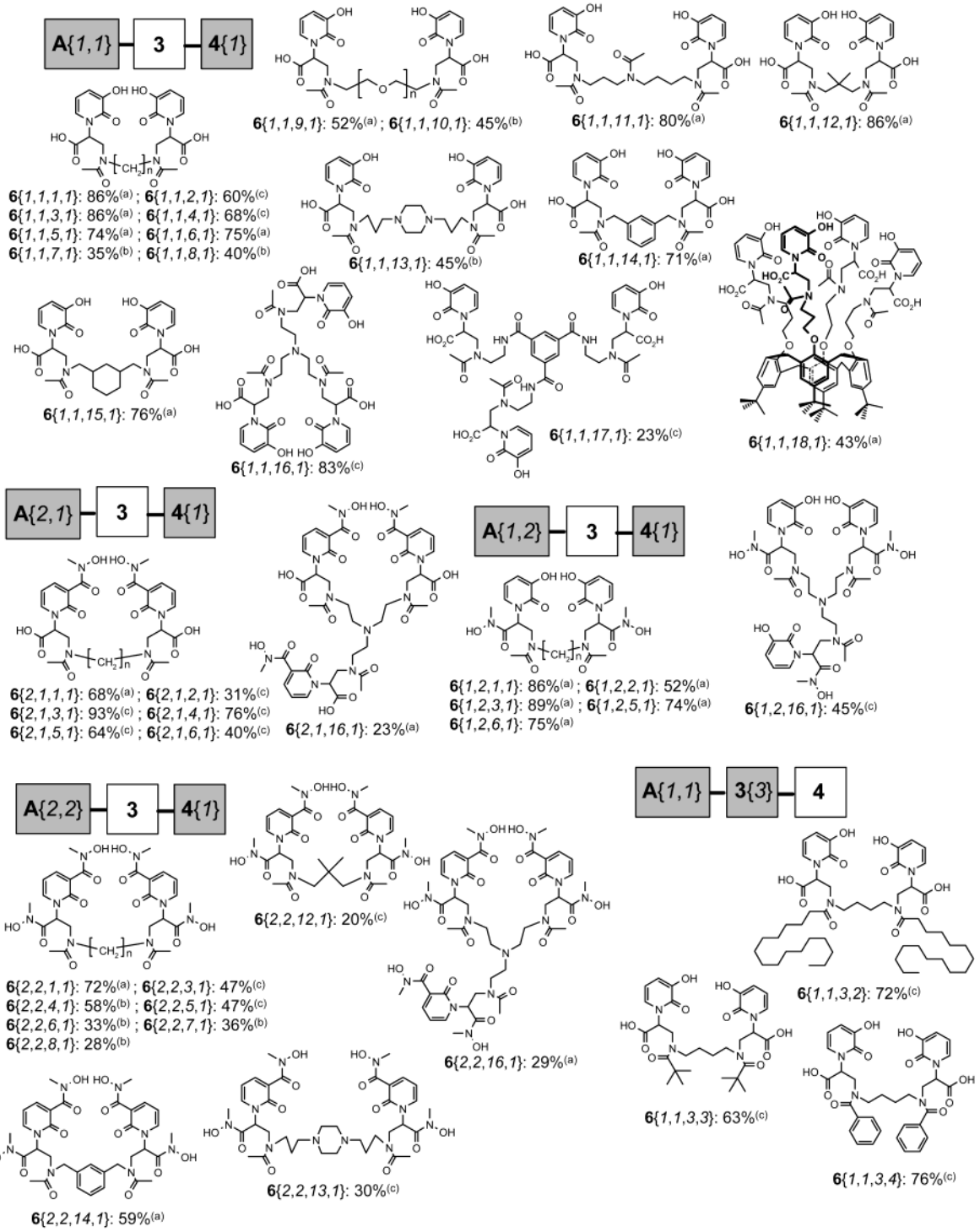


Figure 5. Library of chelates **6**. Michael addition and acylating procedures are given as Supporting Information. Hydrogenation procedures: (a) H_2−Pd/C, 25°C, DMF, 14 h; (b) 1,4-cyclohexadiene-Pd/C, DMF, 24 h; (c) $HCOO^-/NH_4^+$, Pd/C ,DMF/H_2O, 25°C, 2 h. Global yields are indicated.

The use of spermidine **3**{*11*} illustrates the chemoselectivity for primary amines of the reaction. In the reaction of 2.1 equiv of the acrylate **A**{*1,1*}, and after the acylating step with **4**{*1*}, **5**{*1,1,11,1*} is obtained as the single product (Scheme 4).

The benzyl protective groups are removed by catalytic hydrogenation using 5% Pd/C, affording the target chelates in high purities and good yields. Three different sources of hydrogen, namely H_2 gas, 1,4-cyclohexadiene, and ammonium formate, were used. The latter was found to be the most efficient.

Following the methodologies outlined above, we synthesized a library of 45 chelates (Figure 5). All of these molecules, except those containing tripodal or tetrapodal scaffolds **3**{*16*−*18*}, were prepared in 3-mL-well microplates using fast purification protocols by filtration through silica (normal and reverse-phase) cartridges. Members of chemset **5** have been characterized by ^1H NMR analysis, which revealed

estimated >85% purity in each case and yields ranging from 48 (**5**{1,1,18,1}) to 95%. After the quantitative deprotection step, ligands **6** are obtained with good purities. However, for handling reasons, the ligands were dissolved in methanol and precipitated by addition of diethyl ether. The precipitation step affords compounds **6** as solids (from 10 to 40 mg), but in some cases, this is the reason for poor yields (Figure 5). Each chemset **6** member has been characterized by ^{1}H NMR analysis, which revealed estimated >85% purity in all cases. Mass spectral analysis of all products afforded molecular ions, except for **6**{*1,1,17,1*}, **6**{*1,1,18,1*}, **6**{*1,1,3,2*}, and **6**{*1,1,3,3*}; however, ^{1}H NMR analysis confirms the structures.

In conclusion, we have developed a modular synthesis of new multidentate metal ligands, allowing the incorporation of four sources of diversity. This synthetic strategy allows modulation of the architecture, denticity, nature of the chelating functions, and lipophilicity of chelates. The general value of the approach was demonstrated by synthesis and characterization of 45 highly structurally diverse compounds. Thus, the developed methodology opens a rather general access to a broad variety of new ligands. The binding of these molecules to "hard" metals, including iron(iii), plutonium(iv), and uranium(vi), is under investigation. All of these results will be reported separately.

Supporting Information Available. General Experimental Section with characterization data (NMR, MS) for chemsets **A**, **5**, and **6**. Spectral reproduction for chemset **A**, and representative spectral reproduction for chemsets **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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