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Synthesis of Enantiopure Axially Chiral C_3-Symmetric Tripodal Ligands and Their Application as Catalysts in the Asymmetric Addition of Dialkylzinc to Aldehydes†

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The enantioselective synthesis of a novel-type C_3-symmetric tripodal ligand that is composed of a central mesitylene-derived core and three functionalized, axially chiral biaryl subunits is described. The triol *(M,M,M)*-**3** is a suitable catalyst for the enantioselective addition of dialkylzinc to various aromatic aldehydes with asymmetric inductions of up to 98% ee.

Introduction

Symmetry elements are important structural features in many chiral metal catalysts since they can reduce the number of possible diastereomeric intermediates or transition states.[1] They prevent the transient formation of an intermediate additional stereogenic center at the active metal site, which would be created in a dissymmetric complex upon coordination of the substrate(s) or by ligand−substrate exchange processes, thus strongly increasing the probability of an efficient chirality transfer. C_2-Symmetric bidentate ligands are well-known to fulfill this task in tetrahedral and square-planar complexes, a concept frequently and highly successfully applied in the field of asymmetric synthesis.[2] Extension of this strategy to octahedral complexes leads to the requirement of C_3-symmetric tridentate ligands.[1] Whereas a large number of tripodal systems assembled from three centrochiral subunits have been investigated during the past years,[1,3] there have as yet been only few reports about the combination of C_3-symmetry and axial chirality,[4] even though biaryls in general provide powerful tools in asymmetric synthesis.[5]

Our initial efforts in this area resulted in the preparation of the tris(oxybiarylmethylene)amine (*M,M,M*)-**1**,[6,7] which possesses three axially chiral biaryl subunits tied together by an amino function (Figure 1). The introduction of metal fragments into the central cage of (*M,M,M*)-**1** to give, e.g., the titanium complex (*M,M,M*)-**2**, however, proved to be difficult; the low stability of (*M,M,M*)-**2** and its high tendency to extrude the metal with destruction of the chelate complex indicated that the cavity of (*M,M,M*)-**1** is very small and not sufficiently suited for the incorporation of transition metals. In this paper, we present the synthesis of two novel C_3-symmetric, 3-fold axially chiral tripodal ligands of types **3** and **4** possessing a more spacious cavity, and their highly successful application as chiral catalysts in the enantioselective addition of dialkylzinc to various aromatic aldehydes.

Results and Discussion

Design of the C_3-Symmetric Tripodal Ligands. One possibility to increase the size of the chiral cavity of the ligand (*M,M,M*)-**1** would be to change the topology[8] of the tripodal system from acyclic[1] [sketch **A**, Figure 2, already realized in (*M,M,M*)-**1**] to exocyclic[1] (sketch **B**), where the three axially chiral biaryl subunits are connected to a joint cyclic spacer whose trivalent structure is in agreement with C_3-symmetry, for which a mesitylene-derived core was expected to be a simple and suitable building block.[9] The three homochiral biaryl moieties can be attached in two principally different ways (sketch **C**, options $\mathbf{C_I}$ and $\mathbf{C_{II}}$), either via their phenolic oxygen atoms or via their benzylic *N*- or *O*-functionalities. As an example of the first option, $\mathbf{C_I}$, the trisaryl ether (*M,M,M*)-**3** was chosen. In the desired C_3-symmetric

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† Part 107 in the series Novel Concepts in Directed Biaryl Synthesis. For part 106, see ref 6.

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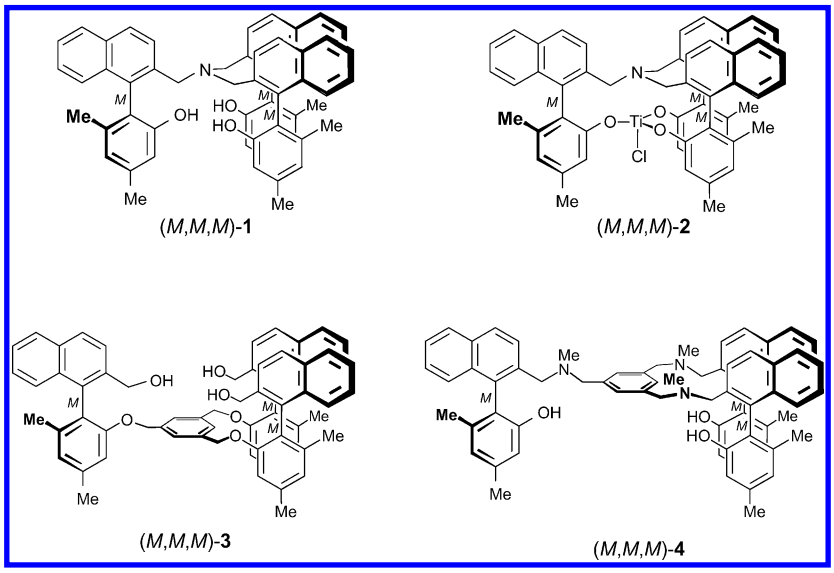

FIGURE 1. The axially chiral tripodal ligand (*M*,*M*,*M*)-**1** and its titanium complex (*M*,*M*,*M*)-**2**, and the concrete target ligands (*M*,*M*,*M*)-**3** and (*M*,*M*,*M*)-**4**.

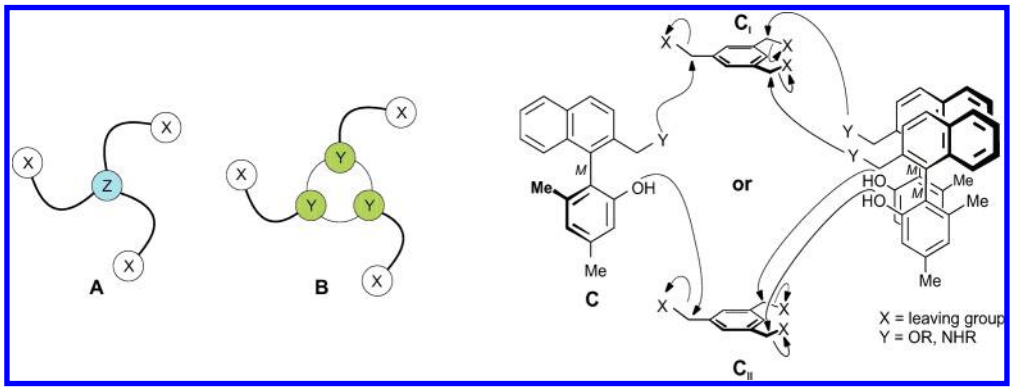

FIGURE 2. Schematic sketches of acyclic and exocyclic C_3-symmetric systems.

conformation, the three hydroxymethylene groups are directed into the interior of the central cavity, which should be distinctly larger as compared to that of (*M*,*M*,*M*)-**1**, thus providing an ideal "anchor site" for metal fragments to be embedded. The second possibility, $\mathbf{C_{II}}$, would be realized in the tripodal ligand (*M*,*M*,*M*)-**4**, in which the three biaryl subunits are tethered to the central benzene ring by three flexible bismethylenamino spacers, thus leading to a wide and open cage.

Synthesis of the C_3-Symmetric Tripodal Ligands (*M*,*M*,*M*)-3 and (*M*,*M*,*M*)-4. The synthesis of (*M*,*M*,*M*)-**3** and (*M*,*M*,*M*)-**4** started with (*M*)-**5** (Scheme 1).[10] This enantiomerically pure, axially chiral biaryl diol can be prepared in a multigram scale from commercially available materials in just three steps, with the atropoenantioselective reductive ring cleavage of a configurationally labile biaryl lactone precursor as the stereochemically decisive step.[11] The second building block, 1,3,5-tris-bromomethylbenzene (**6**), was obtained in 78% yield from the corresponding triacid by a modified literature procedure.[12] Treatment of **6** with 3.3 equiv of (*M*)-**5** delivered the tripodal ligand (*M*,*M*,*M*)-**3** in just a single step and 89% yield. Etherification occurred at the phenolic position as proven by HMBC correlation experiments. Conversion of the diol (*M*)-**5** into the *O*-protected secondary amine (*M*)-**7** was accomplished according to literature protocols.[13] Deprotonation of (*M*)-**7** and reaction with 0.3 equiv of **6** led to (*M*,*M*,*M*)-**8**, which was deprotected by treatment with BCl_3 to give the desired tripodal ligand (*M*,*M*,*M*)-**4** in 68% yield over the two steps.

Conformational Behavior of (*M*,*M*,*M*)-3 in Solution. The ^{1}H NMR spectra of (*M*,*M*,*M*)-**3** permitted preliminary insight into its conformational behavior (Figure 3): In solvents such as CD_3OD or [D_8]-THF, which favor the formation of intermolecular H-bridges,

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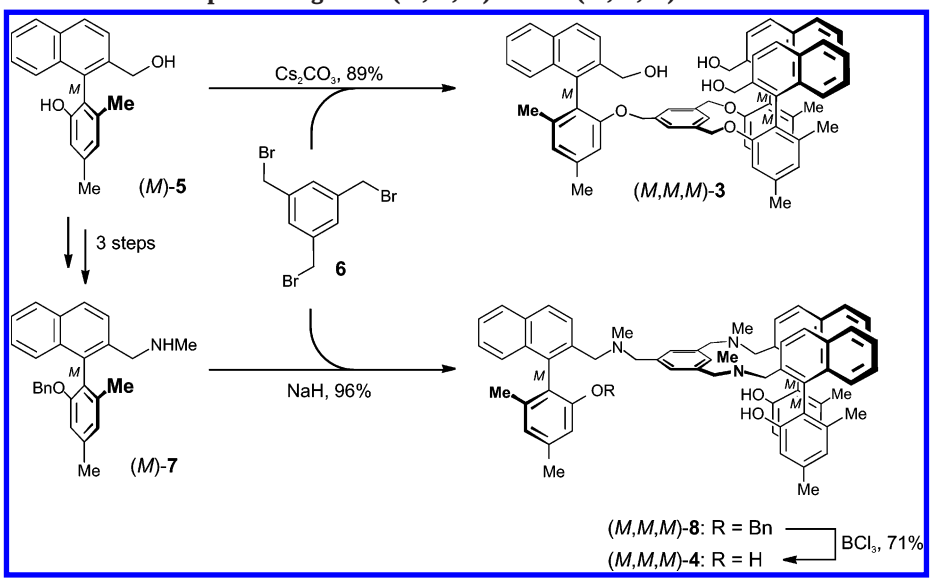
SCHEME 1. Synthesis of the Tripodal Ligands (*M,M,M*)-3 and (*M,M,M*)-4



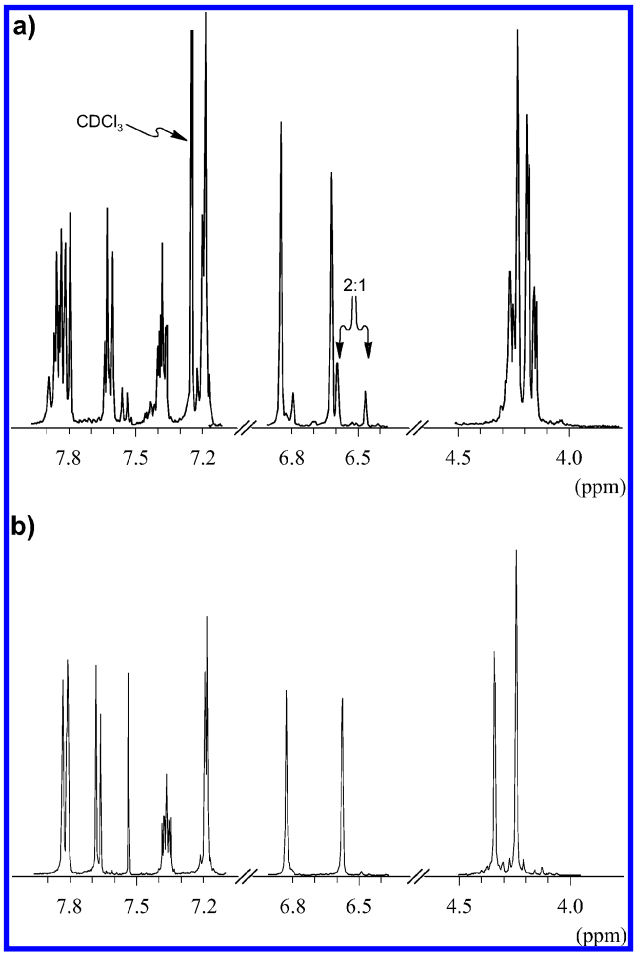


FIGURE 3. Diagnostically decisive part of the ^{1}H NMR spectra of (*M,M,M*)-**3** (a) in $CDCl_3$ and (b) in CD_3OD.

only a single set of signals with three spectroscopically identical biaryl subunits was observed, probably the averaged set of signals over all conformers. In the aprotic solvents C_6D_6, CD_3CN, and $CDCl_3$, by contrast, two sets of signals in an 85:15 ratio were found, with the main isomer again providing a single set of signals. In the minor isomer, only two of the three biaryl subunits still deliver isochronous signals, which hints at the existence of a pseudo-C_2-symmetric conformer like (*M,M,M*)-**3A** (Figure 4). Since the formation of H-bridges with the solvent is not possible, two biaryl substituents might now be locked on the one side of the central core by an intramolecular H-bridge between the phenolic hydroxy groups, while the third biaryl unit should retain its conformational freedom. Direct evidence of the C_3-symmetric conformer (*M,M,M*)-**3B**, in which all three biaryls are tied together by intramolecular H-bridges, was not found. ^{1}H NMR measurements in $CDCl_3$ at lower temperatures down to −60 °C indicated a "freezing out" of at least one more conformer, the structure and symmetry properties of which, however, could not be clarified due to the increasing complexity of the spectra. The formation of intramolecular H-bridges is also supported by semiempirical calculations (AM1),[14] which predict the C_3-symmetric conformer (*M,M,M*)-**3B** (Figure 4, bottom) as an energetically favored minimum structure in the gas phase.[15]

Application of the Tripodal Ligands as Chiral Catalysts in the Enantioselective Addition of Dialkylzinc to Aldehydes. The potential of the axially chiral tripodal ligands as a novel type of catalysts for asymmetric synthesis was investigated in the enantioselective addition of diethylzinc to aldehydes, since this well-established reaction should permit a convenient comparison with other successful catalysts known in the literature.[16] To our knowledge, there has as yet been only one other report on C_3-symmetric tripodal ligands applied in this type of reaction, which, however, failed to produce satisfying levels of asymmetric induction.[17]

The reaction conditions were optimized with benzaldehyde (**9a**) as the model substrate (Table 1). Disappointingly, only the acyclic tripodal ligand (*M,M,M*)-**1** cata-

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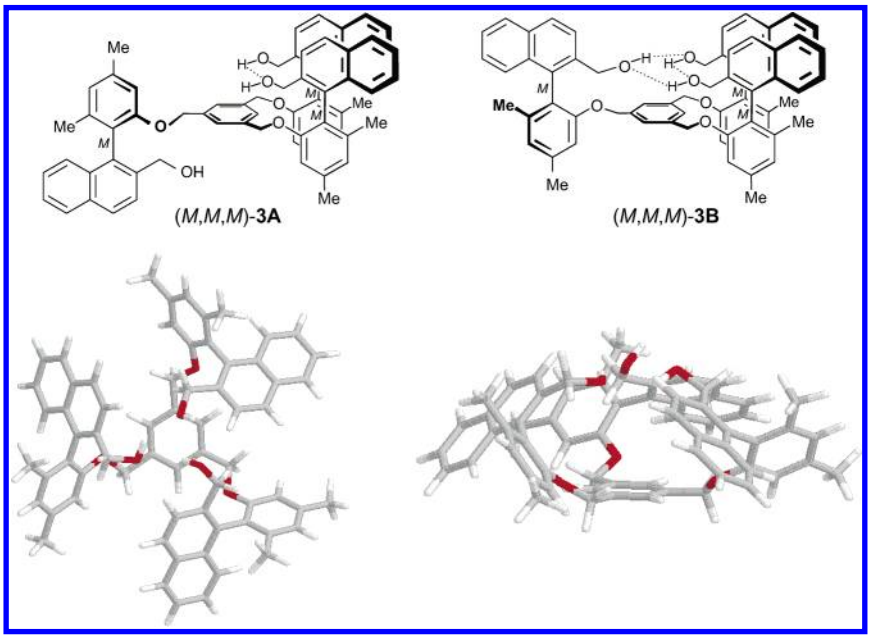
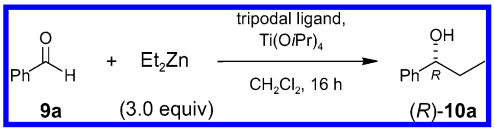


FIGURE 4. Conformers of (*M*,*M*,*M*)-**3**, (*M*,*M*,*M*)-**3A**, and (*M*,*M*,*M*)-**3B**, and the AM1-calculated minimum structure of (*M*,*M*,*M*)-**3B**.

TABLE 1. Optimization of the Reaction Conditions for the Addition of Diethylzinc to Benzaldehyde (9a) Catalyzed by (*M*,*M*,*M*)-1, (*M*,*M*,*M*)-3, or (*M*,*M*,*M*)-4[a]



ligand (mol•%)[b]	$Ti(OiPr)_4$ (equiv)[b]	*T* (°C)	conversion[c]	ee (%) (config)[d]
(*M*,*M*,*M*)-**1** (20)[e]	0	20	quant	56 (*R*)
(*M*,*M*,*M*)-**3** (20)[f]	0	20	0	
(*M*,*M*,*M*)-**4** (20)[f]	0	20	0	
(*M*,*M*,*M*)-**3** (20)	0.4	20	trace	
(*M*,*M*,*M*)-**3** (20)	1.4	20	quant	78 (*R*)
(*M*,*M*,*M*)-**4** (20)	1.4	20	0	
(*M*,*M*,*M*)-**3** (20)	3.0	20	quant	60 (*R*)
(*M*,*M*,*M*)-**3** (20)	1.4	0	quant	24 (*R*)
(*M*,*M*,*M*)-**3** (20)	1.4	40	quant	98 (*R*)
(*M*,*M*,*M*)-**3** (10)	1.4	40	quant	90 (*R*)
(*M*,*M*,*M*)-**3** (5)	1.4	40	quant	68 (*R*)

[a] All reactions were carried out with 10 μmol of benzaldehyde **9a**. [b] Relative to benzaldehyde **9a**. [c] Estimated according to TLC. [d] Determined by HPLC on a Chiracel OD-H column; config = configuration of the main enantiomer. [e] Solvent: *n*-hexane. [f] In *n*-hexane or toluene as the solvent, no reaction occurred.

lyzed the ethylation of **9a** with a moderate ee of 56%. No product formation was observed in the presence of (*M*,*M*,*M*)-**3** and (*M*,*M*,*M*)-**4**, even though the latter is built up of three biarylic amino alcohol units, a substructure that is known to catalyze this type of reaction.[13,18] For further experiments, we tried *C*-ethylations in the presence of $Ti(OiPr)_4$, since we expected—besides an acceleration of the reaction due to Lewis-activation of **9a**—an in situ incorporation of a Ti(O*i*Pr) fragment into the central

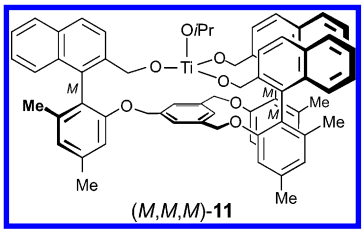


FIGURE 5. Structure of the C_3-symmetric titanium catalyst (*M*,*M*,*M*)-**11**.

cavities of (*M*,*M*,*M*)-**3** and (*M*,*M*,*M*)-**4**. Under these conditions, the tripodal ligand (*M*,*M*,*M*)-**3**, but not (*M*,*M*,*M*)-**4**, catalyzed the ethylation of benzaldehyde (**9a**) to give the desired ethyl carbinol (*R*)-**10a** quantitatively and with good to excellent asymmetric inductions of up to 98% ee. The proposed in situ formation of the rigid, C_3-symmetric titanium complex (*M*,*M*,*M*)-**11** (Figure 5) was proven by NMR spectroscopy of a 1:1 mixture of (*M*,*M*,*M*)-**3** and $Ti(OiPr)_4$. Optimum conditions for the addition of diethylzinc were found to be 20 mol•% of (*M*,*M*,*M*)-**3** in refluxing CH_2Cl_2 in the presence of 1.4 equiv of $Ti(OiPr)_4$. At room temperature, the ee decreased to 78%, and at 0 °C, it dropped to merely 24%.[19] Furthermore, the data reveal that an excess of $Ti(OiPr)_4$ is necessary to achieve quantitative conversion of **9a**; only traces of **10a** were formed if the reaction was carried out with a substoichiometric amount of $Ti(OiPr)_4$. Lower catalyst loading (10 or 5 mol•%) or a larger excess of $Ti(OiPr)_4$ (3 equiv) led to significantly lower degrees of asymmetric induction.

Finally, the synthetic use of (*M*,*M*,*M*)-**3** as a catalyst was evaluated in the ethylation of a series of different aromatic aldehydes (Table 2). All reactions were carried out under optimized conditions affording the *R*-configured ethylcarbinols **10** in >90% chemical yield and with high

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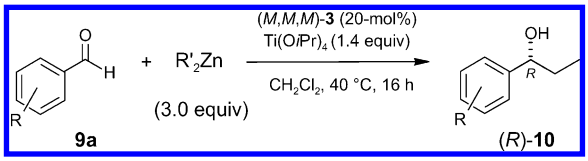
(19) This is one of the rare cases where diethylzinc additions deliver higher asymmetric inductions at higher temperatures. The same effect was observed for a chiral titanium−sulfonamide complex, see: Ramón, D. J.; Yua, M *Tetrahedron*: *Asymmetry* **1997**, *8*, 2479−2496.

TABLE 2. Enantioselective Alkylation of Various Aromatic Aldehydes 9 Catalyzed by 20 mol·% of (*M,M,M*)-3[a]



aldehyde	R	R′	alcohol	yield (%)[b]	ee (config)[c]
9a		Et	**10a**	93	90 (*R*)
9b	"2,3-benzo"	Et	**10b**	96	86 (*R*)
9c	4-MeO	Et	**10c**	97	96 (*R*)
9d	2-MeO	Et	**10d**	81	96 (*R*)
9e	4-Cl	Et	**10e**	91	44 (*R*)
9f	2-Cl	Et	**10f**	91	94 (*R*)
9g	3,5-MeO	Et	**10g**	94	96 (*R*)
9h	4-Me	Et	**10h**	95	98 (*R*)
9a		*n*Bu	**10i**	84	97 (*R*)
9a		Me	**10j**		

[a] All reactions were carried out with 50 μmol of the aromatic aldehyde **9**; the amounts of the other reagents are given relative to **9**. [b] Isolated yields after PLC. [c] Determined by HPLC (Chiracel OD-H); config = configuration of the main enantiomer.

to excellent enantioselectivities of up to 98% ee.[20] Only with 2-chlorobenzaldehyde (**9f**) as the substrate was a moderate asymmetric induction (ee 44%) obtained. The reasons for this are not evident, since both the likewise 2-substituted derivative **9d** (R = OMe) and the aldehyde **9e** with its chlorine substituent in the para position delivered high enantiomeric excesses. The dialkylzinc reagent was varied exemplarily for benzaldehyde (**9a**) as the substrate. The addition of $(n\text{Bu})_2\text{Zn}$ delivered (*R*)-1-phenylpentan-2-ol (**10i**) in 84% yield and an excellent ee of 97%. With the less reactive Me_2Zn, however, no reaction occurred.

(20) *n*-Heptanal as a representative of an aliphatic aldehyde did not react under these conditions.

Conclusion

In summary, we have developed an economical and simple access to a novel type of enantiomerically pure, C_3-symmetric tripodal ligands possessing three axially chiral biaryl subunits. The ligand (*M,M,M*)-**3** was successfully utilized as the catalyst in the enantioselective addition of dialkylzinc to various aromatic aldehydes, delivering enantiomeric excesses of up to 98%.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, and ^{1}H and ^{13}C NMR spectra for (*M,M,M*)-**3**, (*M,M,M*)-**4**, and (*M,M,M*)-**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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