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Chelation-Controlled Addition of Organozincs to α-Chloro Aldimines

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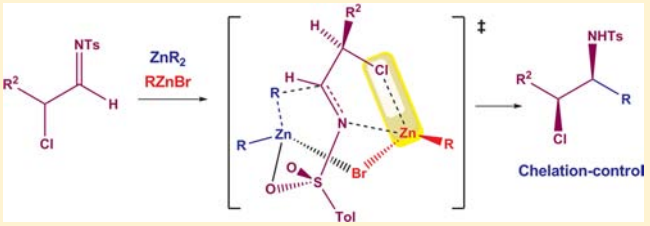
Supporting Information

ABSTRACT: Nucleophilic additions to α-chiral α-halo carbonyl derivatives are well-known to generate Cornforth–Evans products via a nonchelation pathway. What was unprecedented before this report is C–X bonds reversing the diastereoselectivity through coordination to metals during C–C bond-forming reactions (chelation control). Herein we describe chelation control involving C–X bonds in highly diastereoselective additions of organozinc reagents to a variety of α-chloro aldimines. The unique ability of alkylzinc halide Lewis acids to coordinate to the Cl, N, and O of α-chloro sulfonyl imine substrates is supported by computational studies.



1. INTRODUCTION

The traditional approach to complex molecule synthesis is to use existing substrate stereochemistry to guide the reaction of achiral reagents and introduce new stereogenic centers.[1] As a result, substrate control continues to be a powerful tool for the synthesis of small and complex molecules and new methods to control diastereoselectivity remain in great demand.

Among substrate-controlled approaches to the construction of carbon skeletons in organic synthesis, the addition of nucleophiles to C–O and C–N double bonds containing neighboring stereocenters is important both in the development of a conceptual understanding of organic chemistry and in its broad utility. From a practical standpoint, the introduction of stereogenic centers on addition of organometallic reagents to C–O and C–N double bonds is essential for the formation of C–C bonds and assembly of oxygen- and nitrogen-containing natural products.[2] The seminal work of Cram and Elhafez almost 60 years ago introduced concepts for predicting and controlling diastereoselectivity in nucleophilic additions to C=O bonds adjacent to stereogenic centers.[3] Since these pioneering studies, key contributions from Cornforth,[4] Felkin,[5] Anh and Eisenstein,[6] and Evans[7] among others[8] have collectively formed the foundation for the current stereoinduction models. Within this conceptual framework, the Cornforth–Evans model[7,9] is used to rationalize stereochemical outcomes in additions to α-halogenated carbonyl derivatives.[10] This model is based on the premise that dipole (or electrostatic) effects are responsible for the low energy *anti*-parallel orientation of the C=Y (Y = O, N(PG)) and C–X (X = halogen) bonds leading to an acyclic transition state (Figure 1A). Although distinct from the Felkin–Anh model, the stereochemical outcome is identical. The significance of these principles has resulted in their coverage in advanced organic chemistry textbooks.[11]

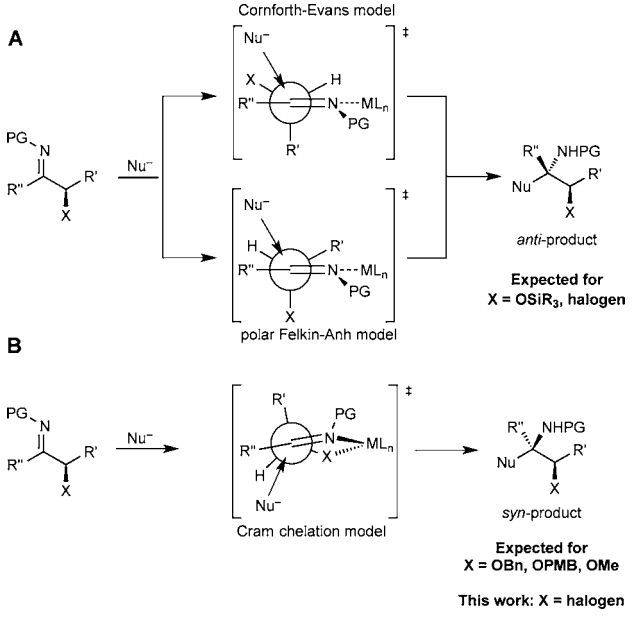


Figure 1. Models for 1,2-asymmetric induction. (A) Polar Felkin–Anh and Cornforth–Evans models leading to 1,2-*anti* addition products. (B) Cram chelation model leading to 1,2-*syn* addition products.

Similarly, α- and β-silyloxy aldehydes and ketones undergo nucleophilic additions following the Felkin–Anh model with few exceptions (Figure 1A).[8a,12] In our studies readdressing this paradigm, we identified a remarkable class of Lewis acids, alkyl zinc halides (RZnX) and fluorinated sulfonates ($RZnO_3SR^F$), which chelate to α- and β-silyloxy aldehydes and ketones and

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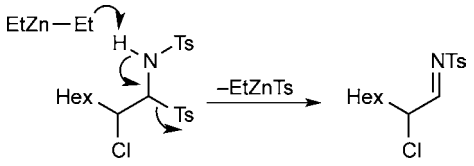


Figure 2. *In situ* generation of α-chloro aldimine.

enable the *chelation-controlled* addition of organozinc reagents to these substrates.[13]

These surprising results led us to wonder if even less Lewis basic groups might coordinate to alkyl zinc halide Lewis acids. Far less Lewis basic than silyl ethers are alkyl halides. Coordination of alkyl halides to transition metals has been documented.[14] However, we are aware of only three examples of chelation-controlled addition of nucleophiles to α-halo carbonyl or imino substrates, and all involve hydride addition to α-fluoro carbonyl derivatives.[15] Addition of carbon-based nucleophiles presents a distinct set of challenges compared to additions of the smaller hydride nucleophile. Herein we report a highly diastereoselective approach for chelation-controlled addition of a variety of alkyl and vinyl zinc reagents to α-chloro aldimines to generate products arising from chelation of the chlorine, nitrogen, and sulfonyl oxygen. Computational studies to probe the reversal of selectivity predicted by the Cornforth–Evans model support chelation of α-chloro aldimines to RZnBr. These reactions represent the first examples of highly diastereoselective halide directed chelation-controlled C–C bond-forming reactions.

2. RESULTS AND DISCUSSION

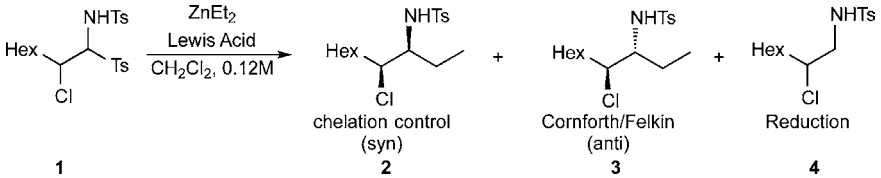
To demonstrate the feasibility of developing an efficient approach for chelation-controlled additions to α-chloro aldimines, we examined the reaction of commercially available diethylzinc with aldimine precursor **1**.[16] We envisioned a one-pot procedure in which an excess of diethylzinc first acts as base to generate the reactive α-chloro aldimine in situ, as outlined in Figure 2.[17] In the absence of a Lewis acid, the reaction of diethylzinc with **1** provides reduction product **4** predominantly and only trace amounts of addition product (Table 1, entry 1). Reduction most likely occurred via a β-hydride transfer mechanism.[18] Employing 1.5 equiv of EtZnBr with $ZnEt_2$ resulted in the formation of addition products with a 8:1 diastereomeric ratio (dr) favoring the *syn* diastereomer, albeit in low yield (50%). Encouraged by the 8:1 dr, we set out to minimize the formation of reduction product (**4**) and optimize the diastereoselectivity of the reaction. Lowering the reaction temperature to −15 °C resulted in a slightly improved yield of 60% but a diminished dr (entry 3). Increasing the EtZnBr to 3 equiv and reducing the amount of Et_2Zn provided the chelation-controlled product with a 11:1 dr and 6.8:1 ratio of ethyl addition to reduction products (entries 4 and 5). Use of EtZnBr without Et_2Zn gave product with a 1.5:1 dr (entry 6). Employing other zinc Lewis acids did not improve the diastereoselectivity of the reaction (entries 7 and 8).

Using the optimized conditions in Table 1 (entry 5), various α-chloro aldimine precursors afforded chelation-controlled addition products with good to excellent diastereoselectivity (Table 2). Similar results were obtained when the isolated aldimine was used (Table 2, entries 1 and 3). Additionally, commercially available dimethylzinc can be employed with comparable diastereoselectivities and improved yields. The R group on ZnR_2 and RZnX should be identical due to rapid alkyl exchange between zinc species.[19]

To determine the generality of chelation control with more reactive organozinc nucleophiles, we investigated the addition of vinylzinc reagents to α-chloro aldimines. It is noteworthy that the addition products are valuable functionalized allylic amines.[20] We conceived a one-pot procedure in which both the vinylzinc reagent and aldimine are formed *in situ*. Toward this end, the Oppolzer–Srebnik procedure[21] was utilized to generate the (*E*)-vinylzinc intermediates. Thus, hydroboration of a terminal or internal alkyne and subsequent B to Zn transmetalation[21c] with $ZnMe_2$ were followed by the addition of EtZnBr and the aldimine precursor.

After extensive screening, we found that optimal yields and diastereoselectivities were accomplished by initiating the addition step at −78 °C and then warming the reaction mixture to −45 °C. As illustrated in Table 3 (entries 1–7), a variety of terminal and internal alkynes can be used to generate allylic β-chloroamines with excellent dr values (≥20:1). Moreover, substitution at the α-position can be varied while maintaining high levels of diastereoselectivity (entries 8–11). Notably, despite the structural variation of the vinylzinc

Table 1. Optimization of Addition Product Formation and *syn*-Diastereoselectivity in the Addition of Diethylzinc to α-Chloro Aldimine 1



1 **2** **3** **4**

entry	Lewis acid (LA)	1:LA:Et_2Zn	temp (°C)	addition:reduction[a]	dr (2:3)[a]
1	–	1.0:0:5.0	0	trace addition	–
2	EtZnBr	1.0:1.5:5.0	0	1:1	8:1
3	EtZnBr	1.0:1.5:5.0	−15	1.5:1	2:1
4	EtZnBr	1.0:1.5:3.0	0	3.5:1	8:1
5	**EtZnBr**	**1.0:3.0:3.0**	**0**	**6.8:1**	**11:1**
6	EtZnBr	1.0:3.0:0	0	1:0	1.5:1
7	EtZnCl	1.0:3.0:3.0	0	6.3:1	7:1
8	EtZnONf	1.0:3.0:3.0	0	1:1.5	3:1

[a]Ratios determined by analysis of ^1H NMR spectra of unpurified products.

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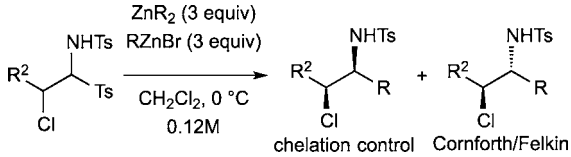
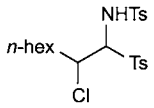
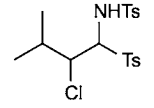
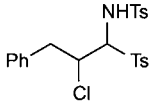
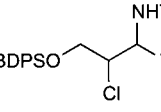
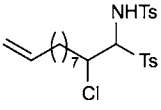
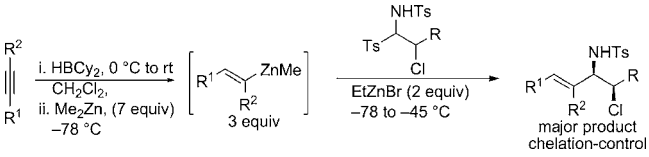
Table 2. Chelation-Controlled Addition of Diethyl- and Dimethylzinc to in Situ Generated α-Chloro Aldimines

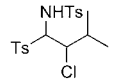
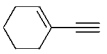
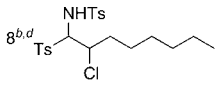
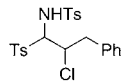
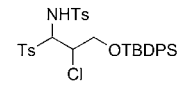
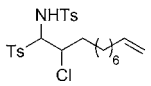


entry	aldimine precursor	ZnR_2	yield (%)[a]	dr[b]	product
1[c]		$ZnEt_2$	80	11:1	**2**
2		$ZnMe_2$	83	10:1	**5a**
3[c]		$ZnEt_2$	84	>20:1	**5b**
4[d]		$ZnMe_2$	80	>20:1	**5c**
5		$ZnEt_2$	76	12:1	**5d**
6		$ZnMe_2$	82	20:1	**5e**
7		$ZnEt_2$	69	7:1	**5f**
8		$ZnMe_2$	85	6:1	**5g**
9		$ZnEt_2$	60	5:1	**5h**
10		$ZnMe_2$	68	11:1	**5i**

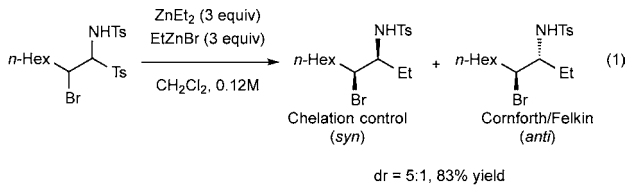
[a]Aldimine generated *in situ* from sulfone precursor unless otherwise stated. [b]dr determined by analysis of ^{1}H NMR spectra of the unpurified reaction products and refers to the ratio of chelation:Cornforth/Felkin products. [c]Isolated aldimine can be used, and comparable diastereoselectivity and yield were observed. [d]Relative product stereochemistry was confirmed by X-ray analysis.

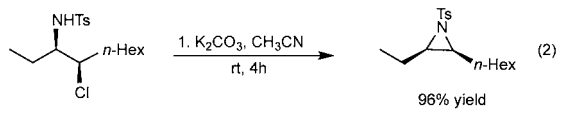
Table 3. One-Pot Chelation-Controlled Addition of Vinylzinc Reagents to α-Chloro Aldimines

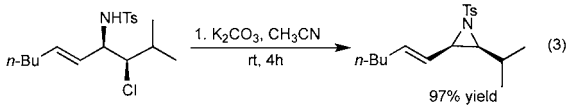


entry	aldimine precursor	alkyne	yield (%)	dr[a]	product
1[b,c]		*n*-Bu	89[c]	>20:1	**6a**
2		Ph	72	>20:1	**6b**
3		t-Bu	72	>20:1	**6c**
4		$Cl(H_2C)_3$	83	>20:1	**6d**
5			70	>20:1	**6e**
6		*i*-Pr—Me	70	>20:1	**6f**
7		Me—Me	69	>20:1	**6g**
8[b,d]		*n*-Bu	79	>20:1	**6h**
9		*n*-Bu	77	>20:1	**6i**
10		*n*-Bu	81	20:1	**6j**
11		*n*-Bu	61	>20:1	**6k**

[a]dr determined by ^{1}H NMR of the crude reaction products and refers to the ratio of chelation:Cornforth/Felkin products. [b]Comparable diastereoselectivity and yield obtained in the reaction using isolated imine. [c]Reaction on 5 mmol scale. [d]Reaction carried out using enantioenriched starting material with no erosion of ee (see Supporting Information).







reagents and aldimine substrates, all reactions proceeded via chelation control.

In addition to the fundamental significance of chelation-controlled diastereoselectivity involving C−Cl bonds, these addition reactions have practical utility. The reaction in entry 1 was performed on a 2 g scale to furnish the chelation-controlled product in 89% yield with a >20:1 dr. Equally important for practical application is the compatibility of the reaction conditions with enantioenriched substrates. When the reaction was conducted using an enantioenriched aldimine precursor, no erosion of ee was observed in the addition product (entry 8; see Supporting Information for details).

To gain insight into the generality of C−X bond participation in chelation-controlled diastereoselective processes, we investigated the reaction of diethylzinc with an α-bromo aldimine (eq 1). Upon subjecting the α-bromo aldimine precursor to diethylzinc and EtZnBr, the chelation controlled addition product was isolated in 83% yield with 5:1 dr.

It is noteworthy that the products of the addition reactions can be readily converted to the aziridines. Exposure of the β-chloroamine products to K_2CO_3 in acetonitrile resulted in ring closure to provide aziridines in high yield (eqs 2 and 3).

Computational Studies.[22] Alkyl zinc additions to carbonyls have been extensively studied both experimentally[23] and theoretically.[22,24] In the widely accepted mechanism, one Zn moiety plays two roles: as a Lewis acid the Zn coordinates the substrate while also binding a Lewis basic group to which the dialkylzinc moiety bonds and reacts with the activated carbonyl. In the current case, we hypothesize the alkyl zinc halide fills the role of the activating moiety, with the halide available for coordination to the second zinc. In most cases, it is believed

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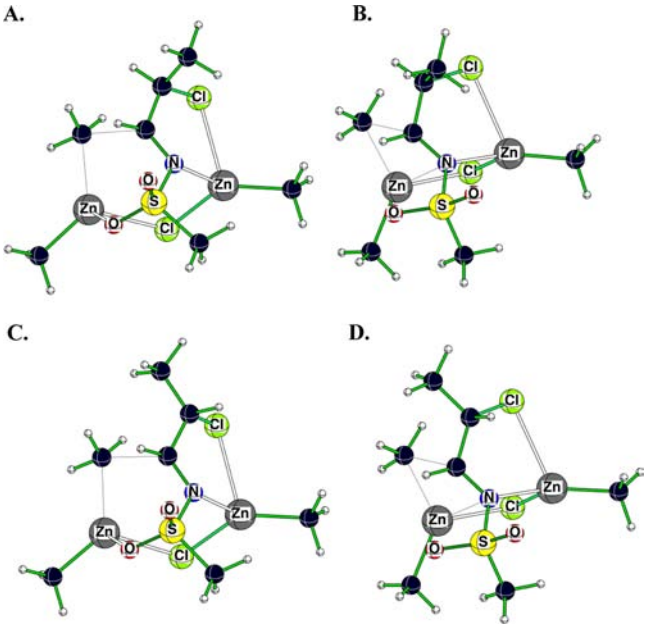

Figure 4. Transition states leading to *syn* and *anti* products based on computational studies. (A) Six-membered ring TS leading to *syn* product, 90% (best TS, M06/II, other levels >90%). (B) Four-membered ring TS leading to *syn* product, 9% (ca. 6 kJ/mol higher than best TS, M06/II). (C) Six-membered ring TS leading to *anti* product, 0.9% (ca. 12 kJ/mol higher than best TS, M06/II). (D) Four-membered ring TS leading to *anti* product, 0.1% (ca. 18 kJ/mol higher than best TS, M06/II). Structures are drawn in Figure 5 and highlight the four- and six-membered rings.

Table 4. Relative Calculated Barriers for Different Additions (kJ mol^{-1})[a]

product	TS ring size	B3LYP/BSI	M06/BSII	M06/BSIII
anti	4	36	27	17
anti	6	15	14	12
syn	4	22	10	6
syn	6	0	0	0

[a]Comparison of four- and six-membering ring transition states leading to *syn* or *anti* addition products. See Figures 4 and 5 for transition state structures.

that the dialkylzinc forms a four-membered ring transition state (TS) with the carbonyl.[22] However, it has been suggested that a six-membered ring TS is also possible.[24a,j] In the current case, we elected to investigate both possible addition types, with the dialkylzinc moiety coordinated to either the N or O of the sulfonyl imine in the TS. As a computational model system, we selected the reaction of *N*-mesyl-protected α-chloro-propanimine, CH_3—CHCl—CH═N—SO_2Me, with methyl zinc chloride (MeZnCl) and dimethylzinc (Me_2Zn). Upon geometry optimization of the reactants, MeZnCl and Me_2Zn form a loose complex with the α μ-Cl bridge. Attempts to bring this species into a chelate formed by the imine nitrogen and α-Cl moiety instead result in a complex where the two sulfonyl oxygens each coordinate one Zn atom. This complex has virtually free rotation of the N═C—C—Cl bond and would not be expected to lead to the high diastereoselectivities observed. Interestingly, contrary to the expectation from earlier studies of related systems, the six-membered ring TS is preferred over the more commonly seen four-membered ring TS (Figures 4A and 4B).[24a,j,k] This is true at all levels of theory,

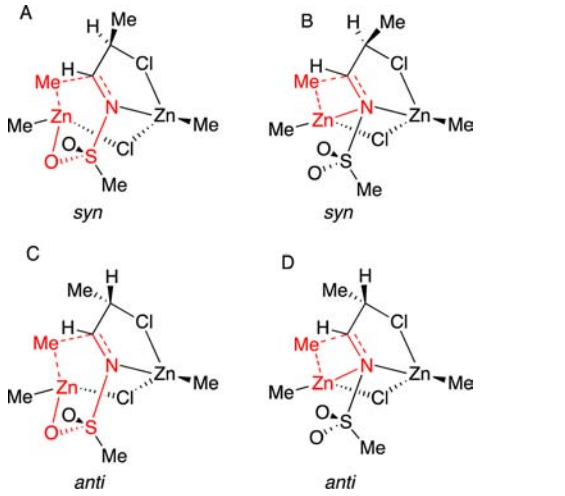

Figure 5. Simplified transition states leading to the *syn* and *anti* products. The four- and six-membered transition states are highlighted in red. Note that for the purpose of clarity, enantiomeric aldimines are used in drawings A,B vs C,D. In all cases, the dimethylzinc is attacking the imine from the bottom face.

even if the energy difference decreases with the larger basis set (Table 4). It is noteworthy that when two fairly different methods of calculations (B3LYP and MO6 in this case) give the same qualitative results, the conclusions can be considered more reliable. Figure 5 highlights the key four- and six-membered rings in the transition states in red. As shown in the calculated structure, in the attack of dimethylzinc on the imine carbonyl, the chelate structure with MeZnCl coordination to the α-Cl is favored, restricting the bond rotation and enforcing a specific orientation of the α-methyl group (Figure 4A). In the TS leading to the *syn*-product, the α-methyl group points away from the reaction center, giving a facile addition. For addition leading to the *anti*-product (Figure 4C and 4D), the α-methyl group is forced close to the reaction center, at a high steric cost, irrespective of whether the four- or six-membered addition path is followed. The relative barriers, at different levels of theory, are shown in Table 4, with the highest accuracy expected from the dispersion-corrected functional with the larger basis set, MO6/BSIII.[25] The high-energy difference between paths to *anti* and *syn* products correspond well to the excellent experimental selectivity.

3. CONCLUSION

Substrate control has become a cornerstone in asymmetric synthesis. In particular, the models used to predict stereochemical outcomes in nucleophilic additions to α-chiral carbonyl and imine derivatives have been widely accepted for quite some time. We disclosed a highly diastereoselective addition reaction that proceeds through an unusual chelation-controlled pathway involving binding of the α-chloro aldimine N, O, *and Cl* to zinc, reversing the inherent selectivity predicted by the Cornforth–Evans model (Figure 6).

The chelation-controlled pathway is strongly supported by the experimentally observed stereochemical outcomes of the addition reactions and by computational studies at several levels of theory.

4. EXPERIMENTAL SECTION

General procedure for (*E*)-vinylzinc addition to α-chloro aldimine: A dry 10 mL Schlenk flask, which was evacuated under vacuum and

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Figure 6.

backfilled with N_2 (g) three times, was charged with dicyclohexylborane (Cy_2BH) (107 mg, 0.6 mmol) and dichloromethane (0.7 mL). The solution was cooled to 0 °C followed by slow addition of alkyne (0.6 mmol). After 5 min the reaction was warmed to room temperature and stirred for an additional 15 min. The solution was cooled to −78 °C, and dimethylzinc (Me_2Zn) (0.75 mL, 2 M in dichloromethane) was added. After stirring at −78 °C for 30 min, EtZnBr (0.4 mmol) was added under a steady flow of N_2 (g). Immediately thereafter, the aldimine precursor (0.2 mmol, in 0.2 mL of dichloromethane) was added. The reaction mixture was warmed to −45 °C and monitored until completion as determined by TLC (usually 4−6 h). The reaction mixture was quenched with 1 M HCl (2 mL) followed by addition of 5 mL of EtOAc. The organic layer was separated, and the aqueous layer was extracted successively with EtOAc (2 × 5 mL). The combined organic layers were successively washed with aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel.

Computational Details. Reported free energies (in kJ mol^{-1}) are calculated with Jaguar (version 7.7, Schrodinger, LLC, New York, NY, 2010) using the M06 level at B3LYP geometries,[26] with corrections for thermodynamic contributions and continuum benzene solvation,[27] as described in detail in the Supporting Information. For B3LYP calculations, we use the LACVP*[28] basis set (BSI). For single-point M06 calculations, we use the cc-PVTZ*+ basis set[29] for light elements, with either the Hay−Wadt ECP(BSII) or an all-electron TZV* basis set[12f,30] (BSIII) for Zn.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures, full characterization of new compounds, calculated structures and energies, and crystallographic data for **5c** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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