JOC The Journal of Organic Chemistry

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Synthetic Factors Governing Access to Tris(β-diketimine) Cyclophanes versus Tripodal Tri-β-aminoenones

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Cite This: https://dx.doi.org/10.1021/acs.joc.0c01708 Read Online

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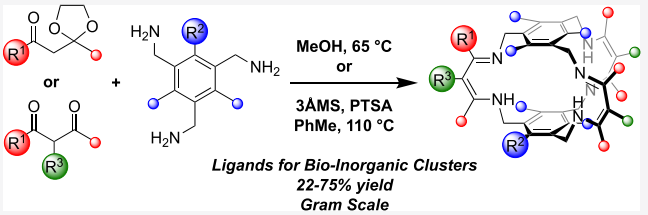
ABSTRACT: Tris(β-diketimine) cyclophanes are an important ligand class for investigating cooperative multimetallic interactions of bioinorganic clusters. Discussed herein are the synthetic factors governing access to tris(β-diketimine) cyclophanes versus tripodal tri-β-aminoenones. Cyclophanes bearing Me, Et, and MeO cap substituents and β-Me, Et, or Ph arm substituents are obtained, and a modified condensation method produced α-Me β-Me cyclophane. These operationally simple procedures produce the ligands in gram quantities and in 22−94% yields.



INTRODUCTION

Macrobicyclic compounds hold a privileged place in the synthetic toolbox; indeed, Lehn's seminal and important discoveries in this area contributed to the work recognized in his Nobel Prize.[1] The chemical utility of macrobicycles has long resided in the ability to tailor these molecules to recognize or sequester chemical species of interest with high selectivity. For example, cryptands and cyclophanes bind alkali cations, halide anions, and small molecules (e.g., formate and dioxygen) with high affinity.[2] Subsequent to Lehn's initial discoveries, macrobicycles have garnered interest as ligands for d- and f-block metal ions. For example, monometallic cryptates have been developed as contrast agents for magnetic resonance imaging among other applications.[3] With respect to reactivity, one aim has been to accommodate reactive metal-based intermediates (e.g., peroxo- and superoxo-metal species) within the internal cavity of the macrobicycle, allowing for the enzyme-like recognition and orientation of a substrate to selectively affect a desired chemical transformation.[4]

Relatedly, the development of ligands capable of supporting multiple designed metal ion binding sites is a long-standing and ongoing research area. Multimetallic complexes of such ligands have expanded our understanding of the reactivity of metal−metal bonds, metal-ion redox cooperativity, and the mechanism of biocatalysis at metal cluster active sites.[5] As an example, multimetallic complexes of tripodal ligand systems structurally mimic enzymes involved in phosphate metabolism.[6]

Designing macrobicycles as ligands for di- and tri-metallic complexes provides an intersection of these two research areas. Multimetallic macrobicyclic compounds have been reported as selective receptors for cyanide[7] and carbonate,[8] competent for heterolysis of the C−C bond in acetonitrile,[9] capable of imparting reactivity typical of transition metals to heavy main group elements,[10] and functional as photocatalysts for the reduction of carbon dioxide to carbon monoxide.[11] Recently, there have been an increasing number of reports on the synthesis of polynucleating cyclophane ligands;[12] however, employing these macrobicycles remains limited by fundamental synthetic challenges inherent to their synthesis.[13,14]

Our group has previously reported the synthesis and metalation of a tris(β-diketimine) cyclophane **1** (H_3**L**) and the reactivity of the resultant trimetallic complexes.[15,16] A survey of the reactivity of the trimetallic cyclophanates is depicted in Figure 1 and includes carbon dioxide reduction to formate[17] and oxalate,[18] stabilization of copper(I)-dinitrogen interactions,[19] and catalytic silylation of dinitrogen.[20] We sought to modify this ligand to tune cluster properties and reactivity. Specifically, we postulated that minor changes in ligand sterics or electronics (i.e., Me or OMe vs Et) could modulate substrate access and selectivity and more substantial steric or electronic changes could allow for isolation of intermediates and new reaction manifolds.[21]

Numerous methods have been reported for the synthesis of β-diketimines. The breadth of approaches to access these ligands is a consequence of the rich coordination and organometallic chemistry of the supported metal complexes.[22] The most common preparations implement condensation of amines with a dione; however, this approach can readily afford

Received: July 17, 2020

https://dx.doi.org/10.1021/acs.joc.0c01708
J. Org. Chem. XXXX, XXX, XXX−XXX

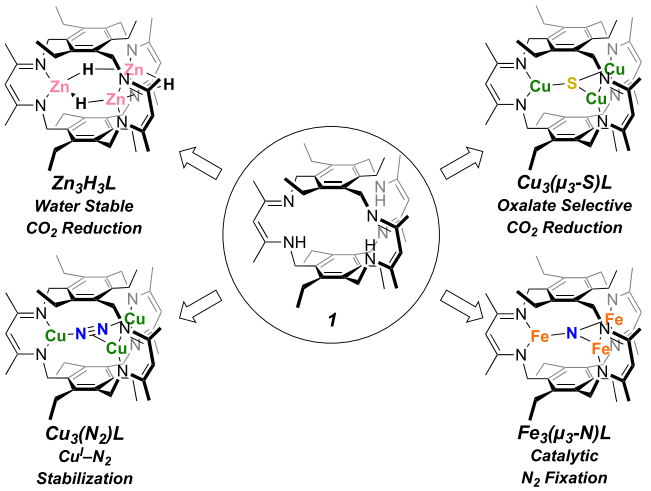


Figure 1. Complexes and catalysts derived from tris(β-diketimine) cyclophane **1**.

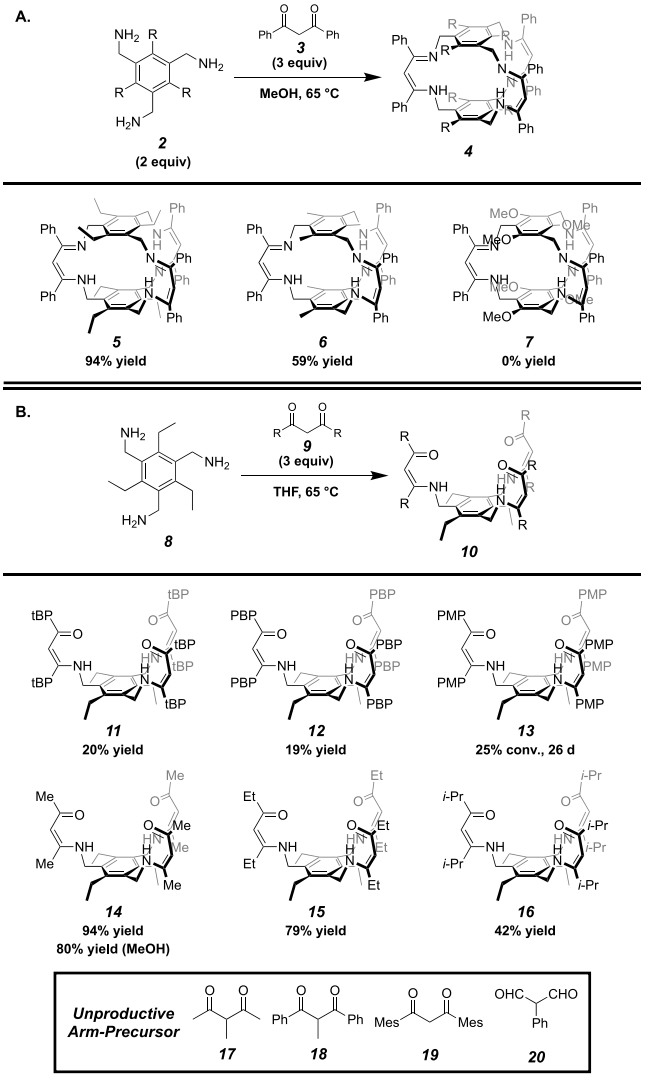
β-aminoenone, which requires activation of carbonyl (e.g., Lewis acids, alkylation, and microwave excitation) for a second condensation.[23] Condensation with a dione monoketal is often preferable because the β-aminoenone intermediate is avoided and β-diketimine is accessed in one step.[24] Herein, we report the synthetic factors governing access to tris(β-diketimine) cyclophanes or tripodal tri-β-aminoenones. These findings resulted in a family of cyclophanes with varied substituents on the arene caps and β-diketimine arms.

RESULTS AND DISCUSSION

We began our studies by investigating the condensation of triamine caps with a series of diones toward the direct formation of tris(β-diketimine) cyclophanes (Scheme 1A). To our delight, β-phenyl-substituted cyclophanes **5** and **6** precipitate from 65 °C MeOH reaction mixtures, and both were isolated by filtration in 94% and 59% yield, respectively. These compounds exhibit poor solubility in MeOH and are only partially soluble in boiling THF and boiling toluene. To our surprise, the methoxy-substituted triamine cap did not produce the cyclophane product (**7**), and the crude reaction mixture contained unreacted starting materials. Additionally, reacting other β-aryl-substituted diones with cap **8** (1 or 2 equiv) in THF or MeOH solutions produced tri-β-aminoenones (**11**–**13**) instead of the corresponding cyclophanes in low yield. When the aryl substituent was *p*-methoxyphenyl (PMP), the reaction proceeded especially slowly with only 25% conversion to tri-β-aminoenone after 26 d of heating at reflux in THF. The addition of 3 Å molecular sieves to these reaction mixtures or heating at elevated temperatures in *n*-BuOH did not significantly vary the product outcome.

We then explored the effects of β-alkyl substitution on the condensation reaction. Once again, tri-β-aminoenones were observed instead of tris(β-diketimine) cyclophanes with decreasing yield as the alkyl substituents increased in size (when R = Me, Et, and *i*-Pr, the yields were 94, 79, and 42%, respectively). Additionally, this condensation afforded higher isolated yield when THF, instead of MeOH, was utilized (Scheme 1B, substrate **14**). However, NMR yields of this condensation reaction appear largely unaffected by the solvent (Table 1, entries 2–8). Arm precursors with α-substituents (**17**, **18**, and **20**) or considerable sterics (**19**) were not compatible with this condensation procedure.

Scheme 1. (A) Condensation of Triamines with Dione 3 to Afford β-Substituted Tris(β-diketimine) Cyclophanes; (B) Condensation of Triamine 8 with Diones to Afford Tri-β-aminoenones



With access to tri-β-aminoenones, we pursued coupling a second triamine cap toward the desired cyclophanes. A dehydrative procedure employing *p*-toluenesulfonic acid and 3 Å molecular sieves successfully afforded cyclophane **1** (Scheme 2A). The reaction outcome was dramatically affected by the solvent's polarity (e.g., ∼57% NMR yield in fluorobenzene and DME compared to 15% NMR yield in PhMe). Increasing the sterics of the β-alkyl substituents, once again, dramatically affected the reaction. Changing the substituent to Et resulted in ∼5% conversion to the cyclophane after 48 h, while the desired products were not observed with *i*-Pr and *p*-*tert*-butylphenyl (tBP) substituents. Despite the generally poor reactivity observed, we were optimistic that this condensation may be utilized toward the synthesis of cyclophanes bearing differentiated caps. Tri-β-aminoenone **14** and triamine **22** were subjected to condensation conditions (Scheme 2B). The desired mixed cap cyclophane was not observed, and instead, cyclophanes **1** and **23** were formed. This result is reminiscent of Schaper's observation of scrambling between β-aminoenones and amines prior to β-diketimine formation[22a] and Lehn's observation of self-sorting

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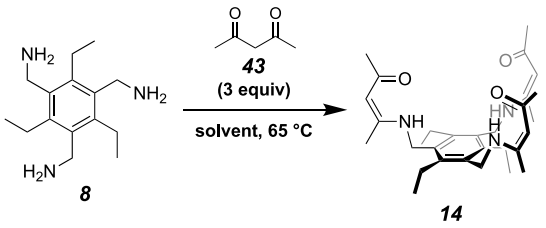
J. Org. Chem. XXXX, XXX, XXX–XXX

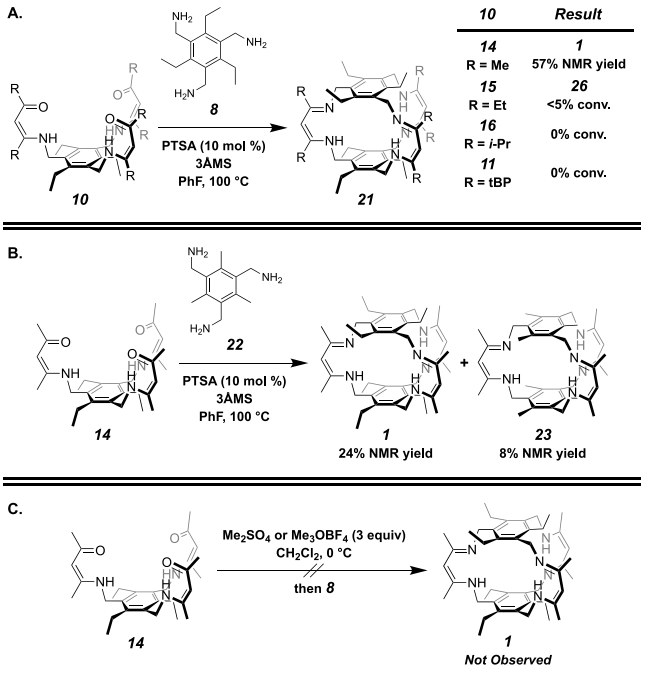
Table 1. Optimization of Tri-β-aminoenones 14[a]



entry	solvent	NMR yield (%)
1	neat	77
2	MeOH	88
3	EtOH	92
4	*i*-PrOH	92
5	THF	92
6	MeCN	88
7	DCE	90
8	PhMe	87

[a]Reaction conditions: **8** (25.0 mg, 0.100 mmol) and **43** (30.0 mg, 0.300 mmol) in the reported solvent (1.0 mL, 0.10 M) were heated at 65 °C for 18 h.

Scheme 2. (A) Coupling of Triamine cap 8 with Tri-β-aminoenones to Generate Tris(β-diketimine) Cyclophanes; (B) Attempt to Make a Mixed-cap Cyclophane from Tri-β-aminoenone 14 and Triamine 22; (C) Attempt to Activate the Tris(β-diketimine) Cyclophanes with Alkylating Agents



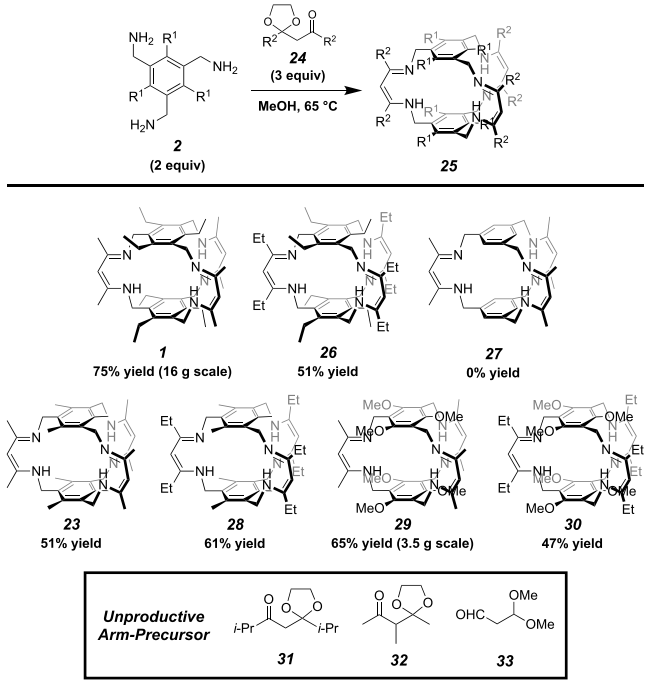
in the formation of imine-based macrobicyclic cryptand-type organic cages.[25]

Alternative coupling tactics were even less successful. Alkylation methods employing tri-β-aminoenone **14**, triamine **8**, and 3 equivalents of either Me_2SO_4 or Me_3OBF_4 produced complex mixtures (Scheme 2C).[26] Here, the desired intermediate would be the triply methylated trication, and such a species is likely to be challenging to access based on the size of the molecule and the anticipated decreases in the pK_a of the enones with each subsequent alkylation.

A crystal structure of tri-β-aminoenone **14** was obtained to elucidate any conformational features that may complicate the condensation of triamines (Figure S1). The average carbonyl C−O and enamine C−N bond lengths are 1.247(4) and 1.337(3), respectively, consistent with the β-aminoenone tautomer.[27] We note that the crystal structure of tri-β-aminoenone **14** does not indicate the alternating up-down conformation required to produce cyclophanes from these hexasubstituted benzenes.[28] However, the major species in the **14**, **15**, and **16** ^{1}H NMR spectra evidence C_{3v} geometry in solution consistent with an alternating up-down confirmation. These ^{1}H NMR data suggest that tri-β-aminoenones are conformationally oriented in solution for cyclization. Interestingly, the ^{1}H NMR of **15** in methanol-d_4 indicates two species, and the minor species has C_s symmetry. This isomer may have a similar conformational orientation as tri-β-aminoenone **14** in its crystal structure. These combined data illustrate how energetic differences in solvation compared to crystallization can produce conformational changes in these tripodal compounds.

Accessing cyclophanes through the direct cyclization of diones and triamines or cyclization with tri-β-aminoenones and triamines was generally unsuccessful. We, therefore, explored an alternative approach to circumvent these synthetic challenges. As for our reported synthesis of **1**, dialkyldiones were converted to their corresponding monoketals and then reacted with triamine caps in MeOH at 65 °C (Scheme 3).[15]

Scheme 3. Synthesis of β-Substituted Tris(β-diketimine) Cyclophanes from Triamines and Dione Monoketals



The corresponding β-alkyl tris(β-diketimine) cyclophanes precipitate from the reaction mixtures analytically pure and are isolated by filtration. As seen in Table 2, alcoholic solvents are preferable for this transformation. In our laboratory, this condensation is regularly performed in an open flask on a 16 g scale affording cyclophane **1**.

Substituents on the arms varied between Me and Et, with ketal **31** and acetal **33** failing to afford cyclophanes with larger

https://dx.doi.org/10.1021/acs.joc.0c01708
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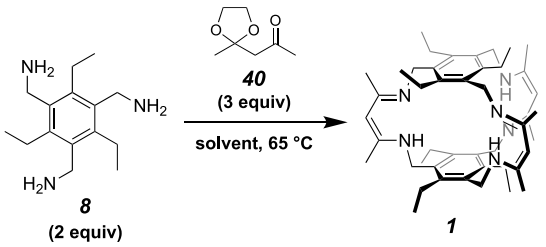
Table 2. Optimization of Cyclophane 1[a]



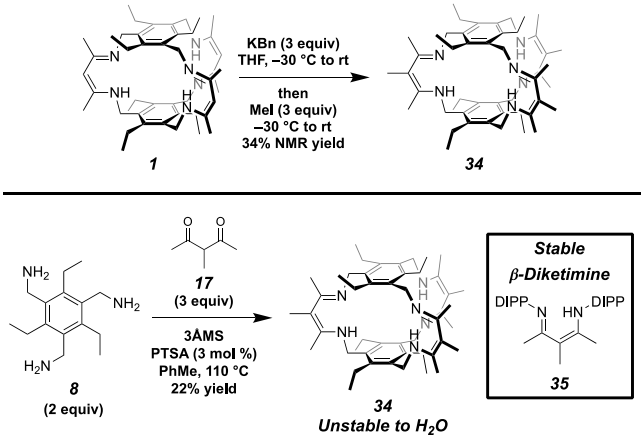
entry	solvent	NMR yield
1	neat	31%
2	MeOH	51% (75%)[b]
3	EtOH	51%
4	*i*-PrOH	51%
5	*n*-BuOH	49%
6	THF	21%
7	MeCN	38%
8	DCE	41%
9	PhMe	39%

[a]Reaction conditions: **8** (50.0 mg, 0.200 mmol) and **40** (43.0 mg, 0.300 mmol) in the reported solvent (1.0 mL) were heated at 65 °C for 5 h. [b]Isolated yield of cyclophane **1** using **8** (16.2 g, 65.0 mmol) and **40** (25.5 g, 101 mmol) in MeOH (60.0 mL) at 65 °C for 5 h.

or smaller sterics, respectively. This series includes substitution of the Et groups on the cap for Me or OMe creating access to a collection of new ligands. When comparing cyclophanes with similar cap substituents and either Me- or Et-arm substituents, the Et substituted product was generally more soluble in common organic solvents. Since the products precipitate from the reaction mixtures, we initially surmised that cyclophane solubility in MeOH was a significant factor affecting the yield. However, this explanation is challenged by Me-substituted cyclophane **23**, which was the least soluble *β*-alkyl tris(*β*-diketimine) cyclophane and was not isolated in higher yield compared to the other products. Cyclophane **23** exhibited such limited solubility in organic solvents that full characterization required the substitution of standard ^{13}C NMR with HMBC NMR. When an unsubstituted cap was used (R^1 = H), a precipitate was isolated. Crude ^{1}H NMR contains signals that are assigned to cyclophane **27** and undefined decomposition. Attempts to isolate this product by crystallization or chromatography were unsuccessful and resulted in partial decomposition of the product. We were interested in using this method to produce *β*-aryl-substituted cyclophanes but met with challenges in producing the necessary monoketal precursor.[29]

As noted above, neither *α*-substituted diones **17** or **18** nor monoketal **32** afforded the respective *α*-substituted cyclophanes. Alkylations of **1** with methyl iodide provided cyclophane **34**; however, this method presented purification challenges (Scheme 4). To address these limitations, a modified condensation procedure was developed employing 3 Å molecular sieves in toluene under anhydrous and air-free conditions. Cyclophane **34** was isolated analytically pure in 22% yield by filtration of the reaction mixture and the addition of methanol inducing precipitation. This product decomposed slowly under ambient conditions and more rapidly when exposed to water but was indefinitely stable when left in an inert environment. In contrast, *β*-diketimine **35** is reported to be isolated through an aqueous work-up.[30]

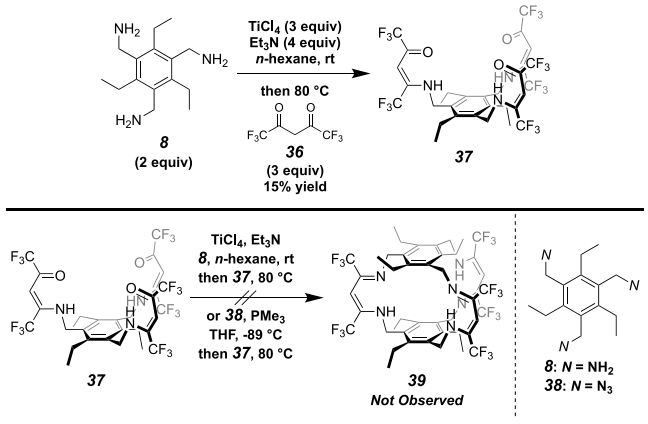
Scheme 4. Synthesis of *α*-Me Tris(*β*-diketimine) Cyclophane 34



To investigate the origin of this lability, a crystal structure was obtained of cyclophane **34** (Figure S2). Between cyclophanes **1** and **34**, the solid-state structures display a decrease in the average *β*-diketimine C_{sp^2}–C_{sp^2}–C_{sp^2} angle from 125.38(1) to 122.2(2) with the average $N_L\cdots N_L$ distance decreased by 0.073(2) Å within the *β*-diketimine units and the average circumcircle radii of the nitrogen atoms increased by 0.023(1) Å between these units. This compression is a consequence of the increase in $A^{1,3}$ strain upon exchanging an *α*-H for an *α*-Me. In these cyclophanes, *β*-diketimines are in a semirigid architecture where small changes in bond angles can produce large changes with regard to compression with few conformational options to accommodate the increased strain. These steric effects provide a plausible reason for why the *α*-substituted diones or monoketals fail to afford cyclophane products (e.g. **17**, **18**, and **32**).

During the course of our investigations, we also explored conditions toward the goal of installing *β*-CF_3 substituents on the cyclophane arms. The synthesis of these *β*-diketimines is typically accomplished in low to moderate yield (10–65%) by pretreating aryl amines with $TiCl_4$ before heating with hexafluoroacetylacetone (Hhfac).[31] We employed these conditions toward *β*-CF_3-substituted cyclophane **39** (Scheme 5). Instead, the corresponding tri-*β*-aminoenone (**37**) was obtained in 15% yield. Utilizing microwave conditions, modifying the reaction concentration, or varying the

Scheme 5. Efforts toward *β*-CF_3 Tris(*β*-diketimine) Cyclophane 39



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J. Org. Chem. XXXX, XXX, XXX–XXX

equivalents of the reagents did not significantly change the reaction outcome, and there were no conditions in which the desired cyclophane was observed.

We attempted to convert tri-β-aminoenone **37** to its corresponding cyclophane by subjecting it to the $TiCl_4$-mediated conditions above; however, the crude reaction mixtures contained unreacted starting materials. These results may suggest an unexpected cooperativity between the aminoenone arms inhibiting this otherwise reliable procedure. An alternative tactic was therefore required. Though implemented less frequently, β-CF_3 diketimines have been synthesized using aza-Wittig conditions.[32,33] Triazide **38** was treated with PMe_3 at −89 °C followed by the addition of tri-β-aminoenone **37** and heating. All attempts suggested polymerization. Unlike the condensation reactions utilized in the synthesis of the tris(β-diketimine) cyclophanes above, highly irreversible reactions are likely incompatible toward the synthesis of these products. Unfortunately, β-CF_3 remains a highly desirable substituent for this ligand class.

CONCLUSIONS

We have described herein our studies toward the synthesis of tris(β-diketimine) cyclophanes, an important ligand class for investigating multimetallic interactions relevant to bioinorganic clusters. Two operationally simple and scalable methods were developed capable of installing Et-, Me-, and OMe-substituted caps and β-Me-, Et-, or Ph-substituted arms. A modified procedure allowed access to an α-methyl-substituted cyclophane. Conditions that are selective for the similar tripodal tri-β-aminoenones are also described. Further efforts are underway toward expanding analogous cyclophane ligand systems and exploring the chemistry of their resulting multimetallic complexes.

EXPERIMENTAL SECTION

General Information. Unless specified otherwise, reactions were performed under nitrogen without special care taken to remove moisture. Reactions that were heated were placed in a temperature-regulated oil bath. When specified, reactions were instead set up in an argon-filled Vigor Sci-Lab or dinitrogen-filled Inert PureLab glove box, sealed with a Teflon lined cap, removed from the glove box, and heated in an oil bath for the reported amount of time. ^{1}H NMR spectra were recorded on either a 500 MHz Inova or a 300 MHz Mercury spectrophotometer. Chemical shifts were referenced to solvent resonances: δ_H = 7.27 ppm for $CDCl_3$ and δ_H = 3.31 ppm for methanol-d_4. ^{13}C NMR spectra were recorded on a 500 MHz Inova spectrophotometer with the spectra referenced to solvent resonances: δ_C = 77.16 ppm for $CDCl_3$ and δ_C = 49.00 ppm for methanol-d_4. ^{19}F NMR spectra were recorded on a 500 MHz Inova spectrophotometer with the spectra referenced to an internal standard resonance: δ_F = −113.15 ppm for fluorobenzene. Infrared spectra were recorded as films on a Bruker Vertex 80v FTIR using a Pike GladiATR stage using the Agilent Microlab software package or a Thermo Fischer Scientific Nicolet iS5 with an iD7 ATR diamond crystal using OMNIC software package. Solvents were either purchased anhydrous and used as received or extracted from an Innovative Technologies solvent purification system. Fluorobenzene was distilled from CaH_2. Solvents in glove boxes were stored over 3 Å molecular sieves prior to use. The water content of anhydrous solvents was measured using a Mettler Toledo C20 Coulometric Karl Fischer titrator prior to use and was below 1 ppm in all cases. Deuterated solvents were purchased from Cambridge Isotope Laboratories or Sigma Aldrich. 3 Å molecular sieves were heated at 200 °C overnight under reduced pressure (<5 torr) and then transferred to a glove box. All reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, Matrix Scientific, or SynQuest Labs and used without further purification.

Experimental Procedure. Tri(aminomethyl)-2,4,6-triethylbenzene (**8**),[34] 1,3,5-tri(aminomethyl)benzene,[35] 1,3,5-tri(aminomethyl)-2,4,6-trimethylbenzene (**22**),[36] 1,3,5-tri(aminomethyl)-2,4,6-trimethoxybenzene,[37] 1,3-di-(4-*tert*-butylphenyl)propan-1,3-dione,[38] 1,3-di-(*p*-bromophenyl)propan-1,3-dione,[39] 1,3-di-(*p*-methoxyphenyl)propan-1,3-dione,[39] 3-methylpenta-2,4-dione (**17**),[40] 2-methyl-1,3-diphenylpropan-1,3-dione (**18**),[41] 1,3-dimesitylpropan-1,3-dione (**19**),[42] penta-2,4-dione-2,2-(ethylene glycol) monoketal,[23b] 3-methylpenta-2,4-dione-2,2-(ethylene glycol) monoketal (**32**),[43] 3,3-dimethoxyproponal (**33**),[44] and 1,3,5-tri(azidomethyl)-2,4,6-triethylbenzene (**38**)[45] were synthesized according to the previously reported procedures.

Cyclophane ***5***. Triamine **8** (222 mg, 892 μmol) and 1,3-diphenylpropan-1,3-dione (**3**, 300 mg, 1.34 mmol) dissolved in methanol (4.5 mL) were stirred and heated at 65 °C in an oil bath for 6 h. Upon completion as determined by TLC, the resulting suspension was filtered, and the precipitate was dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. Cyclophane **5** was isolated as a beige solid (448 mg, 94% yield). ^{1}H NMR (500 MHz, methanol-d_4): δ 7.93 (d, J = 7.1 Hz, 12H), 7.43 (app. t, 6H), 7.36 (t, J = 7.3 Hz, 12H), 4.16 (s, 12H), 2.85 (q, J = 7.5 Hz, 12H), 1.14 (t, J = 7.5 Hz, 18H). Note that the methine peak of β-diketimine was not observed in methanol-d_4 nor was the methylene peak of the starting dione observed in $CDCl_3$. ^{13}C{^{1}H} NMR (125 MHz, methanol-d_4): δ 175.0, 147.0, 138.1, 131.8, 131.3, 130.2, 128.9, 37.9, 24.4, 16.3. Note that the methine peak of β-diketimine was not observed in methanol-d_4. IR (film): ν 2967, 2864, 2626, 1588, 1550, 1522, 1495, 1371, 830, 719, 671 cm^{-1}. Note: The molecular ion was not observed in either positive or negative mode using either ESI or DART; however, the parent ion observed was the triamine cap (i.e. the product of hydration). HRMS (ESI$^+$) m/z: calc'd for $(2 \times \mathbf{8} + H)^+$ $[C_{30}H_{54}N_6 + H]^+$, 499.4486; found, 499.4483.

Cyclophane ***6***. Triamine **22** (60.0 mg, 289 μmol) and 1,3-diphenylpropan-1,3-dione (**3**, 100 mg, 0.446 mmol) dissolved in methanol (1.0 mL) were stirred and heated at 65 °C in an oil bath for 18 h. Upon completion as determined by TLC, the resulting suspension was filtered, and the precipitate was dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. Cyclophane **6** was isolated as a white solid (127 mg, 59% yield). ^{1}H NMR (500 MHz, methanol-d_4): δ 7.88 (d, J = 8.0 Hz, 12H), 7.42 (t, J = 8.0 Hz, 6H), 7.35 (app. t, J = 7.3 Hz, 12H), 4.19 (s, 12H), 2.46 (s, 18H). Note that the methine peak of β-diketimine was not observed in methanol-d_4 nor was the methylene peak of the starting dione observed in $CDCl_3$. ^{13}C{^{1}H} NMR (125 MHz, methanol-d_4): δ 174.2, 139.4, 137.5, 133.2, 131.8, 130.3, 128.9, 39.5, 16.5. Note that the methine peak of β-diketimine was not observed in methanol-d_4. IR (film): ν 2857, 2646, 1598, 1529, 1371, 1067, 1023, 718, 672 cm^{-1}. Note that the molecular ion was not observed in either positive or negative mode using either ESI or DART; however, the parent ion observed was the triamine cap (i.e. the product of hydration). HRMS (ESI$^+$) m/z: calc'd for $(2 \times \mathbf{22} + H)^+$ $[C_{24}H_{42}N_6 + H]^+$, 415.3544; found, 415.3514.

Tri-β-aminoenone ***11***. Triamine **8** (49.4 mg, 198 μmol) and 1,3-di-(4-*tert*-butylphenyl)propan-1,3-dione (200 mg, 594 μmol) dissolved in THF (2.0 mL) were stirred and heated at 65 °C in an oil bath for 8 days. Upon completion as determined by TLC, the resulting solution was cooled to ambient temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2 eluent) to afford tri-β-aminoenone **11** (23.9 mg, 20% yield) as a yellow solid. TLC: R_f = 0.21 (CH_2Cl_2 eluent). ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.16 (br s, 3H), 7.76 (d, J = 8.1 Hz, 6H), 7.52 (d, J = 8.1 Hz, 6H), 7.45 (d, J = 8.1 Hz, 6H), 7.34 (d, J = 8.1 Hz, 6H), 5.78 (s, 3H), 4.34 (s, 6H), 2.56 (q, J = 6.8 Hz, 6H), 1.39 (s, 27H), 1.30 (s, 27H), 1.00 (t, J = 6.8 Hz, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 188.0, 165.7, 153.9, 153.0, 143.9, 137.7, 133.0, 132.4, 127.6, 127.0, 125.7, 125.1, 93.4, 43.5, 35.0, 34.9, 31.44, 31.36, 23.5, 16.0. IR (film): ν 2965, 2869, 1584, 1552, 1487, 1462, 1328, 1269, 1063, 786 cm^{-1}. HRMS (DART+) m/z: calc'd for $(M + H)^+$ $[C_{84}H_{105}N_3O_3 + H]^+$, 1204.8229; found, 1204.8260.

https://dx.doi.org/10.1021/acs.joc.0c01708
J. Org. Chem. XXXX, XXX, XXX−XXX

Tri-β-aminoenone ***12***. Triamine **8** (15.2 mg, 60.9 μmol) and 1,3-di-(*p*-bromophenyl)propan-1,3-dione (70.0 mg, 183 μmol) dissolved in THF (0.61 mL) were stirred and heated at 65 °C in an oil bath for 6 d. Upon completion as determined by TLC, the resulting solution was cooled to ambient temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes → 1:1 Et_2O/hexanes eluent) to afford tri-β-aminoenone **12** (7.9 mg, 19% yield) as an orange film. TLC: R_f = 0.42 (1:1 Et_2O/hexanes eluent). ^1H NMR (500 MHz, $CDCl_3$): δ 11.14 (t, *J* = 5.0 Hz, 3H), 7.67 (d, *J* = 8.4 Hz, 6H), 7.66 (d, *J* = 8.6 Hz, 6H), 7.47 (d, *J* = 8.6 Hz, 6H), 7.39 (d, *J* = 8.4 Hz, 6H), 5.69 (s, 3H), 4.30 (d, *J* = 5.0 Hz, 6H), 2.55 (q, *J* = 7.5 Hz, 6H), 1.02 (t, *J* = 7.5 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 187.2, 164.7, 144.0, 138.8, 134.4, 132.2, 131.5, 129.4, 128.8, 125.7, 124.4, 93.3, 43.5, 23.5, 16.01. IR (film): ν 2981, 1591, 1575, 1555, 1473, 1323, 1070, 1010, 833, 773 cm^{-1}. HRMS (ESI+) *m/z*: calc'd for $(M + H)^+$ $[C_{60}H_{51}Br_6N_3O_3 + Na]^+$, 1363.8867; found, 1363.8860.

Tri-β-aminoenone ***13***. A solution of triamine **8** (58.4 mg, 234 μmol) and 1,3-di-(*p*-methoxyphenyl)propan-1,3-dione (200 mg, 702 μmol) in THF (2.3 mL) was stirred and heated at 65 °C in an oil bath for 26 d. An aliquot was removed from the reaction, concentrated under reduced pressure, and analyzed by ^1H NMR indicating ∼25% conversion to tri-β-aminoenone **13**.

Tri-β-aminoenone ***14***. Triamine **8** (1.00 g, 4.01 mmol) and acetylacetone (**43**, 1.24 mL, 12.0 mmol) dissolved in THF (40 mL) were stirred and heated at 65 °C in an oil bath for 18 h. Upon completion as determined by TLC, the resulting yellow solution was concentrated under reduced pressure. The residue was washed with Et_2O (10 mL) and then dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. The product was isolated as a beige solid (1.87 g, 94% yield). Single crystals suitable for X-ray diffraction were obtained by slowly evaporating a solution of **14** in benzene. TLC: R_f = 0.30 (EtOAc eluent). ^1H NMR (500 MHz, $CDCl_3$): δ 10.60 (app. s, 3H), 5.00 (s, 3H), 4.42 (d, *J* = 4.7 Hz, 6H), 2.72 (q, *J* = 7.6 Hz, 6H), 2.07 (s, 9H), 1.94 (s, 9H), 1.21 (t, *J* = 7.6 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 194.9, 161.8, 144.0, 131.8, 95.6, 41.4, 28.9, 23.4, 19.4, 16.2. IR (film): ν 2884, 1619, 1553, 1491, 1433, 1332, 1277, 1028, 728 cm^{-1}. Anal. Found (calc'd) for $C_{30}H_{45}N_3O_3$: C, 72.62 (72.69); H, 9.10 (9.15); N, 8.15 (8.48).

Tri-β-aminoenone ***14***. Triamine **8** (2.00 g, 8.02 mmol) and acetylacetone (**43**, 2.47 mL, 24.1 mmol) dissolved in MeOH (80 mL) were stirred and heated at 65 °C in an oil bath for 18 h. Upon completion as determined by TLC, the resulting yellow solution was concentrated under reduced pressure. The residue was washed with Et_2O (10 mL) and then dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. The product was isolated as a beige solid (3.19 g, 80% yield).

Tri-β-aminoenone ***15***. Triamine **8** (649 mg, 2.60 mmol) and 3,5-heptanedione (1.06 mL, 7.80 mmol) dissolved in THF (78 mL) were stirred and heated at 65 °C in an oil bath for 31 h. Upon completion as determined by TLC, the mixture was cooled to ambient temperature and concentrated under reduced pressure to afford a yellow-orange oil that solidified overnight. The crude material was purified by flash column chromatography (7:3 hexanes/EtOAc eluent) to afford tri-β-aminoenone **15** (1.19 g, 79% yield) as an off-white solid. TLC: R_f = 0.34 (7:3 hexanes/EtOAc eluent). ^1H NMR (500 MHz, methanol-d_4): δ 5.26 (s, 0.5H), 5.12 (s, 3H), 4.59 (s, 6H), 4.24 (s, 1H), 2.85−2.68 (comp. m, 8H), 2.51 (q, *J* = 7.5 Hz, 6H), 2.38 (q, *J* = 7.5 Hz, 1H), 2.19 (q, *J* = 7.5 Hz, 6H), 1.28 (t, *J* = 7.5 Hz, 9H), 1.26−1.17 (comp. m, 10.5H), 1.12 (t, *J* = 7.5 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, methanol-d_4): δ 200.5, 170.5, 170.4, 169.5, 145.83, 145.77, 145.3, 133.4, 133.2, 133.1, 93.2, 93.1, 91.6, 42.9, 41.91 37.8, 35.7, 35.6, 27.5, 26.3, 24.09, 24.05, 24.01, 16.64, 16.58, 16.5, 14.1, 12.38, 12.37, 10.90, 10.85. IR (film): ν 2972, 2935, 2877, 1607, 1559, 1497, 1236, 1170, 1075, 730 cm^{-1}. HRMS (ESI+) *m/z*: calc'd for $(M + H)^+$ $[C_{36}H_{57}N_3O_3 + H]^+$, 580.4473; found, 580.4479. Note that the ^1H NMR of tri-β-aminoenone **15** in methanol-d_4 was observed as a mixture of two C_{3v} symmetric species. The ^{13}C NMR of tri-β-aminoenone **15** in methanol-d_4 was observed as a mixture of C_{3v} and C_s symmetric species.

Tri-β-aminoenone ***16***. Triamine **8** (160 mg, 640 μmol) and 2,6-dimethylheptane-3,5-dione (330 μL, 1.92 mmol) dissolved in THF (6.5 mL) were stirred and heated at 65 °C in an oil bath for 2 days. Upon completion as determined by TLC, the resulting yellow solution was cooled to ambient temperature and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3:1 hexanes/EtOAc eluent) to afford tri-β-aminoenone **16** (210 mg, 42% yield) as a colorless oil. TLC: R_f = 0.43 (3:1 hexanes/EtOAc eluent). ^1H NMR (500 MHz, $CDCl_3$): δ 5.16 (s, 3H), 4.63 (s, 6H), 3.07 (sep, 3H), 2.81 (q, *J* = 7.1 Hz, 6H), 2.40 (sep, 3H), 1.74 (d, *J* = 6.0 Hz, 18H), 1.21 (t, 9H), 1.00 (d, *J* = 6.2 Hz, 18H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 203.6, 174.5, 174.4, 145.3, 133.0, 88.8, 88.6, 88.4, 41.3, 40.7, 40.5, 30.4 30.2, 29.6, 24.0, 21.5, 20.4, 20.33, 20.29, 20.25, 16.50, 16.47. IR (film): ν 2968, 2934, 2874, 1601, 1573, 1469, 1263, 1152, 1073 cm^{-1}. HRMS (ESI+) *m/z*: calc'd for $(M + H)^+$ $[C_{49}H_{69}N_3O_3 + H]^+$, 664.5412; found, 664.5408.

Cyclophane ***1***. In an N_2-filled glovebox, a scintillation vial was charged with tri-β-aminoenone **14** (40.0 mg, 87.0 μmol), triamine **8** (21.9 mg, 87.9 μmol), *p*-toluenesulfonic acid (2.5 mg, 13.5 μmol), 3 Å molecular sieves (60 mg), and fluorobenzene (0.51 mL). The mixture was then sealed and heated at 100 °C in an oil bath for 48 h. The reaction was then concentrated and then analyzed by ^1H NMR, indicating a 57% NMR yield of cyclophane **1**.

Cyclophane ***26***. In an N_2-filled glovebox, a scintillation vial was charged with tri-β-aminoenone **15** (60.0 mg, 103 μmol), triamine **8** (26.1 mg, 105 μmol), *p*-toluenesulfonic acid (2.9 mg, 15.0 μmol), 3 Å molecular sieves (60 mg), and fluorobenzene (0.51 mL). The mixture was then sealed and heated at 100 °C in an oil bath for 48 h. The crude reaction mixture was analyzed by ^1H NMR, which indicated a ∼5% conversion to cyclophane **26**.

Cyclophane ***1*** *and Cyclophane* ***23***. In an N_2-filled glovebox, a scintillation vial was charged with tri-β-aminoenone **14** (100 mg, 218 μmol), triamine **22** (45.6 mg, 220 μmol), *p*-toluenesulfonic acid (6.2 mg, 32.7 μmol), 3 Å molecular sieves (750 mg), and fluorobenzene (1.1 mL). The mixture was then sealed with a Teflon cap, brought outside the box, and heated at 100 °C in an oil bath for 48 h. The crude reaction mixture was concentrated and analyzed by ^1H NMR, which indicated a 24% NMR yield to cyclophane **1** and 8% NMR yield to cyclophane **23**.

Cyclophane ***1***. Triamine **8** (16.2 g, 65.0 mmol) and acetylacetone ethylene glycol monoketal and its corresponding diketal (**40**, 25.5 g, 57% monoketal, 101 mmol) dissolved in methanol (60 mL) were stirred and heated at 65 °C in an oil bath for 5 h. Upon completion as determined by TLC, the resulting suspension was filtered, and the precipitate was dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. Cyclophane **1** was isolated as an off-white solid (16.6 g, 75% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 4.60 (s, 3H), 4.26 (s, 12H), 2.50 (q, *J* = 7.5 Hz, 12H), 2.01 (s, 18H), 1.07 (t, *J* = 7.5 Hz, 18H). The remainder of this compound's characterization data was previously reported.[14]

Cyclophane ***26***. Triamine **8** (144 mg, 581 μmol) and heptane-3,5-dione ethylene glycol monoketal (**41**, 150 mg, 871 μmol) dissolved in methanol (2.9 mL) were stirred and heated to 65 °C in an oil bath for 48 h. Upon completion as determined by TLC, the resulting suspension was filtered, and the precipitate was dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. Cyclophane **26** was isolated as a grey solid (114 mg, 51% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 10.54 (s, 3H), 4.60 (s, 3H), 4.29 (s, 12H), 2.51 (t, *J* = 7.6 Hz, 12H), 2.38 (t, *J* = 7.6 Hz, 12H), 1.22 (t, *J* = 7.6 Hz, 18H), 1.07 (t, *J* = 7.6 Hz, 18H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.1, 142.4, 133.4, 89.8, 44.3, 26.4, 22.7, 16.2, 12.4. IR (film): ν 2967, 2933, 2875, 1619, 1554, 1483, 1341, 1073, 1050, 755 cm^{-1}. HRMS (ESI+) *m/z*: calc'd for $(M + H)^+$ $[C_{51}H_{78}N_6 + H]^+$, 775.6361; found, 775.6302.

Cyclophane ***23***. Triamine **22** (100 mg, 482 μmol) and acetylacetone ethylene glycol monoketal and its corresponding diketal (**40**, 112 mg, 93% monoketal, 724 μmol) dissolved in methanol (2.4 mL) were stirred and heated at 65 °C in an oil bath for 22 h. Upon

https://dx.doi.org/10.1021/acs.joc.0c01708
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completion as determined by TLC, the resulting suspension was filtered, and the precipitate was dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. Cyclophane **23** was isolated as a beige powder (74.5 mg, 51% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.79 (br s, 3H), 4.64 (s, 3H), 4.20 (s, 12H), 2.13 (s, 18H), 2.02 (s, 18H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 160.7, 135.5, 133.5, 93.5, 45.9, 19.8, 14.7. IR (film): ν 2883, 1618, 1548, 1491, 1435, 1379, 1329, 1023, 727 cm^{-1}. HRMS (ESI+) *m/z*: calc'd for $(M + H)^+$ $[C_{39}H_{54}N_6 + H]^+$, 607.4483; found, 607.4473.

Cyclophane 28. Triamine **22** (50.0 mg, 241 μmol) and heptane-3,5-dione ethylene glycol monoketal (**41**, 62.3 mg, 362 μmol) dissolved in methanol (1.2 mL) were stirred and heated to 65 °C in an oil bath for 14 h. Upon completion as determined by TLC, the resulting suspension was filtered, and the precipitate was dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. Cyclophane **28** was isolated as a yellow solid (50.7 mg, 61% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.96 (s, 3H), 4.64 (s, 3H), 4.23 (s, 12H), 2.39 (q, J = 7.5 Hz, 12H), 2.13 (s, 18H), 1.22 (t, J = 7.5 Hz, 18H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 166.0, 135.7, 133.7, 89.5, 45.3, 26.2, 15.1, 12.3. IR (film): ν 2968, 2880, 1613, 1547, 1485, 1341, 1275, 1050, 736 cm^{-1}. HRMS (ESI+) *m/z*: calc'd for $(M + H)^+$ $[C_{45}H_{66}N_6 + H]^+$, 691.5422; found, 691.5554.

Cyclophane 29. 1,3,5-tri(aminomethyl)-2,4,6-trimethoxybenzene (3.54 g, 13.9 mmol) and acetylacetone ethylene glycol monoketal and its corresponding diketal (**40**, 10.9 g, 57% monoketal, 43.1 mmol) dissolved in methanol (13 mL) were stirred and heated at 65 °C in an oil bath for 2 d. Upon completion as determined by TLC, the resulting suspension was filtered, and the precipitate was dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. Cyclophane **29** was isolated as a pale-yellow powder (3.18 g, 65% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.48 (br s, 3 H), 4.56 (s, 3 H), 4.31 (s, 12 H), 3.64 (s, 18 H), 2.03 (s, 18 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 160.0, 158.8, 123.3, 93.8, 63.8, 40.8, 20.2. IR (film): ν 1619, 1587, 1550, 1437, 1419, 1338, 1236, 1109, 1008, 719 cm^{-1}. HRMS (ESI$^+$) *m/z*: calc'd for $(M + H)^+$ $[C_{39}H_{54}N_6O_6 + H]^+$, 703.4183; found, 703.4197.

Cyclophane 30. 1,3,5-tri(aminomethyl)-2,4,6-trimethoxybenzene (76.9 mg, 301 μmol) and heptane-3,5-dione ethylene glycol monoketal (**41**, 77.8 mg, 0.452 mmol) dissolved in methanol (1.5 mL) were stirred and heated to 65 °C in an oil bath for 48 h. Upon completion as determined by TLC, the resulting suspension was filtered, and the precipitate was dried at 60 °C in an oil bath for 2 h under reduced pressure affording an analytically pure material. Cyclophane **30** was isolated as an off-white solid (55.7 mg, 47% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.50 (s, 3H), 4.56 (s, 3H), 4.34 (s, 6H), 3.64 (s, 18H), 2.38 (q, J = 7.5 Hz, 12H), 1.23 (t, J = 7.5 Hz, 18H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.3, 158.9, 123.4, 90.3, 63.8, 40.1, 26.6, 12.5. IR (film): ν 2971, 2939, 1618, 1552, 1460, 1422, 1239, 1102, 1045, 803, 728, 636 cm^{-1}. HRMS (ESI+) *m/z*: calc'd for $(M + H)^+$ $[C_{45}H_{66}N_6O_6 + H]^+$, 787.5117; found, 787.5151.

Cyclophane 27. 1,3,5-Tri(aminomethyl)benzene (350 mg, 2.12 mmol) and acetylacetone ethylene glycol monoketal and its corresponding diketal (**40**, 486 mg, 93% monoketal, 3.15 mmol) dissolved in methanol (21 mL) were stirred and heated at 65 °C in an oil bath for 16 h. Upon completion as determined by TLC, the resulting suspension was filtered producing a beige solid (230 mg). ^{1}H NMR analysis of this material suggested ~40% cyclophane **27** and ~60% unidentified material suggesting a crude yield of ~17%. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.09 (s, 3H), 6.94 (s, 6H), 4.58 (s, 3H), 4.19 (s, 12H), 1.97 (s, 18H).

Cyclophane 34. In an N_2-filled glovebox, a scintillation vial charged with a suspension of cyclophane **1** (400 mg, 579 μmol) in THF (5.5 mL) chilled to −30 °C in a fridge was added dropwise with a solution of BnK (248 mg, 1.90 mmol) in THF (5.5 mL) also chilled to −30 °C. The resulting dark purple solution was stirred at rt for 50 min. Then, the solution was cooled to −30 °C and charged with MeI (110 μL, 1.77 mmol) in a single portion. The mixture produced a gray-brown solution upon stirring. This mixture was stirred overnight and then concentrated to a solid. The crude reaction mixture was analyzed by ^{1}H NMR, which indicated a 34% NMR yield of cyclophane **34**.

Cyclophane 34. In an N_2-filled glovebox, triamine **8** (400 mg, 1.60 mmol), 3-methyl-2,4-pentadione (**17**, 270 mg, 2.37 mmol), *p*-toluenesulfonic acid (10.0 mg, 52.8 μmol), 3 Å molecular sieves (1.5 g), and toluene (15 mL) were added to a Teflon-sealed pressure vessel. The reaction was brought out of the glove box and stirred at 115 °C in an oil bath for 4 d, at which point the light−pink reaction mixture was cooled to room temperature and brought into the glove box. The reaction mixture was filtered through a fine-fritted glass funnel equipped with a Celite plug. The frit was washed with toluene (5.0 mL), and the filtrate was dried under reduced pressure to yield a red solid. The addition of methanol (20 mL) resulted in the precipitation of a white solid which was collected by filtering the mixture through a 0.2 μm nylon filter, and the precipitate was rinsed with methanol (3 × 2.0 mL) and then dried under reduced pressure to afford cyclophane **34** (128 mg, 22% yield) as an off-white solid. Single crystals suitable for X-ray diffraction were obtained by slowly evaporating a solution of **34** in toluene. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.64 (br s, 3H), 4.28 (s, 12H), 2.51 (q, J = 7.4 Hz, 12H), 2.11 (s, 18H), 1.96 (s, 9H), 1.08 (t, J = 7.4 Hz, 18H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 159.8, 142.2, 133.4, 94.8, 45.7, 22.8, 16.8, 16.5, 16.2. IR (film): ν 1605, 1528, 1410, 1368, 1341, 1228, 1261, 1060, 996, 783, 729 cm^{-1}. HRMS (ESI$^+$) *m/z*: calc'd for $(M + H)^+$ $[C_{48}H_{72}N_6 + H]^+$, 732.5891; found, 732.5879. Note that cyclophane **34** is sensitive to aqueous conditions.

Tri-β-aminoenone 37. In an Ar-filled glovebox, a 100 mL pressure vessel containing triamine **8** (100 mg, 0.401 mmol), Et_3N (669 μL, 4.81 mmol), and *n*-hexane (40 mL) was charged with $TiCl_4$ (132 μL, 1.20 mmol) generating a purple suspension. The reaction was stirred at ambient temperature for 1 h, and it was then charged with dione **36** (250 μL, 1.20 mmol) changing the mixture to a green suspension. The reaction vessel was sealed, removed from the glovebox, and heated at 80 °C in an oil bath for 2 h. Over this period of time, the reaction changed to an amber yellow suspension. The mixture was charged with CH_2Cl_2 (40 mL) and filtered through a medium-fine filter paper to afford a fluorescent yellow-orange solution, which was concentrated to an oil. The crude material was purified by flash column chromatography (9:1 hexanes/EtOAc eluent) to afford tri-*β*-aminoenone **37** (47.7 mg, 15% yield) as a bright yellow film. Tri-*β*-aminoenone **37**: TLC: R_f = 0.50 (9:1 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.18 (br s, 3H), 5.92 (s, 3H) 4.71 (d, J = 4.5 Hz, 6H), 2.74 (q, J = 7.5 Hz, 6H), 1.21 (t, J = 7. 5 Hz, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 180.2 (q, $^2J_{C,F}$ = 35.4 Hz), 153.0 (q, $^2J_{C,F}$ = 33.1 Hz), 145.9, 130.9, 119.4 (q, $^1J_{C,F}$ = 277.0 Hz), 116.5 (q, $^1J_{C,F}$ = 286.8 Hz), 87.1 (q, $^3J_{C,F}$ = 4.8 Hz), 42.9 (q, $^4J_{C,F}$ = 2.2 Hz), 23.3, 16.1. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ −68.9, −78.5. IR (film): ν 2984, 1654, 1602, 1456, 1273, 1203, 1145, 793, 739 cm^{-1}. HRMS (ESI$^+$) *m/z*: calc'd for $(M + NH_4)^+$ $[C_{30}H_{27}F_{18}N_3O_3 + NH_4]^+$, 837.2103; found, 837.2121.

Monoketal 41. A 150 mL flask with an attached Dean−Stark apparatus and condenser was charged with a solution of heptane-3,5-dione (4.21 mL, 31.2 mmol), ethylene glycol (1.75 mL, 31.2 mmol), PTSA·H_2O (593 mg, 3.12 mmol), and benzene (80 mL). The mixture was gently refluxed and stirred for 4 d in an oil bath. Upon completion as determined by TLC, the reaction mixture was charged with saturated $NaHCO_3$ solution (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organics were washed with brine (50 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (4:1 hexanes/Et_2O eluent) to afford monoketal **41** (1.74 g, 36% yield) as a colorless oil. TLC: R_f = 0.28 (4:1 hexanes/Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (app. s., 4H), 2.71 (s, 2H), 2.51 (q, J = 7.2 Hz, 2H), 1.71 (q, J = 7.4 Hz, 2H), 1.01 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 208.7, 110.2, 65.1, 49.3, 37.7, 30.8, 8.0, 7.7. IR (film): ν 2966, 2878, 1709, 1259, 1083, 1037, 952, 861, 794 cm^{-1}. HRMS (ESI$^+$) *m/z*: calc'd for $(M + Na)^+$ $[C_9H_{16}O_3 + Na]^+$, 195.0992; found, 195.0987.

https://dx.doi.org/10.1021/acs.joc.0c01708
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Monoketal **42**. A 150 mL flask with an attached Dean–Stark apparatus and condenser was charged with 2,6-dimethylheptane-3,5-dione (3.30 mL, 19.2 mmol), ethylene glycol (1.07 mL, 19.2 mmol), PTSA·H_2O (36.5 mg, 192 μmol), and benzene (50 mL). The mixture was gently refluxed and stirred for 2 d in an oil bath. Upon completion as determined by TLC, the reaction mixture was charged with a saturated $NaHCO_3$ solution (100 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash column chromatography (10:1 pentane/Et_2O eluent) to afford monoketal **42** (1.48 g, 38% yield) as a colorless oil. TLC: R_f = 0.28 (10:1 pentane/Et_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.93–3.80 (comp. m., 4H), 2.72 (s, 2H), 2.68 (sep, J = 7.0 Hz, 1H), 1.96 (sep, J = 6.9 Hz, 1H), 0.99 (d, J = 7.0 Hz, 6H), 0.87 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 212.1, 112.5, 65.3, 44.7, 41.8, 35.7, 18.0, 17.0. IR (film): ν 2969, 2878, 1707, 1611, 1467, 1076, 1042, 951, 794 cm^{-1}. HRMS (ESI$^+$) m/z: calc'd for $(M + Na)^+$ $[C_{12}H_{20}O_3 + Na]^+$, 223.1305; found, 223.1309.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01708.

Spectroscopic characterization and crystallographic date for the reported compounds (PDF)

X-ray crystallographic data for tri-β-aminoenone **14** and cyclophane **34** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

L.J.M. acknowledges the University of Florida departmental instrumentation award (NSF CHE-1048604) and awards from NSF (CHE-1464876) and the National Institutes of Health (R01-GM123241). The University of Florida Mass Spectrometry Research and Education Center acknowledges an award from the National Institutes of Health (S10 OD021758-01A1). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Yousoon Lee is acknowledged for experimental support.

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