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Nd(OTf)$_3$-Catalyzed Cascade Reactions of Vinylidenecyclopropanes with Enynol: A New Method for the Construction of the 5–7–6 Tricyclic Framework and Its Scope and Limitations

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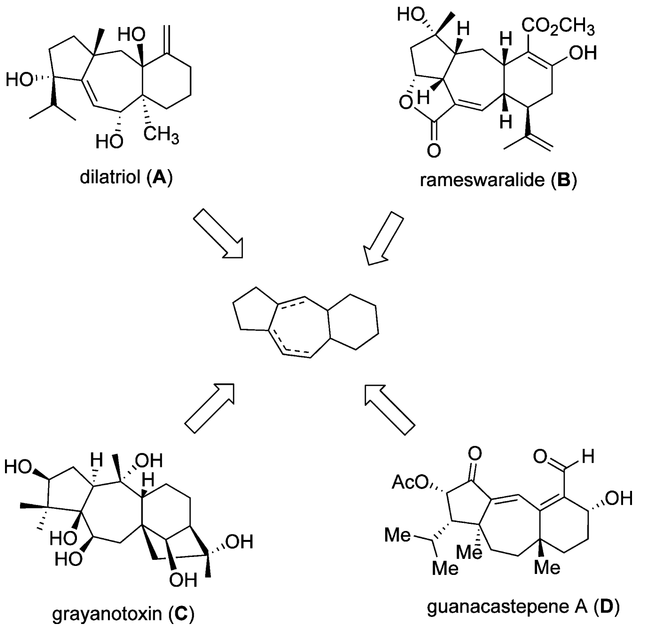
Keywords: Lewis acids / Small ring systems / Fused-ring systems / Enynes

We report in this paper a Lewis acid [Nd(OTf)$_3$]-catalyzed protocol to construct compounds containing a 5–7–6 tricyclic framework in good yield from readily accessible starting materials vinylidenecyclopropanes (VDCPs) **1** and enynols **2a**–**c** under mild conditions. Upon examination of the scope and limitations of this reaction, it was found that the corresponding highly functionalized cyclopentane derivatives could be formed in good yields from the reaction VDCPs **1** and enol **2e** or dienol **2c** under identical conditions.

Introduction

Polycyclic natural products that contain an embedded polyhydroazulene subunit, for example, dilatriol (**A**),[1a] rameswaralide (**B**),[1b] grayanotoxin (**C**),[1c] and guanacastepene A (**D**),[2] possess diverse biological activities. Furthermore, these natural products contain a common 5–7–6 tricyclic framework. By far, the most commonly used strategy in the synthesis of the 5–7–6 framework involves a Ru-catalyzed intramolecular [5+2] cycloaddition reaction involving cyclopropyl enynes.[3] Although this method effectively forms the 5–7–6 ring system, it requires the reaction of complex starting materials with expensive transition-metal catalysts. Considering this result, a much more appealing strategy that accesses the assembly of the 5–7–6 tricyclic framework from readily available starting materials and catalysts is still highly desired.



Vinylidenecyclopropanes (VDCPs) **1**[4] are one of the most remarkable organic compounds known in the area of highly strained small ring systems. They have an allene moiety connected to a cyclopropane ring, and yet, they are thermally stable and reactive substances in organic synthesis. Thermal and photochemical skeletal conversions of VDCPs **1** have attracted much attention from mechanistic, theoretical, spectroscopic, and synthetic viewpoints.[5] Recently, we and others reported the Lewis acid catalyzed reaction of arylvinylidenecyclopropanes with a number of electrophiles such as acetals and imines as well as 3-methoxy-1,3,3-triarylprop-1-yne or 1,1,3-triarylprop-2-yn-1-ol under mild conditions, affording the corresponding products with complex molecular frameworks in good yields.[6] These interesting results have stimulated us to further explore such cascade electrophilic attack, followed by Friedel–Crafts reaction processes with VDCPs as the substrates with a number of interesting electrophiles in the presence of Lewis acids or Brønsted acids. Herein, we wish to present an interesting cascade reaction to construct compounds containing the 5–7–6 tricyclic framework by the Lewis acid catalyzed intermolecular reaction of VDCPs with enynols as well as the results of VDCPs with enol and dienol to show its scope and limitations.

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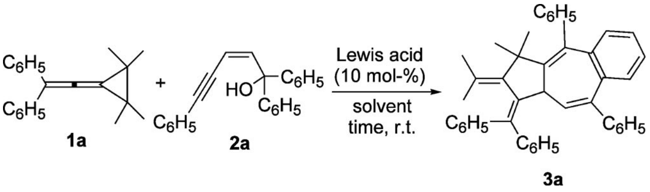
Results and Discussion

In an initial examination, the reaction of arylvinylidenecyclopropane **1a** (0.24 mmol) and enynol **2a** (0.2 mmol)[7] was performed in dichloromethane (DCM) in the presence of $BF_3{\cdot}OEt_2$ (10 mol-%) at room temperature (20 °C) and it was found that product **3a** was obtained in 68% yield after 24 h (Table 1, Entry 1). The structure of **3a** was unambiguously determined by X-ray diffraction (Figure 1).[8] Next, we screened several other Lewis acids and solvents to determine the optimal reaction conditions, and the results of these experiments are summarized in Table 1. The examination of Lewis acid revealed that $Nd(OTf)_3$ was the optimal catalyst for this transformation among others such as $Sc(OTf)_3$, $Zr(OTf)_4$, $Zn(NTf_2)_2$, $Sm(OTf)_3$, and TMSOTf, as well as the Brønsted acid trifluoromethanesulfonic acid (CF_3SO_3H, TfOH) (Table 1, Entries 2–8). Meanwhile, we also found that DCM was the most suitable solvent in this reaction (Table 1, Entries 9–12). Moreover, adjustment of the ratio of **1a**/**2a** from 1.2:1 to 1:1.2 improved the yield of **3a** slightly, affording **3a** in 93% yield under identical conditions (Table 1, Entry 13). Therefore, the optimized reaction conditions involve carrying out the reaction in DCM at room temperature by using **1a** (1.0 equiv.) and **2a** (1.2 equiv.) as the substrates in the presence of $Nd(OTf)_3$ (10 mol-%).

Table 1. Optimization of the reaction conditions of **1a** and **2a**.



Entry[a]	Lewis acid	Solvent	Time [h]	Yield of **3a** [%][b]
1	$BF_3{\cdot}OEt_2$	DCM	24	68
2	$Sc(OTf)_3$	DCM	32	72
3	$Zr(OTf)_4$	DCM	28	83
4	$Zn(NTf_2)_2$	DCM	29	73
5	$Sm(OTf)_3$	DCM	23	74
6	$Nd(OTf)_3$	DCM	30	91
7	TMSOTf	DCM	12	87
8	TfOH	DCM	19	87
9	$Nd(OTf)_3$	toluene	11	55
10	$Nd(OTf)_3$	DCE	22	72
11	$Nd(OTf)_3$	CH_3CN	24	complex
12	$Nd(OTf)_3$	THF	30	48[c]
13	$Nd(OTf)_3$	DCM	22	93[d]

[a] All reactions were carried out with **1a** (0.24 mmol) and **2a** (0.2 mmol) in various solvents (2.0 mL) in the presence of a variety of Lewis acids (10 mol-%) at room temperature. [b] Isolated yield. [c] The reaction was carried out at 50 °C. [d] The reaction was carried out with **1a** (0.2 mmol) and **2a** (0.24 mmol).

Under these optimized reaction conditions, we then turned our attention to examine the generality of this $Nd(OTf)_3$-catalyzed interesting reaction and the results are summarized in Table 2. It was found that the corresponding tricyclic products **3** were obtained in moderate to excellent yields from a variety of VDCPs **1**. In the case of substrates **1b**, **1c**, **1d**, and **1e**, the corresponding products **3b**, **3c**, **3d**, and **3e** were obtained in excellent yields, and the electronic nature of the substituents on the aromatic rings of **1** did not significantly affect the outcomes of the reactions (Table 2, Entries 1–4). The reaction of unsymmetrical substrates **1f**–**h** with **2a** afforded annelated derivatives **3f**–**h** in moderate to excellent yields as *E*- and *Z*-isomeric mixtures in a ratio of 1:1 to 4:1 (Table 2, Entries 3–7) and the reaction of **1i**, having a monoaliphatic group (R^1 = Et and R^2 = C_6H_5), furnished the corresponding product **3i** in 62% yield as a single stereoisomer with *Z*-configuration on the basis of NOE investigation (see Supporting Information; Table 2, Entry 8). Substrates **1j** and **1k** (R^3 and R^4 are aromatic groups and R^5 and R^6 are hydrogen atoms) could also provide the corresponding products **3j** and **3k** in 63 and 45% yield, respectively, under the standard conditions (Table 2, Entries 9 and 10). Moreover, using aliphatic VDCP **1l** as the substrate, in which R^1 and R^2 are butyl groups and R^3 and R^4 are aromatic groups, the corresponding product **3l** was formed in 40% yield along with the recovery of 20% of starting materials (Table 2, Entry 11). By using 2-en-4-yn-1-osl **2b** and **2c** as the substrates, similar reaction outcomes were obtained under identical conditions (Table 2, Entries 12 and 13).

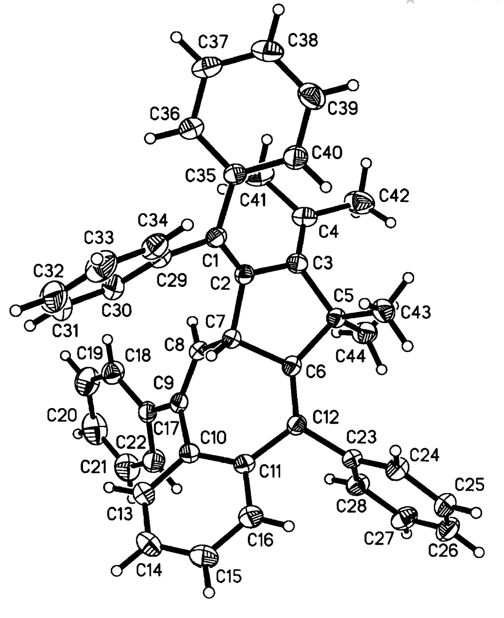
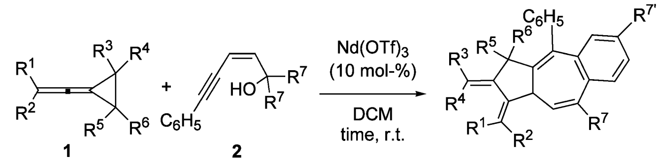


Figure 1. ORTEP drawing of **3a**.

A plausible mechanism for the formation of tricyclic products **3** is outlined in Scheme 1. Initially, the reaction of **2a** with $Nd(OTf)_3$ generates cationic intermediate **A**, which can furnish its mesomeric cationic intermediate **B**. The reaction of intermediate **B** with **1a** gives the corresponding cyclopropyl ring-opened π-allylic cationic intermediate **C**. The reaction of intermediate **B** with **1a** can take place more easily than that of intermediate **A** with **1a** presumably because intermediate **B** is less sterically hindered than intermediate **A**. Intermediate **C**, through intramolecular electrophilic attack, affords intermediate **D**, which undergoes intramolecular Friedel–Crafts reaction to give final product **3a**.

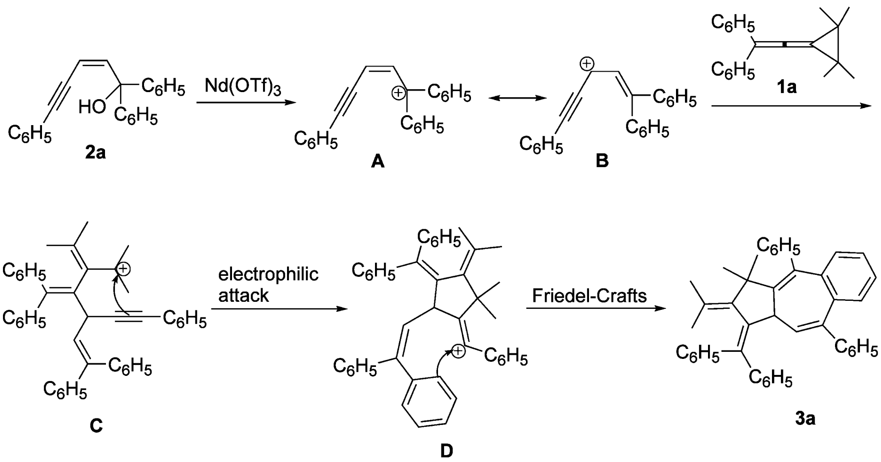
Table 2. Nd(OTf)$_3$-Catalyzed reaction of vinylidenecyclopropanes **1** with enynols **2**.



3, R$^{7'}$ is the substituent on the aromatic group of R^7.

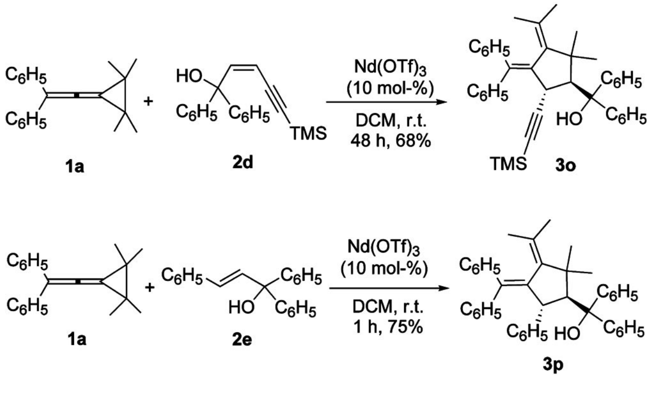
Entry	R^1/R^2/R^3/R^4/R^5/R^6	R^7	Time [h]	Yield of **3** [%]
1	*p*-MeOC$_6$H$_4$/*p*-MeOC$_6$H$_4$/Me/Me/Me/Me, **1b**	C$_6$H$_5$/C$_6$H$_5$, **2a**	30	**3b**, 80
2	*p*-ClC$_6$H$_4$/*p*-ClC$_6$H$_4$/Me/Me/Me/Me, **1c**	**2a**	24	**3c**, 84
3	*p*-MeC$_6$H$_4$/*p*-MeC$_6$H$_4$/Me/Me/Me/Me, **1d**	**2a**	23	**3d**, 84
4	*p*-FC$_6$H$_4$/*p*-FC$_6$H$_4$/Me/Me/Me/Me, **1e**	**2a**	29	**3e**, 94
5	*p*-MeOC$_6$H$_4$/C$_6$H$_5$/Me/Me/Me/Me, **1f**	**2a**	15	**3f**, 75 (61:39)[a]
6	*p*-ClC$_6$H$_4$/C$_6$H$_5$/Me/Me/Me/Me, **1g**	**2a**	24	**3g**, 95 (50:50)[a]
7	*o*-MeC$_6$H$_4$/C$_6$H$_5$/Me/Me/Me/Me, **1h**	**2a**	36	**3h**, 54 (80:20)[a]
8	Et/C$_6$H$_5$/Me/Me/Me/Me, **1i**	**2a**	18	**3i**, 62[b]
9	C$_6$H$_5$/C$_6$H$_5$/C$_6$H$_5$/C$_6$H$_5$/H/H, **1j**	**2a**	6	**3j**, 63
10	C$_6$H$_5$/C$_6$H$_5$/*p*-MeC$_6$H$_4$/*p*-MeC$_6$H$_4$/H/H, **1k**	**2a**	8	**3k**, 45
11	*n*Bu/*n*Bu/C$_6$H$_5$/C$_6$H$_5$/H/H, **1l**	**2a**	48	**3l**, 40[c]
12	**1a**	*p*-MeC$_6$H$_4$, **2b**	48	**3m**, 88
13	**1a**	*p*-MeOC$_6$H$_4$, **2c**	24	**3n**, 71

[a] The ratio of *E*/*Z* or *Z*/*E* was determined on the basis of the ^{1}H NMR spectroscopic data. [b] Isolated as a single stereoisomer on the basis of the ^{1}H NMR spectroscopic data. [c] Compound **1l** was recovered in 20%.



Scheme 1. A plausible mechanism for the formation of **3a**.

Interestingly, by using **2d** as the substrate to react with **1a** under identical conditions, an unexpected product **3o** was formed in 68% yield rather than the desired tricyclic product, perhaps due to the electronic properties of the TMS group (Scheme 2). This result promoted us to examine the reaction of **1a** with several analogues of **2a**. Because the carbon–carbon triple bond of **2d** did not participate in the reaction, we envisaged that the reaction of enol **2e**, in which the alkyne moiety was replaced by phenyl group, with **1a** under identical conditions might produce similar compound **3p** in good yield. The experimental result disclosed that **3p** was indeed obtained in 75% yield as a single diastereoisomer (Scheme 2). The structure of **3p** was unambiguously confirmed by X-ray diffraction (Figure 2).[9]



Scheme 2. The reaction of **1a** with **2d** and **2e**.

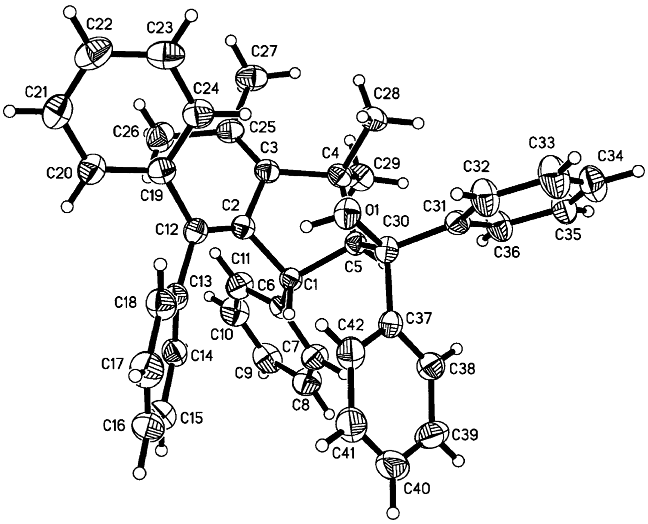
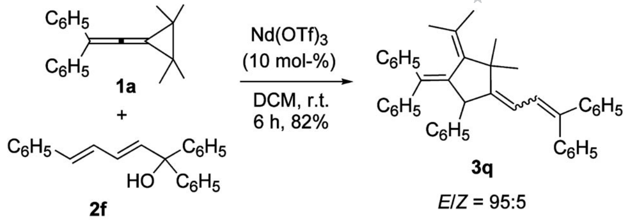


Figure 2. ORTEP drawing of **3p**.



Scheme 3. The reaction of **1a** with **2f**.

In order to further understand the scope and limitations of this reaction, we introduced another carbon–carbon double bond into enol **2e**, namely, by using 2,4-dien-1-ol **2f** as the substrate to examine the reaction outcome. It was found that the reaction of **1a** with **2f** under identical conditions afforded product **3q** in 82% yield with high geometric selectivity (E/Z = 95:5) (Scheme 3). The structure of major product (E)-**3q** was confirmed by X-ray diffraction analysis (Figure 3).[10]

A plausible mechanism for the formation of **3p** and **3q** was depicted in Scheme 4. Initially, the treatment of **2e** or **2f** with Nd(OTf)$_3$ gives cationic intermediate **E**. Intermedi-

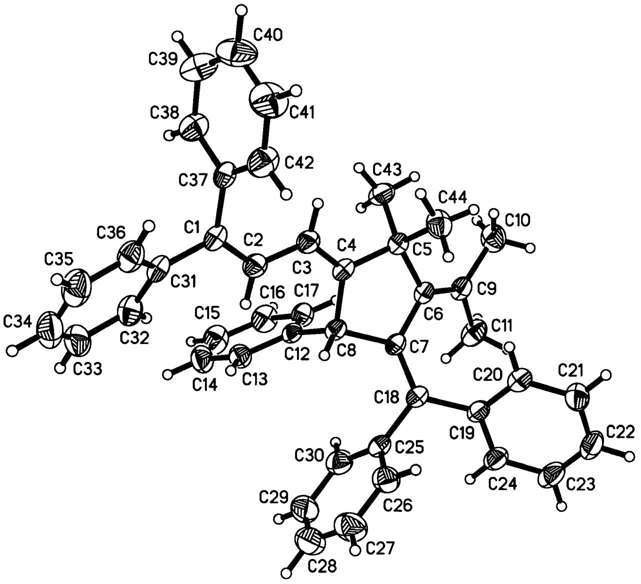
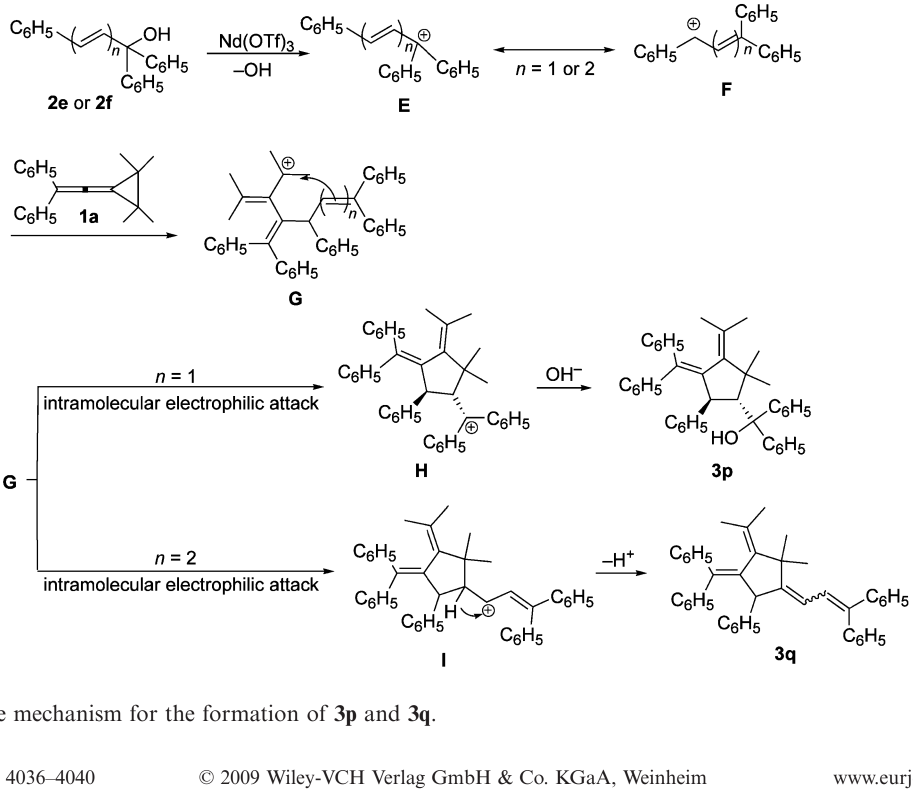


Figure 3. ORTEP drawing of **3q**.



Scheme 4. A plausible mechanism for the formation of **3p** and **3q**.

ate **E** produces its mesomeric intermediate **F**. The reaction of intermediate **F** with **1a** affords cyclopropyl ring-opened π-allylic cationic intermediate **G**, which can either furnish intermediate **H** ($n = 1$) or produce intermediate **I** ($n = 2$) by intramolecular electrophilic attack. Nucleophilic attack by the in situ generated H_2O at intermediate **H** affords final product **3p**. In contrast, intermediate **I** undergoes deprotonation to afford final product **3q**.

Conclusions

In summary, we have developed an effective Lewis acid catalyzed protocol to construct compounds containing a 5–7–6 tricyclic framework in good yields from readily accessible starting materials vinylidenecyclopropanes **1** and enynols **2a**–**c** under mild conditions. This method provides an alternative way to access natural products containing the 5–7–6 tricyclic framework. Upon examination of the scope and limitations of this reaction, it was found that the corresponding highly functionalized cyclopentane derivatives could be formed in good yields from the reaction of **1** and enol **2e** or dienol **2f** under identical conditions. Plausible mechanisms for all of these transformations have been discussed on the basis of the obtained results. Efforts are in progress to elucidate further the mechanistic details and to understand the scope and limitations of these reactions.

Experimental Section

Typical Procedure for the Reaction of Vinylidenecyclopropanes 1 with (*Z*)-1,1,5-Triarylpent-2-en-4-yn-1-ols 2: To a solution of **1a** (55 mg, 0.2 mmol) and **2a** (74 mg, 0.24 mmol) dissolved in DCM (2.0 mL) was added then $Nd(OTf)_3$ (10 mol-%). The mixture was stirred for 22 h at room temperature (25 °C). The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 500:1) to give **3a** (105 mg, 93%) as a white solid.

CCDC-710597 (for **3a**), -721041 (for **3p**), and -733543 (for **3q**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for **2a**–**d** and **3a**–**q**.

Acknowledgments

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[8] Crystal data for **3a** (CCDC-710597): Empirical formula: $C_{44}H_{38}$; *Fw* 566.74; crystal size: $0.269 \times 0.245 \times 0.210$; crystal color, habit: colorless, prismatic; crystal system: triclinic; lattice type: primitive; lattice parameters: $a = 9.7927(8)$ Å, $b = 10.7809(8)$ Å, $c = 15.4960(12)$ Å, $\alpha = 87.2820(10)°$, $\beta = 89.996(2)°$, $\gamma = 85.610(2)°$, $V = 1629.3(2)$ Å^3; space group: $P\bar{1}$; $Z = 2$; $D_{calcd.} = 1.155$ g cm^{-3}; $F(000) = 604$; $R_1 = 0.0604$, $wR_2 = 0.1428$. Diffractometer: Rigaku AFC7R.

[9] Crystal data for **3p** (CCDC-721041): Empirical formula: $C_{42}H_{40}O$; *Fw*: 560.74; crystal size: $0.350 \times 0.313 \times 0.187$; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; lattice parameters: $a = 10.4101(9)$ Å, $b = 26.298(2)$ Å, $c = 11.7200(10)$ Å, $\alpha = 90°$, $\beta = 91.473(2)°$, $\gamma = 90°$, $V = 3207.5(5)$ Å^3; space group: $P2_1/c$; $Z = 4$; $D_{calcd.} = 1.161$ g cm^{-3}; $F(000) = 1200$; $R_1 = 0.0528$, $wR_2 = 0.0960$. Diffractometer: Rigaku AFC7R.

[10] Crystal data for **3q** (CCDC-733543): Empirical formula: $C_{44}H_{40}$; *Fw*: 568.76; crystal size: $0.408 \times 0357 \times 0.211$; crystal color, habit: colorless, prismatic; crystal system: triclinic; lattice type: primitive; lattice parameters: $a = 10.5111(10)$ Å, $b = 11.6798(12)$ Å, $c = 14.4855(15)$ Å, $\alpha = 85.297(2)°$, $\beta = 71.728(2)°$, $\gamma = 83.183(2)°$, $V = 1674.9(3)$ Å^3; space group: $P\bar{1}$; $Z = 2$; $D_{calcd.} = 1.128$ g cm^{-3}; $F(000) = 608$; $R_1 = 0.0540$, $wR_2 = 0.1282$. Diffractometer: Rigaku AFC7R.

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