

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/12030608>

ChemInform Abstract: Palladium-Catalyzed Highly Chemo- and Regioselective Formal [2 + 2 + 2] Sequential Cycloaddition of Alkynes: A Renaissance of the Well Known Trimerization Reac...

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · SEPTEMBER 2010

Impact Factor: 4.72 · DOI: 10.1002/chin.200136038 · Source: PubMed

CITATIONS

32

READS

47

6 AUTHORS, INCLUDING:



Michael Rubin

University of Kansas

85 PUBLICATIONS 2,079 CITATIONS

SEE PROFILE

Palladium-Catalyzed Highly Chemo- and Regioselective Formal [2 + 2 + 2] Sequential Cycloaddition of Alkynes: A Renaissance of the Well Known Trimerization Reaction?[†]

Vladimir Gevorgyan,^{*,‡} Ukkiramapandian Radhakrishnan,^{§,⊥} Akira Takeda,[§] Marina Rubina,[‡] Michael Rubin,[‡] and Yoshinori Yamamoto^{*,§}

Department of Chemistry, University of Illinois at Chicago, 845 Taylor Street, Chicago, Illinois 60607-7061, and Department of Chemistry, Graduate School of Science Tohoku University, Sendai 980-8578, Japan

vlad@uic.edu

Received January 13, 2001

A new concept of highly chemo- and regioselective formation of the benzene ring by a palladium-catalyzed formal [2 + 2 + 2] sequential intermolecular trimerization of alkynes is proposed. Homodimerization of terminal alkynes and subsequent [4 + 2] benzannulation with diynes gives tetrasubstituted benzenes in moderate to good yields. The introduction of two different alkynes (terminal and internal) in the first step of the sequence allows for construction of pentasubstituted benzenes from *three different* acyclic acetylenic units. In all cases the tetra- and pentasubstituted benzenes are formed as a single reaction product without being accompanied by any of regio- or chemoisomers. A significant acceleration of the sequential trimerization reaction in the presence of Lewis acid/phosphine combined system was observed. Mechanistic studies reveal that the Lewis acid assisted isomerization of the E-enyne formed in the first step of the sequence to the more reactive Z-isomer is responsible for the observed acceleration effect. The proposed methodology provides a conceptually new and synthetically useful route to multifunctional aromatic compounds.

Introduction

Transition metal catalyzed trimerization of alkynes is one of the most powerful and general methodologies used to assemble the benzene ring.¹ Though known for more than 50 years,² the intermolecular version of this process is still plagued by poor regio- and chemoselectivity, which severely limits the scope of this method. Vollhardt succeeded in solving these problems for several types of intramolecular^{3a} or partially intramolecular^{3b} modes of cyclotrimerization: three new bonds were formed under the cobalt catalysis affording a cyclophane-type aromatic product in a chemo- and regioselective manner. Indeed, a mixture of two regioisomers, 1,2,4- and 1,3,5-trisubstituted benzenes, is usually obtained in the homotrimer-

ization of terminal alkynes, whereas heterotrimerization of three different acetylenes can yield up to 38 possible regio- and chemoisomers. It is generally accepted that the variety of regio- and chemoisomeric products of transition metal catalyzed intermolecular trimerizations of alkynes arises from the variety of different modes of orientation of the alkynes in assembling the metalocyclopentadiene intermediate **i**.¹ Despite enormous efforts to control regio- and chemoselectivity of formation of **i**, little success was achieved for the intermolecular [2 + 2 + 2] cycloaddition reaction.⁴ Recently, Ladipo et al. succeeded in regioselectively trimerizing terminal alkynes to 1,2,4-substituted benzenes using a calixarene-bound titanium complex.⁵ Though the regioselectivity in this cyclotrimerization reaction is rigorously controlled by the steric demand of the calixarene cavity, this method is applicable only to the homotrimerization of terminal alkynes. A different one-pot approach has been recently reported by Takahashi et al.⁶ in which the multisubstituted benzenes were regioselectively synthesized from zirconocyclopentadienes prepared in situ from two different alkynes and a third alkyne. Yet, this method requires the use of stoichiometric amount of two transition metals: Zr and either Cu^{6a} or Ni.^{6b} Consequently, alternative approaches that are both catalytic in transi-

[†] Presented at the 219th American Chemical Society National Meeting, March 2000, San Francisco, CA.

* Ph: (312) 355-3579. Fax: (312) 355-0836.

[‡] University of Illinois at Chicago.

[§] Tohoku University.

[⊥] Present address: Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, UT 84112-0850.

(1) For recent reviews, see: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (c) Trost, B. M. *Science* **1991**, *254*, 1471. (d) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (e) Grotjahn, D. B. *Transition Metal Alkyne Complexes: Transition Metal-Catalyzed Cyclotrimerization*. In *Comprehensive Organometallic Chemistry II*; Wilkinson, Stone, Abel, Eds.; Pergamon: Oxford, 1995; Vol. 12, p 741. (f) Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, *576*, 232. (g) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

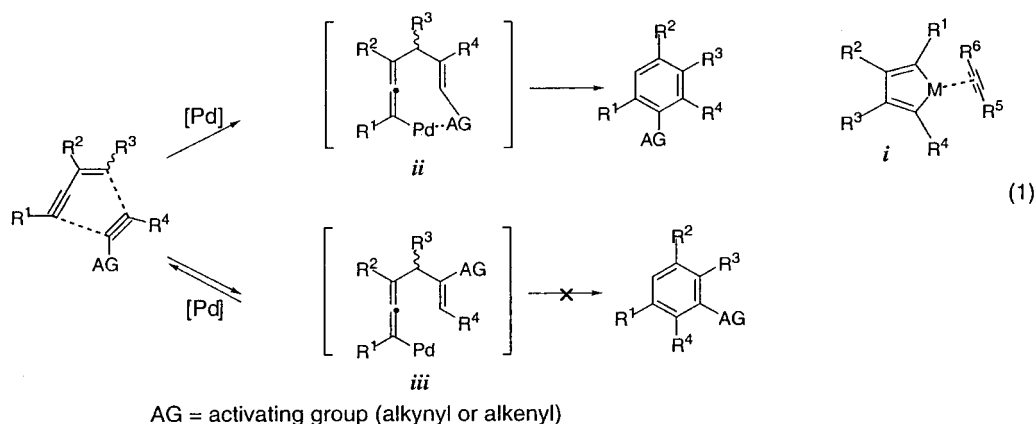
(2) For the first transition metal catalyzed trimerization of alkynes, see: Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1.

(3) For selective intramolecular alkynes trimerization, see for example: (a) Lecker, S. H.; Nguen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 856. For partially intramolecular trimerization, see: (b) Berris, B. C.; Hovakeemian, G. H.; Lai, Y.-H.; Mestdagh, H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1985**, *107*, 5670. See also ref 1 and references therein.

(4) For regioselective stoichiometric reactions of **i** with diphenylacetylene, see: (M = Co) (a) Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* **1974**, 4549. (M = Pd) (b) Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93.

(5) Ozerov, O. V.; Ladipo, F. T.; Patrick, B. O. *J. Am. Chem. Soc.* **1999**, *121*, 7941. Ozerov, O. V.; Patrick, B. O.; Ladipo, F. T. *J. Am. Chem. Soc.* **2000**, *122*, 6423.

(6) (a) Takahashi, T.; Xi, Z.; Yamazaki, A.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1998**, *120*, 1672. (b) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093.



tion metal and allow for regio- and chemoselective construction of the benzene skeleton from three different alkynes would be exceedingly beneficial.

We recently demonstrated that substituted benzenes could be highly regioselectively^{7b} (and in some cases highly chemoselectively^{7g}) constructed from conjugated enynes and activated alkynes in [4 + 2] fashion in the presence of a Pd(0) catalyst (eq 1). The perfect regiocontrol in this case was achieved through the regiospecific formation of reaction intermediate **ii**, which is favored over its possible regioisomer **iii** as a result of the coordination of palladium to an activating group present in the enynophile (eq 1). Encouraged by successful highly regioselective formation of benzenes from conjugated enynes and activated alkynes⁷ and motivated by the challenging goal of regio- and chemoselective intermolecular trimerization of alkynes, we hypothesized that the new [4 + 2] benzannulation methodology⁷ could be applied to the trimerization process in a sequential fashion. Indeed, a simple retrosynthetic analysis of benzene **iv** intimated its possible assembling in a nonclassical way⁸ (Scheme 1). The proposed new concept of a formal [2 + 2 + 2]

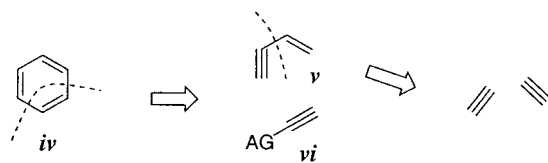
technology to assemble a benzene ring from **vi** and **v**, only the selective formation of conjugated enyne **v** from two alkynes (under the conditions of [4 + 2] benzannulation reaction) would be needed to complete our sequence.⁹

Results and Discussion

Synthesis of 1,2,3,5-Tetrasubstituted Benzenes 3.

To examine the possibility of accomplishing the above-mentioned sequence in the presence of Pd(PPh₃)₄, the following experiment was performed. A mixture of phenylacetylene **1a**, 5,7-dodecadiyne **2a**, and Pd(PPh₃)₄ (5 mol %) was heated in THF (1 mL) for 12 h at 100 °C (method A). The result surpassed all expectations; the tetrasubstituted benzene **3a** was obtained as a sole reaction product in 89% NMR yield (eq 2, Table 1, entry 1). Thus, it is obvious that two molecules of phenylacetylene (**1a**) combined together in the presence of Pd(PPh₃)₄ exclusively in the head-to-tail fashion producing the 2,4-diphenylbut-1-ene-3-yne **4**, which then underwent the [4 + 2] cycloaddition with diyne **2a** to give the tetrasubstituted benzene **3a** as a single chemo- and regioisomer. Furthermore, the formation of enyne **4** was confirmed by GC–MS analysis of the reaction mixture at an early stage, thus unambiguously proving the sequential mode of the observed transformation. Encouraged by the successful sequential trimerization of **1a** with **2a**, we attempted to generalize this methodology with other terminal alkynes and diynes. Thus, methyl propargyl ether **1b** underwent selective trimerization with dibutyl **2a** and diphenyldiyne **2b** to afford the aromatic products **3b** and **3c** respectively, in moderate yields (entries 2 and 3). In contrast to the above cases, the chemoselectivity of analogous reactions using other terminal alkynes under the conditions A did not appear to be perfect. Thus, **1c–f** at the first stage of the sequence produced not only the homodimers **4** but also detectable amounts of the adducts with diyne **2**. These adducts then underwent the benzannulation to give 5–7% of the corresponding chemoisomers together with the major aromatic product **3**, hence decreasing an overall chemoselectivity of the sequential process. It was thought that this low chemoselectivity of alkyne dimerization was due to the rather

Scheme 1. Concept of Formal [2 + 2 + 2] Sequential Trimerization of Alkynes



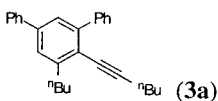
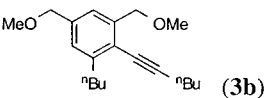
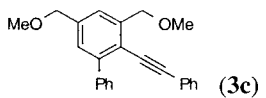
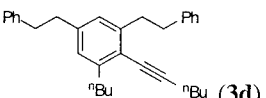
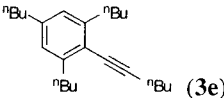
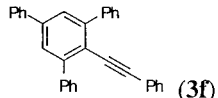
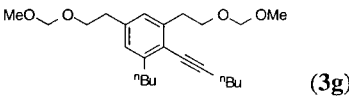
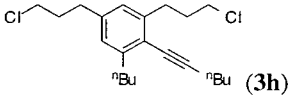
alkyne trimerization sequence presumes consecutive dimerization of two alkynes to form a conjugated enyne **v**, which undergoes subsequent [4 + 2] benzannulation with an enynophile **vi** under the same reaction conditions to give benzene **iv** (Scheme 1). Since we already have the

(7) (a) Saito, S.; Salter, M. M.; Gevorgyan, V.; Tsuboya, N.; Tando, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3970. (b) Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11313. (c) Gevorgyan, V.; Sadayori, N.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 8603. (d) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1244. (e) Weibel, D.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1217. (f) Gevorgyan, V.; Tando, K.; Uchiyama, N.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 7022. (g) Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, U.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 6391. (h) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 568. (i) Saito, S.; Uchiyama, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 4338.

(8) For the thermal and/or Lewis acids catalyzed intramolecular enyne–alkyne benzannulation, see: (a) Danheiser, R. L.; Gould, A. E.; Fernandez, de la Predilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514. (b) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917.

(9) Although various transition metals including Pd(II)¹⁰ are known to catalyze selective dimerization of alkynes, to the best of our knowledge, there are no reports in the literature concerning the use of Pd(PPh₃)₄ in this reaction. For Pd(PPh₃)₄-catalyzed dimerization of silylacetylenes, see: Ishikawa, M.; Ohshita, J. *J. Organomet. Chem.* **1988**, *346*, C58.

Table 1. Synthesis of Tetrasubstituted Benzenes **3a–h** via Sequential Homodimerization of Terminal Alkynes **1**/[4 + 2] Benzannulation with Diynes **2**

entry	Alkyne 1 R ¹	Diyne 2 R ²	Product 3	Method ^a	Time/Temp (h/°C)	Yield (%) ^b
1	Ph (1a)	ⁿ Bu (2a)	 (3a)	A	12/100	89 ^c
2	MeOCH ₂ (1b)	(2a)	 (3b)	A	21/100	56
3	(1b)	Ph(2b)	 (3c)	A	21/100	48
4	(1a)	(2a)	(3a)	B	54/25	82
5	Ph(CH ₂) ₂ (1c)	(2a)	 (3d)	B	72/25→30/60	56
6	ⁿ Bu (1d)	(2a)	 (3e)	B	72/60	59
7	(1a)	(2b)	 (3f)	B	53/60	65
8	MOMO(CH ₂) ₂ (1e)	(2a)	 (3g)	B	72/25	54
9	Cl(CH ₂) ₃ (1f)	(2a)	 (3h)	B	72/25	64

^a For the exact procedures see text and the Experimental Section. ^b Isolated yield. ^c NMR yield.

harsh conditions of method **A**. After optimization, it was found that a Pd₂(dba)₃·CHCl₃/(*o*-Tol)₃P combination enables both sequence steps to be effectively catalyzed at 25–60 °C (method **B**). Reactions of all the terminal alkynes tested under these conditions proceeded in an absolutely regio- and chemoselective manner to afford the desired benzenes **3** in moderate to good chemical yields (Table 1, entries 4–9). It should be noted that for all cases, no traces of any other regio- or chemoisomers of **3** were detected by GC–MS and NMR analyses of the crude reaction mixtures.

Synthesis of 1,2,3,4,5-Pentasubstituted Benzenes **6**.

Inspired by the successful preparation of tetrasubsti-

tuted benzenes **3** via the sequential homodimerization–benzannulation motif, we wished to combine two different alkynes in the first step of the sequential process. If regio- and chemoselectivity of alkyne cross-coupling could be controlled, this reaction mode would allow for the synthesis of polysubstituted benzene from three different acetylenic units. A literature search indicated that the selective cross-coupling of alkynes is possible. Trost et al. demonstrated that 1,2,4-trisubstituted enynes could be efficiently prepared via selective *syn*-addition of a terminal alkyne (donor alkyne) to an internal alkyne, possessing an electron-withdrawing group (acceptor alkyne), in the presence of a Pd(OAc)₂/TDMPP catalyst

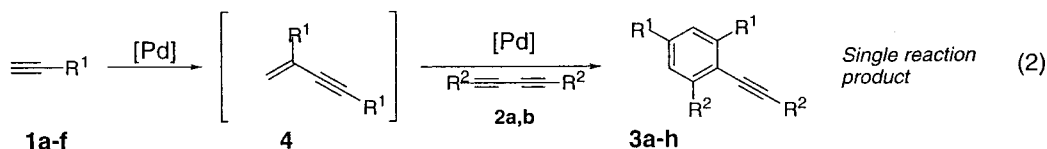
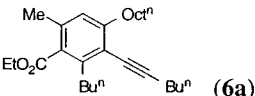
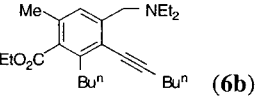
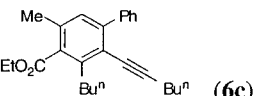
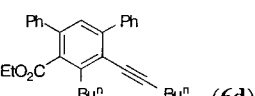
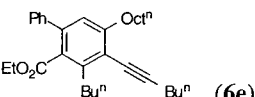
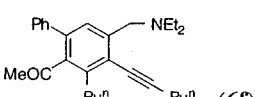
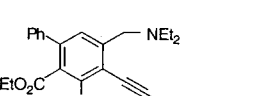

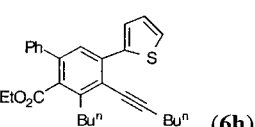


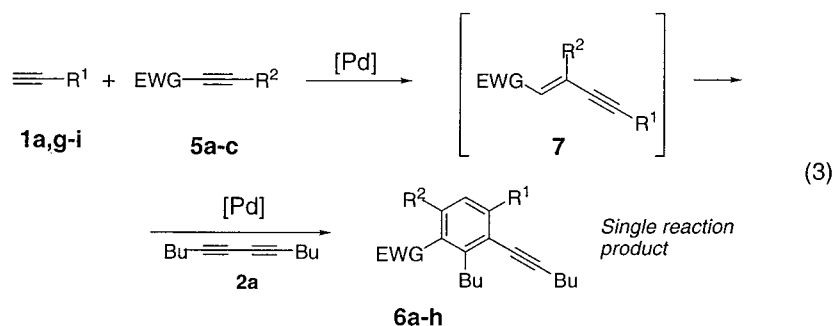
Table 2. Synthesis of Pentasubstituted Benzenes 6a–h via Sequential Cross-Coupling of Terminal Alkynes 1 with Internal Alkynes 5/[4 + 2] Benzannulation with 5,7-Dodecadiyne 2a

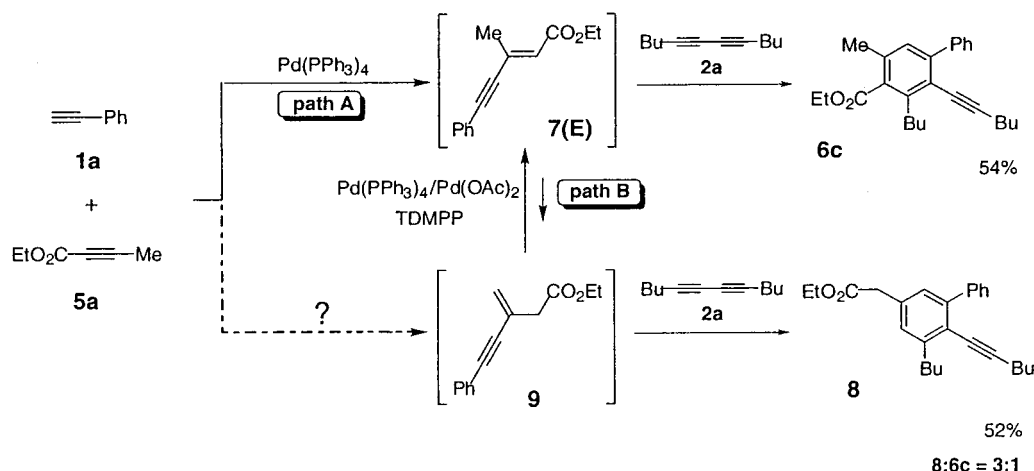
entry	Alkyne 1 R ¹	Alkyne 5 R ² EWG	Product 6	Method ^a	Time/Temp (h/°C)	Yield (%) ^b
1	ⁿ Oct (1g)	Me CO ₂ Et (5a)	 (6a)	A	144/100	60 ^c
2	Et ₂ NCH ₂ (1h)	(5a)	 (6b)	A	96/100	50
3	Ph (1a)	(5a)	 (6c)	A	24/50→120/100	54
4	(1a)	Ph CO ₂ Et (5b)	 (6d)	A	24/50→120/100	55
5	(1g)	(5b)	 (6e)	C	17/25→72/100	61
6	(1h)	Ph COMe (5c)	 (6f)	C	24/25→72/100	50
7	(1h)	(5b)	 (6g)	C	24/25→72/100	53
8	 (1i)	(5b)	 (6h)	C	24/25→72/100	52

^a For the exact procedures see text and the Experimental Section. ^b Isolated yield. ^c NMR yield.

system.¹⁰ Accordingly, we applied this donor/acceptor alkyne cross-coupling concept as the first step in our sequential strategy (eq 3, Table 2). We discovered that in the presence of Pd(PPh₃)₄ (method A), 1-decyne (**1g**), and 1,1-diethylpropargylamine (**1h**) (donor alkynes) selectively coupled with ethylbutynoate (**5a**) (acceptor alkyne) to form trisubstituted enynes **7**, which then

reacted with diyne **2a** to give the pentasubstituted alkylbenzene **6a** and benzylamine derivative **6b**, respectively (entries 1 and 2). Method A was also used for sequential trimerization of **1a** with **5a,b** and **2a** to afford the bis-aryls **6c,d** (entries 3 and 4). Furthermore, combined method C provided the best chemoselectivity for the formation of the pentasubstituted benzenes **6e–h**



Scheme 2. Formation of Tetrasubstituted Benzene **8** via Sequential Trimerization of **1a**, **5a**, and **2a** in the Presence of the $\text{Pd}(\text{PPh}_3)_4/\text{Pd}(\text{OAc})_2/\text{TDMPP}$ Catalytic System (Method C)

(Table 2, entries 5–8). In all cases the pentasubstituted benzenes **6a–h** were obtained as a single reaction product, though in moderate yields.

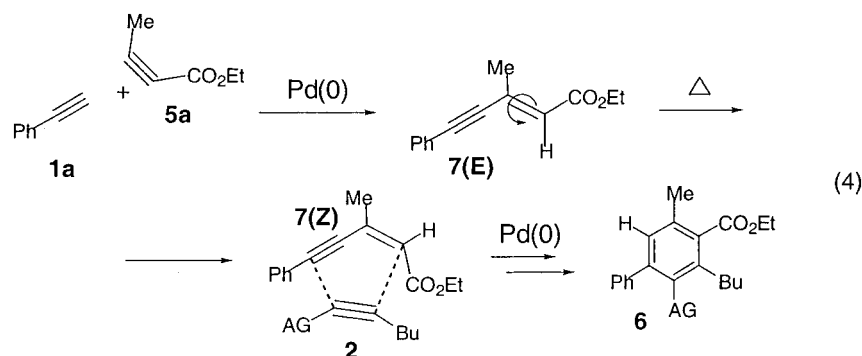
Normally, palladium-catalyzed sequential [2 + 2 + 2] benzannulation of alkynes **1a**, **5a**, and **2a** yielded pentasubstituted benzene **6c** (Path A, Scheme 2, eq 3, Table 2, entry 3). Unexpectedly, employment of method C for the benzannulation of **1a**, **5a**, and **2a** produced the tetrasubstituted benzene **8** as the major reaction product accompanied by a small amount of **6c** (Scheme 2, Path B). It was assumed that the TDMPP-assisted isomerization of double bond **7(E)** \leftrightarrow **9** is responsible for the formation of the tetrasubstituted benzene **8** (Path B, Scheme 2). To prove this idea, an authentic sample **9** was synthesized and subjected to the benzannulation reaction with diyne **2a** under TDMPP-free conditions (Method A). As a result, the tetrasubstituted benzene **8** was obtained in 73% yield as a single reaction product, thus supporting the above proposal. As a working hypothesis, one may propose that basic TDMPP promotes the equilibrium **7(E)** \leftrightarrow **9**. Although **9** is expected to be a minor component in this equilibrium,¹¹ once formed it will immediately undergo benzannulation with **2a**¹² to produce **8** as the major reaction product (Scheme 2).

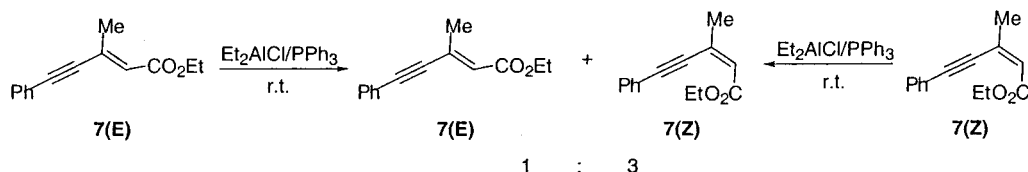
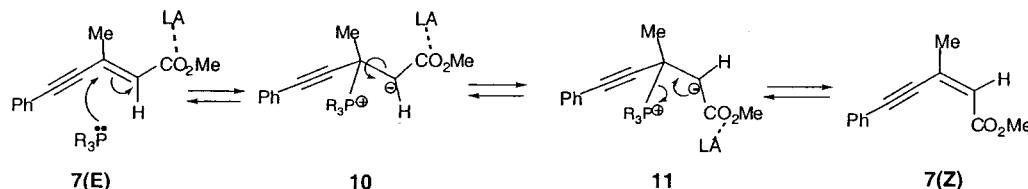
Acceleration of the Sequential Trimerization Reaction of Alkynes in the Presence of Lewis Acids. It was previously shown that the sequential trimerization of three different alkynes gives moderate yields and requires rather high temperatures (Table 2). This result can be reasonably explained as follows. Palladium-catalyzed reductive coupling of alkynes proceeds in syn-fashion to produce the E-enyne **7**. Although the reasons for this are not clearly understood, the benzannulation

process requires the migration of a hydrogen atom exclusively from the E-position of an enyne moiety.^{7g} Accordingly, to proceed to the next step of the sequence, (benzannulation with an enynophile to form the product **6**), the “wrong” E-isomer **7(E)** must somehow be transformed into the “correct” **7(Z)** isomer. Most likely, this inversion proceeds thermally, thereby explaining the requirement for rather harsh reaction conditions (5 days/100 °C) and therefore the moderate yields (Table 2, eq 4). Understandably, we were interested in developing efficient methods for transforming **7(E)** into **7(Z)** that would allow for milder reaction conditions and higher yields.

We found that in the presence of a $\text{Et}_2\text{AlCl}-\text{PPh}_3$ system at room temperature both E and Z isomers equilibrate to produce a 1:3 mixture of **7(E)** and **7(Z)** (Scheme 3). Notably, neither triphenylphosphine nor Et_2AlCl alone were enable to mediate this isomerization.¹³ The mechanism of the **7(E)** \leftrightarrow **7(Z)** isomerization can be rationalized in the following way. Lewis acid coordinates to an ester group of **7(E)**, activating its double bond toward addition of phosphine to form ylide **10**. Rotation around the σ -bond followed by the elimination of phosphine would produce an isomeric enyne **7(Z)** (Scheme 4).

Employment of Et_2AlCl (0.25 equiv) together with a palladium catalyst¹⁴ resulted in a substantial acceleration of the trimerization reaction. The second step of the sequence, the [4 + 2] cycloaddition, was completed after only 1 day at 60 °C (vs 5 days/100 °C in the absence of Lewis acid) to give benzene **6c** as a single reaction product in 56% yield. GC–MS analyses of the crude reaction mixtures at early stage of the reaction proved that the $\text{Et}_2\text{AlCl}/\text{PPh}_3$ system rapidly produces a mixture



Scheme 3. Z ↔ E Isomerization of Conjugated Enyne 7 in the Presence of the Et₂AlCl/PPh₃ System**Scheme 4. Proposed Pathway for Lewis Acid–Phosphine Mediated 7(E) ↔ 7(Z) Reversible Isomerization**

of two enynes, with the more reactive **7(Z)** isomer being a major component. However, after 30 min this equilibrium dramatically slows down, and Et₂AlCl becomes absolutely inactive,¹⁵ thereby not allowing higher yields of aromatic product **6c** to be achieved.

In summary, the first formal [2 + 2 + 2] highly regio- and chemoselective intermolecular trimerization of alkynes via the palladium-catalyzed sequential homo- and cross-coupling/[4 + 2] benzannulation protocol was demonstrated. The multifunctional tetra- and pentasubstituted aromatics, which are not easily available using conventional methods, can now easily be synthesized in one sequence from three different alkynes. A significant acceleration of the sequential trimerization reaction in the presence of Lewis acid/phosphine combined system was observed.

Experimental Section

Instrumentation. NMR spectra were recorded on JEOL JNM LA-300 (300 MHz) and Bruker Avance DPX-400 (400 MHz) instruments. IR spectra were recorded on a Shimadzu FTIR-8200A and Genesis II FT-IR Mattson spectrometers. High-resolution mass spectra were recorded on a Hitachi M-2500S and CONCEPT/EXTREL mass spectrometers. GC–MS analyses were performed on a Hewlett-Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m × 0.25 mm capillary column, HP-5MS).

(10) For selective alkyne coupling in the presence of Pd(OAc)₂, see: Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698. For other transition metal catalyzed alkyne dimerizations, see references therein.

(11) The following facts support that **7(E)** ↔ **9** equilibrium should be heavily shifted to the left: (1) the trace amounts of **9** were detected during the benzannulation reaction under the conditions of the method C; (2) enyne **9** was gradually transformed into **7(E)** upon prolonged storage at room temperature.

(12) It was shown that disubstituted enynes are far more reactive in the palladium-catalyzed [4 + 2] benzannulation reaction compared to trisubstituted enynes.^{7g}

(13) Lewis, F. D.; Oxman, J. D.; Gibson, L. L.; Hampsch, H. L.; Quillen, S. L. *J. Am. Chem. Soc.* **1986**, *108*, 3005.

(14) A mixture of terminal alkyne **1a** (1 equiv), internal alkyne **5a** (1.5 equiv), diyne **2a** (1.5 equiv), Pd(PPh₃)₄ (5 mol %), Pd(OAc)₂ (5 mol %), tris(2,6-dimethoxyphenyl)phosphine (TDMPP) (15 mol %), and Et₂AlCl (0.25 equiv) in toluene (1 M) was stirred for 1 day at room temperature and then for 1 day at 60 °C.

(15) A test ¹H NMR experiment performed at 60 °C in toluene-*d*₈ with **7(E)** as a substrate has shown that the best Z:E ratio of 3:1 is achieved after the first 30 min of the reaction. However, after the successive addition of an additional 1 equiv of **7(E)**, the equilibration **7(E)** ↔ **7(Z)** no longer proceeded.

(16) Medlik-Balan, A.; Klein, J. *Tetrahedron* **1980**, *36*, 299.

(17) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373.

(18) Wu, R.; Schumm, J. S.; Pearson, D. L.; Tour, J. M. *J. Org. Chem.* **1996**, *61*, 6906.

(19) Ma, S.; Shi, Z.; Li, L. *J. Org. Chem.* **1998**, *63*, 4522.

The same GC system with FID (30 m × 0.25 mm capillary column, HP-5) was used for the capillary GLC analyses. Column chromatography was carried out employing Merck silica gel (Kieselgel 40–63 μm), and analytical thin-layer chromatography (TLC) was performed on 0.2 mm precoated silica gel plates (Kieselgel 60 F₂₅₄).

Chemicals. Anhydrous solvents and commercially available chemicals **1a**, **b**, **d**, **f**, **g**, **2a**, **b**, and **5a–c** were purchased from Aldrich and Acros Organics. Compounds **1c**,¹⁶ **1e**,¹⁷ and **1i**¹⁸ were prepared according to known procedures. All reactions were performed under an argon atmosphere in oven-dried Wheaton microreactors.

Synthesis of the Enyne 9. 3-Iodo-3-butenic acid¹⁹ (228 mg, 1 mmol) was stirred in 5 mL of anhydrous EtOH with 2 mol % of *p*-toluenesulfonic acid at 60 °C for 10 h. The reaction mixture was diluted with water and extracted with diethyl ether. Combined ether layers were washed with water, dried over MgSO₄, filtered and concentrated. Purification by column chromatography (eluent hexane/ethyl acetate 10:1) gave 156 mg (0.61 mmol, 61%) of ethyl 3-iodo-3-butenate (**12**) as a yellowish oil. Phenylacetylene **1a** (62 mg, 0.61 mmol) was added to a mixture of Pd(PPh₃)₂Cl₂ (8.5 mg, 2 mol %), CuI (4.6 mg, 4 mol %), ester **12**, and Et₃N (1.5 mL). The mixture was stirred at room temperature for 12 h, filtered (Celite), and concentrated. Purification by column chromatography (eluent hexane/ethyl acetate 10:1) gave enyne **9** (115 mg, 88%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.45 (m, 2H), 7.30 (m, 3H), 5.62 (s, 1H), 5.46 (s, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 3.26 (s, 2H), 1.28 (t, 3H, *J* = 7.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 170.1, 131.6 (×2), 128.4, 128.3 (×2), 124.8, 124.2, 122.9, 89.8, 88.6, 60.9, 42.7, 14.2; IR (CCl₄) cm^{−1} 3059, 2985, 2360, 1741, 1612, 1554, 1491, 1309, 1257, 1191, 1034, 907; HRMS calcd for C₁₄H₁₄O₂ 214.0994, found 214.0992.

Synthesis of the Benzannulation Product 8. The mixture of Pd(PPh₃)₄ (27 mg, 5 mol %), **2a** (87 mg, 0.54 mmol), and **9** (115 mg, 0.54 mmol) was stirred in toluene (1 mL) at 100 °C for 12 h. Purification gave **8** (148 mg, 73%): ¹H NMR (400 MHz, CDCl₃) δ 7.60 (m, 2H), 7.33–7.43 (m, 3H), 7.14 (m, 2H), 4.19 (q, 2H, *J* = 7.1 Hz), 3.63 (s, 2H), 2.86 (t, 2H, *J* = 7.8 Hz), 2.33 (t, 2H, *J* = 6.8 Hz), 1.70 (ps, quint, 2H, *J* = 7.6 Hz), 1.43–1.49 (m, 3H), 1.35 (q, 3H, *J* = 7.2 Hz), 1.28 (t, 3H, *J* = 7.1 Hz), 1.00 (t, 3H, *J* = 7.4 Hz), 0.90 (t, 3H, *J* = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 145.8, 144.4, 141.3, 132.9, 129.5 (×2), 128.4, 127.9, 127.6 (×2), 127.0, 120.7, 97.4, 78.2, 60.9, 41.3, 34.9, 32.8, 30.6, 22.8, 21.9, 19.3, 14.2, 14.0, 13.6; IR (CCl₄) cm^{−1} 3058, 2958, 2874, 2360, 1742, 1604, 1560, 1462, 1372, 1302, 1267, 1153, 1034; HRMS calcd for C₂₆H₃₂O₂ 376.2402, found 376.2398.

Isolation of Aromatic Products 3, 6, and 8. After completion of the sequential aromatization reaction (monitored by GC–MS), the mixture was filtered through a short column (silica gel) and concentrated, and the product purified by column chromatography (silica gel, eluent hexane/ethyl acetate or hexane/toluene).

Synthesis of Polysubstituted Benzenes 3 and 6 (Gen-

eral Procedures). Method A. A mixture of donor alkyne **1** (1 equiv), acceptor alkyne **1** or **5** (1.5 equiv), diyne **2** (1 mmol), and Pd(PPh₃)₄ (5 mol %) in THF (1 M) was stirred under conditions indicated in the Tables 1 and 2.

Method B. A mixture of alkyne **1** (2.5 equiv), diyne **2** (1 equiv), Pd₂dba₃·CHCl₃ (5 mol %), and (*o*-Tol)₃P (40 mol %) in THF (1 M) was stirred under conditions indicated in the Table 1.

Method C. A mixture of terminal alkyne **1** (1 equiv), internal alkyne **5** (1.5 equiv), diyne **2** (1.5 equiv), Pd(PPh₃)₄ (5 mol %), Pd(OAc)₂ (5 mol %), and tris(2,6-dimethoxyphenyl)-phosphine (TDMPP) (15 mol %) in toluene (1 M) was stirred under conditions indicated in the Table 2.

Spectroscopic data for compounds **3a**, **3f**, and **6c** were identical to those of authentic samples described previously.⁷⁸

Data for 3b: ¹H NMR (300 MHz, CDCl₃) δ 7.22 (bs, 1H), 7.09 (d, 1H, *J* = 1.3 Hz), 4.61 (s, 2H), 4.42 (s, 2H), 3.45 (s, 3H), 3.36 (s, 3H), 2.77 (t, 2H, *J* = 7.7 Hz), 2.49 (t, 2H, *J* = 7.7 Hz), 1.67–1.32 (m, 8H), 0.96 (t, 3H, *J* = 7.1 Hz), 0.94 (t, 3H, *J* = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 145.0, 140.0, 137.1, 126.7, 123.8, 121.1, 98.7, 76.5, 74.4, 73.1, 58.4, 58.0, 34.4, 32.7, 30.9, 22.6, 21.9, 19.3, 13.9, 13.5; IR (neat) cm⁻¹ 3584, 2957, 2930, 2858, 2820, 2226, 1466, 1377, 1193, 1150, 1109, 916, 870, 733. Anal. Calcd for C₂₀H₃₀O₂: C, 79.42; H, 10.00. Found: C, 79.38; H, 10.06.

Data for 3c: ¹H NMR (300 MHz, CDCl₃) δ 7.66–7.62 (m, 2H), 7.48–7.24 (m, 10H), 4.79 (s, 2H), 4.52 (s, 2H), 3.54 (s, 3H), 3.42 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 144.5, 140.8, 140.6, 138.5, 131.2 (×2), 129.5 (×2), 128.25 (×2), 128.18, 127.8 (×2), 127.6, 127.4, 125.2, 123.4, 119.2, 97.2, 86.5, 74.3, 73.0, 58.8, 58.3; IR (neat) cm⁻¹ 3057, 2982, 2924, 2889, 2855, 2820, 1597, 1493, 1443, 1371, 1196, 1111, 1028, 970, 916, 878, 773, 756, 700; HRMS calcd for C₂₄H₂₂O₂ 342.1620, found 342.1615.

Data for 3d: ¹H NMR (300 MHz, CDCl₃) δ 7.32–7.12 (m, 10H), 6.82 (d, 1H, *J* = 1.5 Hz), 6.77 (d, 1H, *J* = 1.7 Hz), 3.05–2.96 (m, 2H), 2.94–2.79 (m, 6H), 2.74 (t, 2H, *J* = 7.8 Hz), 2.51 (t, 2H, *J* = 6.9 Hz), 1.67–1.46 (m, 6H), 1.43–1.31 (m, 2H), 0.95 (t, 3H, *J* = 7.2 Hz), 0.94 (t, 3H, *J* = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 145.1, 143.7, 142.5, 141.8, 140.6, 128.47 (×2), 128.46 (×2), 128.3 (×2), 128.2 (×2), 126.6, 126.4, 125.8, 125.7, 120.3, 97.1, 77.6, 37.87, 37.85, 37.4, 37.1, 34.8, 32.9, 31.1, 22.7, 22.1, 19.4, 14.0, 13.6; IR (neat) cm⁻¹ 3084, 3063, 3026, 3001, 2955, 2928, 2858, 1605, 1564, 1497, 1454, 1377, 1329, 1076, 1030, 870, 746, 698. Anal. Calcd for C₃₂H₃₈: C, 90.94; H, 9.06. Found: C, 91.23; H, 9.04.

Data for 3e: ¹H NMR (300 MHz, CDCl₃) δ 6.96 (s, 2H), 2.73 (t, 4H, *J* = 8.7 Hz), 2.47 (t, 2H, *J* = 6.8 Hz), 2.35 (t, 2H, *J* = 7.7 Hz), 1.66–1.26 (m, 16H), 0.96–0.89 (m, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 144.8 (2), 141.7, 126.1 (×2), 120.0, 96.6, 77.8, 35.6, 34.8 (×2), 33.6, 33.0 (×2), 31.1, 22.8 (×2), 22.4, 22.0, 19.4, 14.0 (×2), 13.9, 13.6; IR (neat) cm⁻¹ 2957, 2930, 2858, 1607, 1564, 1466, 1377, 1329, 1105, 862, 745. Anal. Calcd for C₂₄H₃₈: C, 88.27; H, 11.73. Found: C, 87.94; H, 11.71.

Data for 3g: ¹H NMR (300 MHz, CDCl₃) δ 6.93 (bs, 1H), 6.92 (bs, 1H), 4.63 (s, 2H), 4.61 (s, 2H), 3.77 (t, 2H, *J* = 7.4 Hz), 3.73 (t, 2H, *J* = 7.1 Hz), 3.32 (s, 3H), 3.29 (s, 3H), 3.06 (t, 2H, *J* = 7.4 Hz), 2.84 (t, 2H, *J* = 7.1 Hz), 2.73 (t, 2H, *J* = 7.8 Hz), 2.48 (t, 2H, *J* = 6.8 Hz), 1.66–1.30 (m, 8H), 0.95 (t, 3H, *J* = 7.2 Hz), 0.94 (t, 3H, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 145.1, 140.3, 137.6, 127.2 (×2), 121.1, 97.4, 96.3, 96.2, 77.3, 68.3, 67.6, 55.1, 55.0, 36.1, 35.4, 34.7, 32.9, 31.0, 22.7, 22.0, 19.3, 14.0, 13.6; IR (neat) cm⁻¹ 2955, 2930, 2872, 2822, 2226, 2064, 1609, 1566, 1466, 1379, 1217, 1150, 1111, 1072, 1034, 918, 874. Anal. Calcd for C₂₄H₃₈O₄: C, 73.81; H, 9.81. Found: C, 74.00; H, 9.82.

Data for 3h: ¹H NMR (300 MHz, CDCl₃) δ 6.87 (bs, 1H), 6.86 (bs, 1H), 3.54 (t, 2H, *J* = 6.6 Hz), 3.51 (t, 2H, *J* = 6.5 Hz), 2.89 (t, 2H, *J* = 7.5 Hz), 2.73 (t, 2H, *J* = 7.7 Hz), 2.70 (t, 2H, *J* = 7.3 Hz), 2.48 (t, 2H, *J* = 6.8 Hz), 2.16–2.00 (m, 4H), 1.66–1.32 (m, 8H), 0.95 (t, 3H, *J* = 7.2 Hz), 0.94 (t, 3H, *J* = 7.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 145.4, 142.9, 139.6, 126.8, 126.5, 120.8, 97.6, 77.3, 44.8, 44.2, 34.7, 33.9, 33.2, 32.9, 32.6, 32.2, 31.0, 22.7, 22.0, 19.3, 14.0, 13.6; IR (neat) cm⁻¹ 2957, 2932, 2858, 2226, 1607, 1564, 1466, 1379, 1292, 1105, 885, 743, 727, 654; HRMS calcd for C₂₂H₃₂Cl₂ 366.1881, found 366.1907. Anal.

Calcd for C₂₂H₃₂Cl₂: C, 71.92; H, 8.78; Cl, 19.30. Found: C, 72.21; H, 8.55; Cl, 19.19.

Data for 6a: ¹H NMR (300 MHz, CDCl₃) δ 6.83 (s, 1H), 4.34 (q, 2H, *J* = 7.2 Hz), 2.65–2.72 (m, 4H), 2.45 (t, 2H, *J* = 6.6 Hz), 2.24 (s, 3H), 1.25–1.58 (m, 23H), 0.84–0.95 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 146.1, 141.6, 133.2, 127.9 (×2), 121.0, 97.3, 77.2, 60.8, 35.1, 32.8, 31.9, 31.1, 31.0, 30.6, 29.6, 29.5, 29.3, 23.2, 22.7, 22.1, 19.6, 19.4, 14.3, 14.2, 13.9, 13.6; IR (neat) cm⁻¹ 2925, 2275, 1728, 1590, 665; HRMS calcd for C₂₈H₄₄O₂ 412.3341, found 412.3330. Anal. Calcd for C₂₈H₄₄O₂: C, 81.50; H, 10.75. Found: C, 81.37; H, 10.67.

Data for 6b: ¹H NMR (300 MHz, CDCl₃) δ 7.19 (s, 1H), 4.35 (q, 2H, *J* = 7.2 Hz), 3.67 (s, 2H), 2.69 (t, 2H, *J* = 7.1 Hz), 2.44–2.57 (m, 6H), 2.26 (s, 3H), 1.23–1.66 (m, 11H), 0.88–1.05 (m, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 170.5, 141.4, 133.4, 127.9 (×2), 127.5, 121.1, 98.5, 76.8, 60.9, 55.2, 47.0 (×2), 32.7 (×2), 30.9, 23.2, 22.0, 19.6, 19.4, 14.2, 13.9, 13.6 (×2), 11.6; IR (neat) cm⁻¹ 2958, 1705, 1602, 665; HRMS calcd for C₂₅H₃₉O₂N 385.2980, found 385.2987.

Data for 6d: ¹H NMR (300 MHz, CDCl₃) δ 7.29–7.58 (m, 10H), 7.22 (s, 1H), 4.06 (q, 2H, *J* = 7.8 Hz), 2.89 (t, 2H, *J* = 9.2 Hz), 2.32 (t, 2H, *J* = 7.4 Hz), 1.24–1.76 (m, 11H), 0.94 (t, 3H, *J* = 7.3 Hz), 0.85 (t, 3H, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 169.4, 145.2, 142.9, 140.7, 140.5, 138.6, 132.3, 129.4, 129.3, 128.6 (×2), 128.3 (×2), 128.1, 127.6, 127.5, 127.3, 126.9, 122.3, 98.4, 77.8, 60.9, 32.9, 30.5, 23.3, 21.9 (×2), 19.3, 13.9, 13.7, 13.6; IR (neat) cm⁻¹ 3084, 3058, 2956, 2223, 1728, 1602, 756, 698, 665; HRMS calcd for C₃₁H₃₄O₂ 438.2559, found 438.2539. Anal. Calcd for C₃₁H₃₄O₂: C, 84.88; H, 7.82. Found: C, 84.51; H, 7.75.

Data for 6e: ¹H NMR (300 MHz, CDCl₃) δ 7.24–7.36 (m, 5H), 7.03 (s, 1H), 4.02 (q, 2H, *J* = 6.9 Hz), 2.70–2.75 (m, 4H), 2.49 (t, 2H, *J* = 6.6 Hz), 1.26–1.62 (m, 23H), 0.85–0.98 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 169.7, 146.3, 142.4, 140.9, 138.5, 130.8, 128.2 (×2), 128.1, 127.5 (×2), 127.2, 122.8, 98.5, 77.2, 60.8, 35.2, 32.9, 32.7, 31.9, 31.1, 31.0, 30.5, 29.7, 29.5, 23.2, 22.7, 22.1, 19.4, 14.2, 13.9, 13.7, 13.6; IR (neat) cm⁻¹ 2958, 2275, 1724, 1599, 761, 665; HRMS calcd for C₃₃H₄₆O₂ 474.3499, found 474.3485.

Data for 6f: ¹H NMR (300 MHz, CDCl₃) δ 7.33–7.42 (m, 5H), 7.26 (s, 1H), 3.78 (s, 2H), 2.75 (t, 2H, *J* = 8.1 Hz), 2.50–2.63 (m, 6H), 1.92 (s, 3H), 1.37–1.66 (m, 8H), 0.92–1.08 (m, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 207.3, 143.1, 140.6, 140.5, 136.9, 129.0 (×2), 128.4 (×2), 127.6, 127.6, 127.5, 122.9, 99.8, 76.9, 55.6, 47.3 (×2), 34.2, 32.6, 32.2, 30.9, 23.3, 22.1, 19.5, 13.9, 13.6 (×2), 11.9; IR (neat) cm⁻¹ 3058, 2958, 1697, 1600, 665; HRMS calcd for C₂₉H₃₉ON 417.3031, found 417.3033.

Data for 6g: ¹H NMR (300 MHz, CDCl₃) δ 7.31–7.44 (m, 6H), 4.03 (q, 2H, *J* = 7.2 Hz), 3.68 (s, 2H), 2.83 (t, 2H, *J* = 8.1 Hz), 2.44–2.62 (m, 6H), 1.35–1.66 (m, 11H), 0.917–1.06 (m, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 169.6, 142.1, 140.9, 138.5, 131.6, 128.4 (×2), 128.1, 127.4 (×2), 127.2, 126.9, 122.6, 99.6, 76.8, 60.8, 55.6, 47.2 (×2), 32.9, 32.6, 30.9, 23.3, 22.1, 19.5, 13.9 (×2), 13.7, 13.6, 11.9; IR (neat) cm⁻¹ 2958, 2931, 1726, 1590, 700, 665; HRMS calcd for C₃₀H₄₁O₂N 447.3136, found 447.3129.

Data for 6h: ¹H NMR (300 MHz, CDCl₃) δ 6.98–7.49 (m, 9H), 3.98 (q, 2H, *J* = 5.8 Hz), 2.81 (t, 2H, *J* = 8.1 Hz), 2.40 (t, *J* = 6.6 Hz, 2H), 1.18–1.61 (m, 11H), 0.84–0.92 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 169.2, 143.5, 141.9, 140.3, 138.8, 137.1, 132.4, 128.2, 128.1, 128.0, 127.9, 127.5, 127.2, 125.9, 123.1, 120.8, 118.1, 100.3, 78.1, 60.9, 32.9, 32.7, 31.2, 23.3, 22.1, 19.7, 13.9, 13.7, 13.6; IR (neat) cm⁻¹ 3058, 2958, 2223, 1724, 1637, 1587, 665; HRMS calcd for C₂₉H₃₁O₂S 444.2123, found 444.2130. Anal. Calcd for C₂₉H₃₁O₂S: C, 78.34; H, 7.24; S, 7.20. Found: C, 77.99; H, 7.15; S, 6.98.

Acknowledgment. The support of the National Science Foundation (CHE 0096889) is gratefully acknowledged.

Supporting Information Available: ¹H NMR chart for the compound **3c** and ¹H and ¹³C NMR charts for compounds **6b**, **6e**–**g**, and **9** are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>. JO0100392