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

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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 homotrimerization 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 metallocyclopentadiene 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.

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(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.

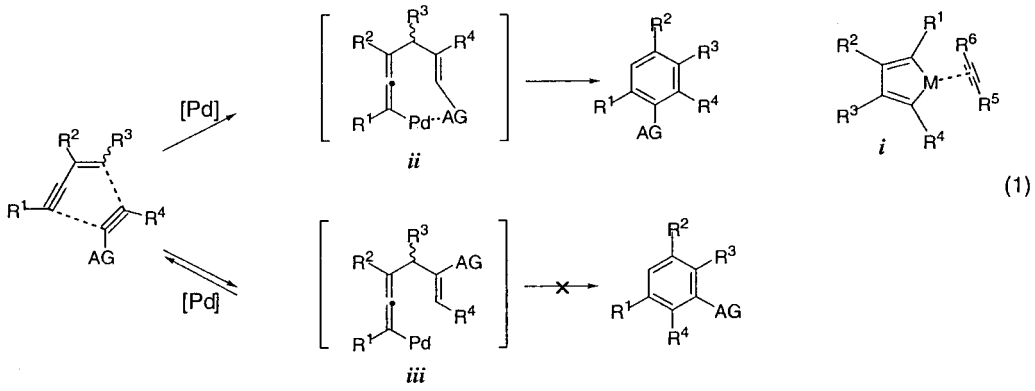
(3) For selective intramolecular alkynes trimerization, see for example: (a) Lecker, S. H.; Nguen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 856. For partially intramolecular trimerization, see: (b) Berris, B. C.; Hovakeemian, G. H.; Lai, Y.-H.; Mestdagh, H.; Vollhardt, K. P. C.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

10.1021/jo0100392 CCC: $20.00
Published on Web 03/23/2001

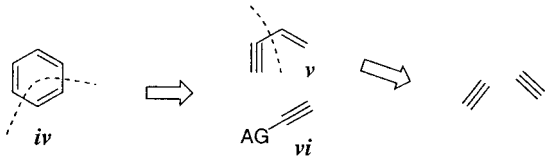


(1)

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 higly 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 alkynes[7] and motivated by the challenging goal of regio- and chemoselective intermolecular trimerization of alkynes, we hypothesized that the new [4 + 2] benzannulation methodology[7] 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 way[8] (Scheme 1). The proposed new concept of a formal [2 + 2 + 2]

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 technology to assemble a benzene ring from ***vi*** and ***v***[7], 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

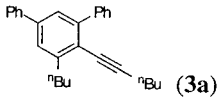
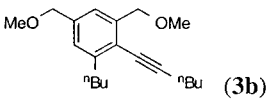
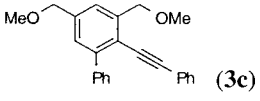
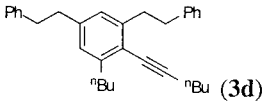
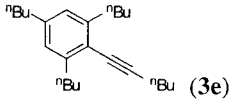
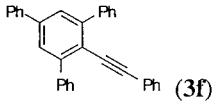
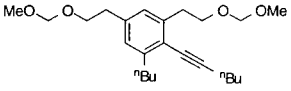
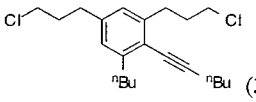
Synthesis of 1,2,3,5-Tetrasubstituted Benzenes 3. To examine the possibility of accomplishing the above-mentioned sequence in the presence of $Pd(PPh_3)_4$, the following experiment was performed. A mixture of phenylacetylene **1a**, 5,7-dodecadiyne **2a**, and $Pd(PPh_3)_4$ (5 mol %) was heated in THF (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 $Pd(PPh_3)_4$ 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

(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 $Pd(PPh_3)_4$ in this reaction. For $Pd(PPh_3)_4$-catalyzed dimerization of silylacetylenes, see: Ishikawa, M.; Ohshita, J. *J. Organomet. Chem.* **1988**, *346*, C58.

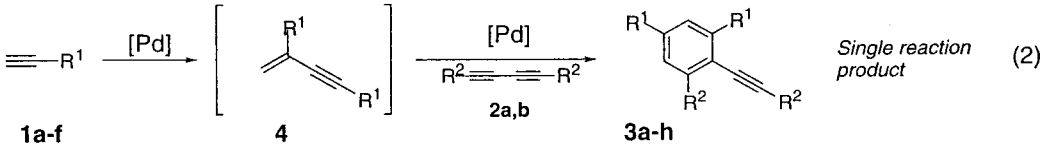
Table 1. Synthesis of Tetrasubstituted Benzenes 3a−h via Sequential Homodimerization of Terminal Alkynes 1/[4 + 2] Benzannulation with Diynes 2

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.

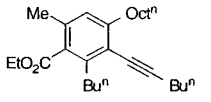
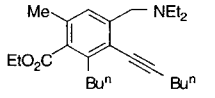
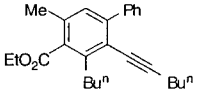
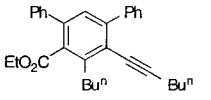
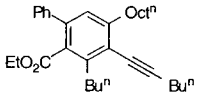
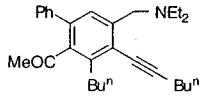
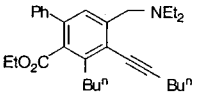
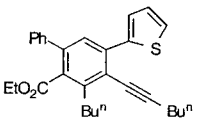
harsh conditions of method **A**. After optimization, it was found that a $Pd_2(dba)_3$·$CHCl_3$/(*o*-Tol)$_3$P combination enables both sequence steps to be effectively catalyzed at 25−60 °C (method **B**). Reactions of all the terminal alkynes tested under these conditions proceeded in an absolutely 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 tetrasubstituted 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



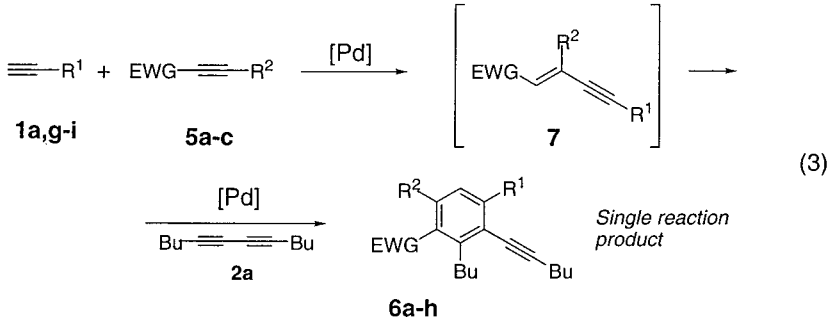
(2)

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

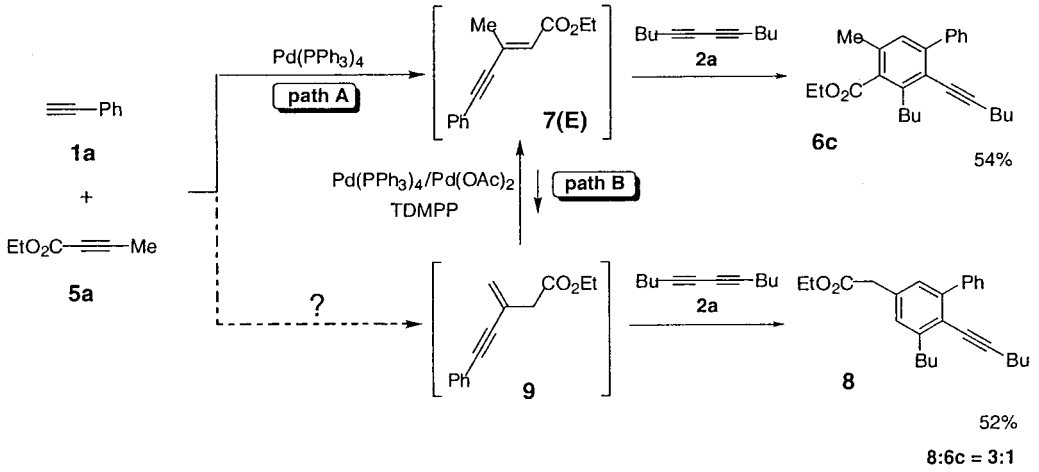
entry	Alkyne **1**	Alkyne **5**		Product **6**	Method[a]	Time/Temp	Yield (%)[b]
	R^1	R^2	EWG			(h/°C)	
1	^{n}Oct (**1g**)	Me	CO_2Et (**5a**)	 (**6a**)	**A**	144/100	60[c]
2	Et_2NCH_2 (**1h**)		(**5a**)	 (**6b**)	**A**	96/100	50
3	Ph (**1a**)		(**5a**)	 (**6c**)	**A**	24/50→120/100	54
4	(**1a**)	Ph	CO_2Et (**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 $Pd(PPh_3)_4$ (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 $Pd(PPh_3)_4/Pd(OAc)_2$/TDMPP Catalytic System (Method C)



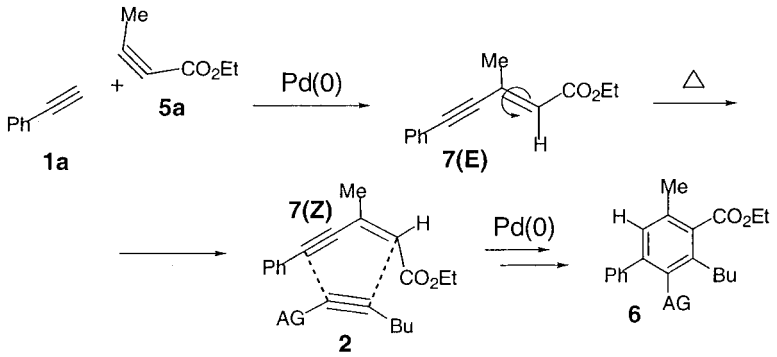
(Table 2, entries 5−8). In all cases the pentasubstituted benzenes **6a**−**h** were obtained as a single reaction product, though in moderate yields.

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)** ↔ **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)** ↔ **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.

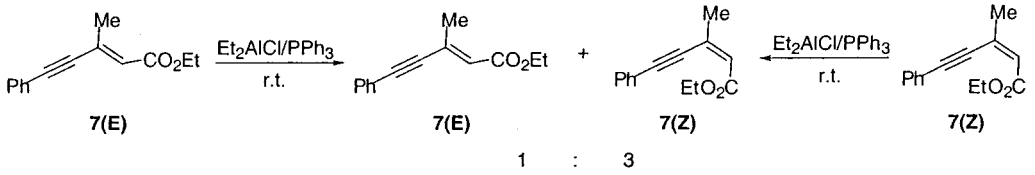
We found that in the presence of a $Et_2AlCl-PPh_3$ system at room temperature both E and Z isomers equilibrate to produce a 1:3 mixture of **7(E)** and **7(Z)** (Scheme 3). Notably, neither triphenylphosphine nor Et_2AlCl alone were enable to mediate this isomerization.[13] The mechanism of the **7(E)** ↔ **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 catalyst[14] 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 Et_2AlCl/PPh_3 system rapidly produces a mixture

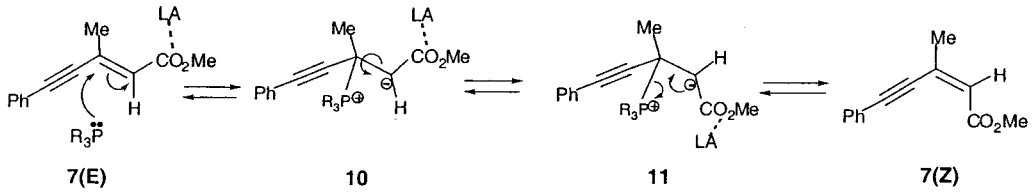


(4)

Scheme 3. Z ↔ E Isomerization of Conjugated Enyne 7 in the Presence of the Et_2AlCl/PPh_3 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 Et_2AlCl 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). 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 F_{254}).

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-butenoic acid[19] (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 $MgSO_4$, 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-butenoate (**12**) as a yellowish oil. Phenylacetylene **1a** (62 mg, 0.61 mmol) was added to a mixture of $Pd(PPh_3)_2Cl_2$ (8.5 mg, 2 mol %), CuI (4.6 mg, 4 mol %), ester **12**, and Et_3N (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: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (CCl_4) cm^{-1} 3059, 2985, 2360, 1741, 1612, 1554, 1491, 1309, 1257, 1191, 1034, 907; HRMS calcd for $C_{14}H_{14}O_2$ 214.0994, found 214.0992.

Synthesis of the Benzannulation Product 8. The mixture of $Pd(PPh_3)_4$ (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%): ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 (CCl_4) cm^{-1} 3058, 2958, 2874, 2360, 1742, 1604, 1560, 1462, 1372, 1302, 1267, 1153, 1034; HRMS calcd for $C_{26}H_{32}O_2$ 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-

(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), $Pd(PPh_3)_4$ (5 mol %), $Pd(OAc)_2$ (5 mol %), tris(2,6-dimethoxyphenyl)phosphine (TDMPP) (15 mol %), and Et_2-AlCl (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 ^{1}H 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.

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 $Pd(PPh_3)_4$ (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), $Pd_2dba_3{\cdot}CHCl_3$ (5 mol %), and $(o\text{-Tol})_3P$ (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), $Pd(PPh_3)_4$ (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.[7g]

Data for 3b: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.38; H, 10.06.

Data for 3c: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{22}O_2$ 342.1620, found 342.1615.

Data for 3d: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{32}H_{38}$: C, 90.94; H, 9.06. Found: C, 91.23; H, 9.04.

Data for 3e: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{38}$: C, 88.27; H, 11.73. Found: C, 87.94; H, 11.71.

Data for 3g: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 74.00; H, 9.82.

Data for 3h: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{22}H_{32}Cl_2$ 366.1881, found 366.1907. Anal. Calcd for $C_{22}H_{32}Cl_2$: C, 71.92; H, 8.78; Cl, 19.30. Found: C, 72.21; H, 8.55; Cl, 19.19.

Data for 6a: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 146.1, 141.6, 133.2, 127.9 (x2), 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 $C_{28}H_{44}O_2$ 412.3341, found 412.3330. Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.37; H, 10.67.

Data for 6b: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{25}H_{39}O_2N$ 385.2980, found 385.2987.

Data for 6d: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (x2), 19.3, 13.9, 13.7, 13.6; IR (neat) cm^{-1} 3084, 3058, 2956, 2223, 1728, 1602, 756, 698, 665; HRMS calcd for $C_{31}H_{34}O_2$ 438.2559, found 438.2539. Anal. Calcd for $C_{31}H_{34}O_2$: C, 84.88; H, 7.82. Found: C, 84.51; H, 7.75.

Data for 6e: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{33}H_{46}O_2$ 474.3499, found 474.3485.

Data for 6f: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{29}H_{39}ON$ 417.3031, found 417.3033.

Data for 6g: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{30}H_{41}O_2N$ 447.3136, found 447.3129.

Data for 6h: ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{29}H_{31}O_2S$ 444.2123, found 444.2130. Anal. Calcd for $C_{29}H_{31}O_2S$: 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: ^{1}H NMR chart for the compound **3c** and ^{1}H and ^{13}C NMR charts for compounds **6b**, **6e**−**g**, **8**, and **9** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0100392