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Palladium-Catalyzed Conjugate Addition to Electron-Deficient Alkynes with Benzenesulfinic Acid Derived from 1,2-Bis(phenylsulfonyl)ethane: Selective Synthesis of (*E*)-Vinyl Sulfones

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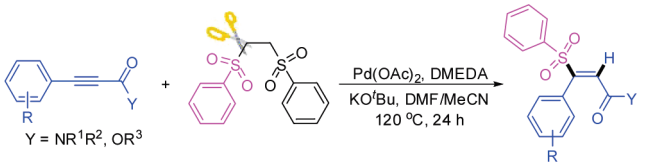
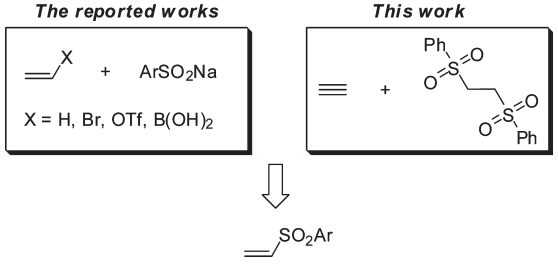


A new, selective method for the synthesis of (*E*)-vinyl sulfones is presence by palladium-catalyzed C−S bond cleavage/conjugate addition. In the presence of Pd(OAc)$_2$ and DMEDA (N^1,N^2-dimethylethane-1,2-diamine), 1,2-bis(phenylsulfonyl)ethane underwent the C−S bond cleavage, followed by conjugate addition to numerous electron-deficient alkynes afforded the corresponding (*E*)-vinyl sulfones in moderate to good yields.

Vinyl sulfones are unique architectures found in several biologically active compounds[1] as well as usefully synthetic intermediates in organic synthesis.[2] For example, α,β-unsaturated sulfones were reported as inhibitors of inducible VACM-1 expression.[3] Therefore, considerable effort has been devoted to the development of new and efficient methods for the synthesis of vinylsulfones. The traditionally available methodologies for vinyl sulfones mainly include the following: (1) the Knoevenagel condensations of aromatic aldehydes with sulfonylacetic acids,[4] (2) Horner−Emmons reactions of carbonyl compounds and sulfonyl phosphones,[5] (3) β-elimination of selenosulfones or halosulfones,[6] and (4) oxidation of the corresponding vinyl sulfides.[7] However, these methods are restricted to relatively harsh reaction conditions, and inaccessible substrates were necessary. Recently, a new and efficient route to these compounds is the cross-coupling of sulfinate salts with vinyl bromides, vinyl triflates, alkenyl boronic acids, or alkenes with Pd or Cu catalysts (Scheme 1).[8] Reeves and co-workers, for instance, have described a valuable protocol for the synthesis of vinyl sulfones in moderate to good yields by palladium-catalyzed coupling of vinyl tosylates with arylsulfinate salts.[8h] Here, we report a new approach to (*E*)-vinyl sulfones via palladium-catalyzed conjugate additions of alkynes with 1,2-bis(phenylsulfonyl)ethane (Scheme 1).[9] To the best of our knowledge, it is the first example of using the commercially available 1,2-bis(phenylsulfonyl)ethane as the sulfone resource to prepare vinyl sulfones by generating phenylsulfonyl intermediates in situ for the conjugate addition to the electron-deficient alkynes.

SCHEME 1. Transition Metal-Catalyzed Synthesis of Vinyl Sulfones



The reaction between *N*-benzyl-*N*,3-diphenylpropiolamide (**1a**) and 1,2-bis(phenylsulfonyl)ethane (**2**) was investigated to explore the optimal reaction conditions, and the results are summarized in Table 1. Initially, a number of solvents, such as dioxane, MeCN, DMF, and DMF/MeCN, were examined in the presence of Pd(OAc)$_2$, DMEDA (**L1**), and KO^{t}Bu

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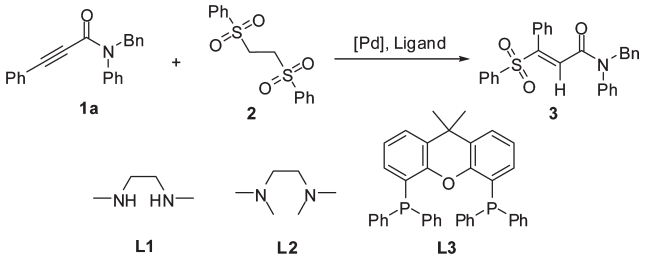
TABLE 1. Screening Optimal Conditions[a]



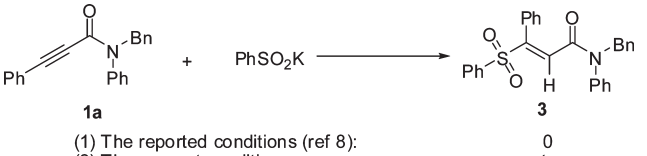
entry	[Pd]/ligand	base	solvent	yield (%)
1	$Pd(OAc)_2$/**L1**	KO^{t}Bu	dioxane	trace
2	$Pd(OAc)_2$/**L1**	KO^{t}Bu	MeCN	21
3	$Pd(OAc)_2$/**L1**	KO^{t}Bu	DMF	62
4	$Pd(OAc)_2$/**L1**	KO^{t}Bu	DMF/MeCN (1:1)	73
5	$Pd(OAc)_2$/**L1**	KO^{t}Bu	DMF/MeCN (1:4)	46
6	$Pd(OAc)_2$/**L1**	KO^{t}Bu	DMF/MeCN (4:1)	37
7	$Pd(OAc)_2$/**L1**	$KHCO_3$	DMF/MeCN (1:1)	40
8	$Pd(OAc)_2$/**L1**	NaOAc	DMF/MeCN (1:1)	44
9	$Pd(OAc)_2$/**L1**	$LiN(TMS)_2$	DMF/MeCN (1:1)	28
10		KO^{t}Bu	DMF/MeCN (1:1)	0
11	$Pd(OAc)_2$	KO^{t}Bu	DMF/MeCN (1:1)	21
12	$PdCl_2$/**L1**	KO^{t}Bu	DMF/MeCN (1:1)	32
13	$Pd(PPh_3)_4$/**L1**	KO^{t}Bu	DMF/MeCN (1:1)	70
14	$Pd_2(dba)_3$/**L1**	KO^{t}Bu	DMF/MeCN (1:1)	40
15	$Pd(OAc)_2$/**L2**	KO^{t}Bu	DMF/MeCN (1:1)	27
16	$Pd(OAc)_2$/**L3**	KO^{t}Bu	DMF/MeCN (1:1)	25
17[b]	$Pd(OAc)_2$/**L1**	KO^{t}Bu	DMF/MeCN (1:1)	66
18[c]	$Pd(OAc)_2$/**L1**	KO^{t}Bu	DMF/MeCN (1:1)	32
19[d]	$Pd(OAc)_2$/**L1**	KO^{t}Bu	DMF/MeCN (1:1)	58

[a]Reaction conditions: **1a** (0.2 mmol), **2** (2 equiv), [Pd] (10 mol %), ligand (20 mol %), base (2 equiv), and solvent (2 mL) at 120 °C for 24 h. [b]At 100 °C. [c]At 80 °C. [d]$Pd(OAc)_2$ (5 mol %).

(entries 1−6). The results demonstrated that the effect of solvents played an important role in the reaction. While a trace amount of the target product **3** was observed in dioxane (entry 1), MeCN enhanced the yield of **3** to 21% yield and DMF gave 62% yield (entries 2 and 3). It was a pleasure to find that a mixture of DMF/MeCN (v/v = 1:1) afforded the best results (73% yield, entry 4). The configuration structure of (*E*)-**3** was unambiguously assigned by the X-ray single-crystal diffraction analysis.[10] Subsequently, three other bases, including $KHCO_3$, NaOAc, and $LiN(TMS)_2$, were evaluated, and they were less effective than KO^{t}Bu (entries 4 and 7−9). The effect of the catalytic systems was also tested (entries 4 and 10−16). The reaction could not take place without Pd catalysts (entry 10). It was disclosed that 21% yield of **3** was isolated by using $Pd(OAc)_2$ alone (entry 11), and $Pd(PPh_3)_4$ combined with **L1** gave the identical results to those of the $Pd(OAc)_2$/**L1** system (entry 13). However, the $PdCl_2$/**L1**, $Pd_2(dba)_3$/**L1**, $Pd(OAc)_2$/**L2**, and $Pd(OAc)_2$/**L3** systems displayed less activity (entries 12 and 14−16). Among the reaction temperature examined, it turned out that 120 °C was the most suitable for the reaction (entries 4, 17, and 18). It is noted that the loading of $Pd(OAc)_2$ affected the reaction, and the yield was decreased to 58% at 5 mol % of $Pd(OAc)_2$ (entry 19).

With the optimal conditions in hand, the alkynes scope was explored (Table 2). The results demonstrated that the reaction could be applied to a wide variety of 3-arylpropiolamides, and several *N*-substituents, either alkyl or aryl groups, were perfectly tolerated under the standard conditions (entries 1−12). *N*-Methyl-*N*,3-diphenylpropiolamide (**1b**), for instance, underwent the reaction with 1,2-bis(phenylsulfonyl)ethane (**2**), $Pd(OAc)_2$, **L1**, and KO^{t}Bu to afford the target product **4** in 65% yield (entry 1). Substrates **1c**−**h**, bearing methyl, methoxy, or fluoro groups on the *N*-aryl moiety, were also suitable for the reaction in moderate to good yields (entries 2−7). To our delight, the optimized conditions were compatible with both *N*,*N*-diethyl-3-phenylpropiolamide (**1i**) and 1-morpholino-3-phenylprop-2-yn-1-one (**1j**), providing two regioselective isomers in 71% and 79% yields, respectively (entries 8 and 9).[10] Subsequently, substituents at the terminal alkyne of *N*-methyl-*N*-arylpropiolamides were investigated (entries 10−12). Treatment of substrate **1k**, bearing a 2-methylpheneyl group, with 1,2-bis(phenylsulfonyl)ethane (**2**), $Pd(OAc)_2$, **L1**, and KO^{t}Bu afforded the corresponding (*E*)-**13** in 60% yield (entry 10). However, amide **1*l*** with a 4-acetylphenyl group reduced the yield of (*E*)-**14** to 43% under the same conditions (entry 11). Gratifyingly, *N*-methyl-*N*-phenyl-3-(thiophen-2-yl)propiolamide (**1m**) was still a suitable substrate in 74% yield (entry 12). We found that the optimized conditions were consistent with alkylpropiolamides **1n** and **1o** in moderate yields (entries 13 and 14). Notably, 43% yield was still achieved from another substrate **1p**, methyl 3-phenylpropiolate, under the standard conditions (entry 15). However, the reactions of 1,3-diphenylprop-2-yn-1-one (**1q**) or *N*,3-diphenylpropiolamide (**1r**) were not successful under the standard conditions with a mixture of products (entries 16 and 17).

SCHEME 2. Controlled Experiments in the Presence of $PhSO_2K$



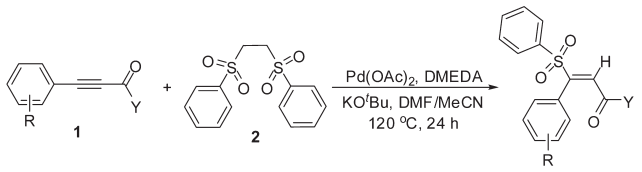
To understand the mechanism, two controlled experiments were carried out using the reported sulfone reagent, $PhSO_2K$ (Scheme 2). No target products **3** were observed by GC-MS analysis from the reaction between substrate **1a** and $PhSO_2K$ under either the reported conditions[8] or the present conditions. Notably, the reaction could not take place even in the presence of *t*-BuOH under the present reaction conditions.

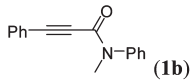
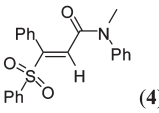
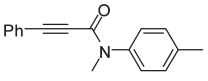
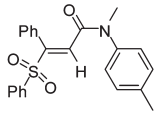
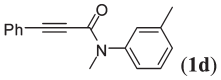
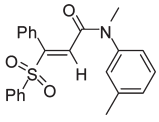
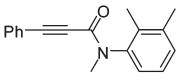
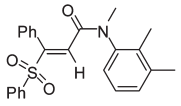
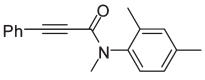
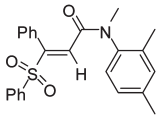
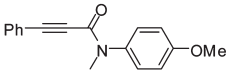
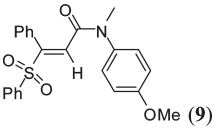
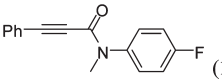
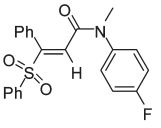
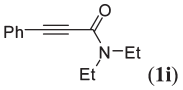
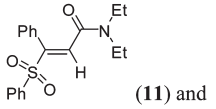
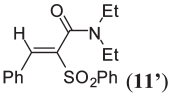
Therefore, a possible mechanism was proposed as outlined in Scheme 3 on the basis of the reported mechanism[8] and the present results. Insertion of Pd(0) into 1,2-bis(phenylsulfonyl)ethane (**2**) affords intermediate **A**, followed by complexation with an alkyne gives intermediate **B**. Two regioselective additions of intermediate **B** take place to yield intermediates **C** and/or **C′** on the basis of

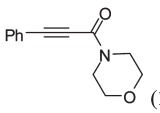
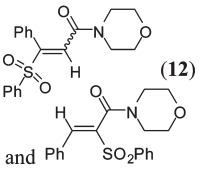
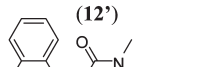
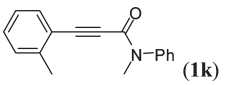
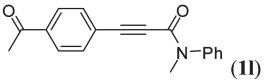
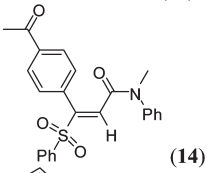
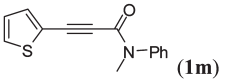
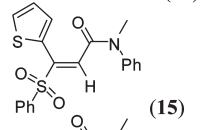
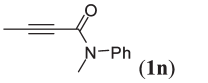
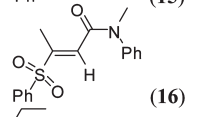
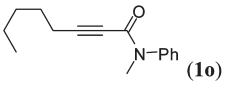
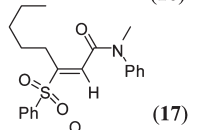
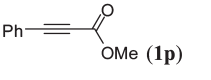
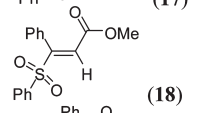
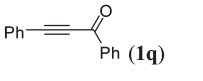
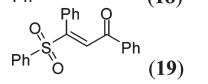
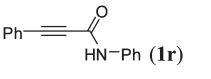
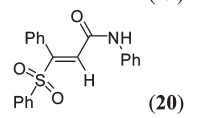
(9) For selected papers on the use of 1,2-bis(phenylsulfinyl)ethane as an efficient ligand in transition metal-catalyzed transformations, see: (a) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274–7276. (b) Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316–3318. (c) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701–11706. (d) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707–11711. (e) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; M.C. White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970–6971. (f) Covell, D. J.; White, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448–6451.

(10) See the Supporting Information for detailed results of the X-ray single-crystal diffraction analysis (**3**) and 2D spectra (**12**).

TABLE 2. Palladium-Catalyzed Conjugate Addition of Alkynes (1) with 1,2-Bis(phenylsulfonyl)ethane (2)[a]



Entry	Substrate **1**	Product	Yield (%)
1	 (**1b**)	 (**4**)	65
2	 (**1c**)	 (**5**)	45
3	 (**1d**)	 (**6**)	62
4	 (**1e**)	 (**7**)	63
5	 (**1f**)	 (**8**)	61
6	 (**1g**)	 (**9**)	64
7	 (**1h**)	 (**10**)	80
8[c]	 (**1i**)	 (**11**) and  (**11'**)	71

Entry	Substrate **1**	Product	Yield (%)
9[d]	 (**1j**)	 (**12**) and  (**12'**)	79
10	 (**1k**)	(**13**)	60
11	 (**1l**)	 (**14**)	43
12	 (**1m**)	 (**15**)	74
13	 (**1n**)	 (**16**)	50
14	 (**1o**)	 (**17**)	54
15[e]	 (**1p**)	 (**18**)	43
16	 (**1q**)	 (**19**)	<5
17	 (**1r**)	 (**20**)	trace

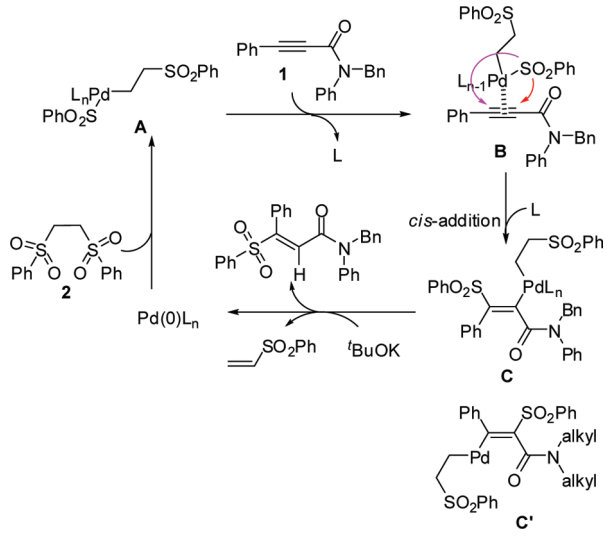
[a]Reaction conditions: **1** (0.2 mmol), **2** (2 equiv), $Pd(OAc)_2$ (10 mol %), DMEDA (20 mol %), KO^{t}Bu (2 equiv), and DMF/MeCN (v/v = 1:1; 2 mL) at 120 °C for 24 h. [b]Isolated yield. [c]A mixture of (*E*)-*N*,*N*-diethyl-3-phenyl-3-(phenylsulfonyl)acrylamide (***E*-11**) and (*Z*)-*N*,*N*-diethyl-3-phenyl-2-(phenylsulfonyl)acrylamide (***Z*-11'**) was obtained, and the ratio of *Z*/*E* is 1:2. [d]***E*-12**/***Z*-12'** = 1:1. [e]18 h.

the *N*-substituents. Finally, reductive elimination/protonation of intermediates **C** affords the target (*E*)-product, 1-(vinylsulfonyl)benzene, and the active Pd(0) species with the aid of *t*-BuOK. It is noteworthy that the generation of 1-(vinylsulfonyl)benzene is obtained and in situ determined by GC-MS analysis.

We deduce that both the steric hindrance and electronic effect of the *N*-substituents may affect the regioselective addition to intermediate **B** leading to intermediates **C** and **C'**. Substrates with an *N*,*N*-dialkyl group give a mixture of two regioselective products due to their less steric hindrance and electron-donating effect, which results in two regioselective products.

In summary, we described a novel, simple protocol for the synthesis (*E*)-vinyl sulfones by palladium-catalyzed conjugate addition reaction. This method allows a variety of electron-deficient alkynes reacted with 1,2-bis(phenylsulfonyl)ethane, $Pd(OAc)_2$, and DMEDA leading to the corresponding (*E*)-vinyl sulfones in moderate to good yields. It is noteworthy that the sulfone resource, phenylsulfonyl intermediates, is prepared in situ from 1,2-bis(phenylsulfonyl)-ethane through a C−S bond cleavage.

SCHEME 3. Possible Mechanism



Experimental Section

Typical Experimental Procedure for Palladium-Catalyzed Conjugate Addition of Alkynes (1) with 1,2-Bis(phenylsulfonyl)ethane (2). A mixture of alkynes **1** (0.2 mmol), 1,2-bis(phenylsulfonyl)ethane **2** (124 mg, 2 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol %), *N*,*N*-dimethylethane-1,2-diamine (**L1**, 3.5 mg, 20 mol %), and KO^{t}Bu (44.8 mg, 2 equiv) was stirred in DMF/MeCN (v/v = 1:1, 2 mL) at 120 °C for 24 h until complete consumption of starting material as monitored by TLC and GC-MS analysis. Then the mixture was diluted with diethyl ether and washed with saturated NaCl. The organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum; the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the pure product.

(11) Volkova, Y. A.; Averina, E. B.; Grishin, Y. K.; Bruheim, P.; Kuznetsova, T. S.; Zefirov, N. S. *J. Org. Chem.* **2010**, *75*, 3047.

(*E*)-*N*-Benzyl-*N*,3-diphenyl(phenylsulfonyl)acrylamide (3): 73% yield (66.1 mg); colorless oil; ^{1}H NMR (500 MHz) δ 7.50 (d, J = 7.5 Hz, 1H), 7.38−7.29 (m, 10H), 7.24 (t, J = 7.5 Hz, 1H), 7.19−7.13 (m, 3H), 6.98 (t, J = 7.5 Hz, 2H), 6.90 (d, J = 7.0 Hz, 2H), 6.74 (t, J = 7.5 Hz, 2H), 4.76 (s, 2H); ^{13}C NMR (125 MHz) δ 164.2, 146.4, 140.5, 137.9, 136.5, 133.5, 132.5, 130.1, 129.5, 129.4, 129.1, 129.0, 128.8 (2C), 128.6, 128.5, 128.4, 128.0 (2C), 127.8, 127.4, 127.3, 52.5; IR (KBr, cm^{-1}) 1653, 1647; LRMS (EI, 70 eV) m/z (%) 453 (M^+, 1), 211 (100), 123 (61); HRMS (EI) for $C_{28}H_{23}NO_3S$ (M^+) calcd 453.1399, found 453.1397.

(*E*)-Methyl 3-phenyl-3-(phenylsulfonyl)acrylate (18): 43% yield (26 mg); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (t, J = 1.5 Hz, 3H), 7.56−7.39 (m, 2H), 7.35−7.33 (m, 1H), 7.21−7.02 (m, 3H), 7.01 (d, J = 1.5 Hz, 2H), 3.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 154.9, 137.5, 133.7, 129.8, 129.6, 129.4, 129.0, 128.8, 127.8, 126.6, 51.9; IR (KBr, cm^{-1}) 1738, 1654; LRMS (EI, 70 eV) m/z (%) 302 (M^+, 1), 160 (100); HRMS (EI) for $C_{16}H_{14}O_4S$ (M^+) calcd 302.0613, found 302.0610.

Vinylsulfonylbenzene:[11] colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (t, J = 8.0 Hz, 2H), 7.65−7.61 (m, 1H), 7.56 (t, J = 7.5 Hz, 2H), 6.69−6.64 (m, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 16.5 Hz, 1H), 6.05 (d, J = 9.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 138.4, 133.6, 129.3, 129.1, 127.9; LRMS (EI 70 eV) m/z (%) 168 (M^+, 21), 125 (100).

Acknowledgment. We thank the Scientific Research Fund of Hunan Provincial Education Department (No. 08A037), Natural Science Foundation of China (No. 20872112), and Hunan Provincial Innovation Foundation for Postgraduate (No. CX2009B104) for financial support.

Supporting Information Available: Analytical data and spectra (^{1}H and ^{13}C NMR) for all the products **3**−**18** and vinylsulfonylbenzene. This material is available free of charge via the Internet at http://pubs.acs.org.