JOC*Note*

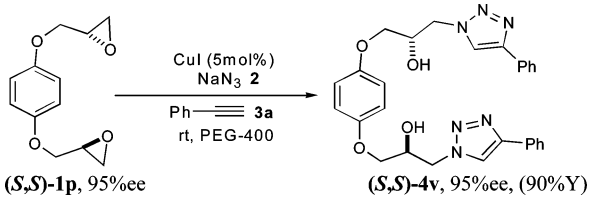
Tandem Epoxide or Aziridine Ring Opening by Azide/Copper Catalyzed [3+2] Cycloaddition: Efficient Synthesis of 1,2,3-Triazolo β-Hydroxy or β-Tosylamino Functionality Motif

Gullapalli Kumaraswamy,* Kukkadapu Ankamma, and Arigala Pitchaiah

Organic Division III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad-500 007, India

gkswamy_iict@yahoo.co.in; gkswamy@iictnet.org

Received August 6, 2007



A novel and practical procedure for the synthesis of small molecules possessing β-hydroxy or *N*-tosylamino 1,2,3-triazole motif by azidation of epoxides or *N*-tosylaziridines with sodium azide followed by "click reaction" using eco-friendly PEG-400 as a reaction medium in the presence of 5 mol % of CuI is described. Enantiomerically pure epoxide and *N*-tosylaziridines were afforded in high yield with excellent ee values maintaining complete stereospecificity.

Cycloaddition reactions involving heteroatoms, such as 1,3-dipolar addition, provide rapid access to an enormous variety of interesting five- and six-member heterocycles which have found wide applications in medicinal chemistry and material science.[1] Among the vast pool of cycloaddition reactions, the Huisgen [3+2] dipolar cycloaddition of alkynes and azides to afford substituted 1,2,3-triazoles has emerged as " the cream of the crop".[2] However, the thermally driven Huisgen [3+2] dipolar cycloaddition of alkynes and azides leads to a regioisomeric mixture of products.[3] Recently, Sharpless[4] and Meldal[5] groups independently reinvigorated the Huisgen [3+2] dipolar cycloaddition by using a substiochiometric amount of Cu(I) metal source. The copper-accelerated [3+2] dipolar cycloaddition reaction of alkynes and azides not only takes place with high yield under mild condition but also leads to exclusively 1,4-regioisomeric product. Since then, this reaction has been used for the construction of a variety of multivalent structures such as sugar heterodimers, glycoconjugates,[6] calix-sugars,[7] and dendritic and polymeric materials.[8] Furthermore, the one-pot multistep reaction involving the Wittig olefination, the Knoevenagel condensation, the Diels−Alder cyclization, and Cu(I)-catalyzed alkyne−azide coupling has been explored.[9] Gratifyingly, the same level of success has been found when compared to the traditional methodology. In another variation, microwave-assisted one-pot reaction has generated a variety of triazoles directly from activated aryl halides and sodium azide.[10] In a similar fashion, taking advantage of anomeric activation, rapid one-pot syntheses of triazole-linked glycoconjugates have also been developed from readily available unprotected saccharides or saccharide acetates.[11] Despite these advances, there is a need to broaden the scope of one-pot multistep reaction in combination with "click chemistry".

As part of our program for the rapid synthesis of bioactive molecules,[12] we focused on multicomponent reactions that use an epoxide−azide−Cu(I)-catalyzed Huisgen [3+2] dipolar cycloaddition sequence to provide a range of heterocyclic structures possessing triazolo β-alcohol as a motif. Epoxides and aziridines have been used for decades in organic synthesis due to their ability to undergo Lewis acid mediated ring opening to provide structurally varied products.[13] Herein, we report our results regarding the synthesis of multivalent structures having 1,2,3-triazolo β-hydroxy functionality with varied substitution pattern.

Initially, we considered performing the one-pot epoxide−azide-click reaction employing phenoxy methyloxirane **1a**, sodiumazide **2**, and terminal alkyne **3a** using polyethylene glycol (PEG-400) as the reaction medium in the presence of 10 mol % of CuI. After 16 h of stirring at ambient temperature, the

* Address correspondence to this author. Phone: +91 40 27193275. Fax: +91 40 27193275.

(1) (a) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128−1137. (b) Malkoch, M.; Schleicher, K.; Drockenmuller, E.; Hawker, C. J.; Russell, T. P.; Wu, P.; Fokin, V. V. *Macromolecules* **2005**, *38*, 3663−3678. (c) Bock, V. D.; Hiemstra, H.; van Maarse Veen, J. H. *Eur. J. Org. Chem*. **2006**, 51−68. (d) Brik, A.; Alexandratos, J.; Lin, Y.-C.; Elder, J. H.; Olson, A. J.; Wlodawer, A.; Goodsell, D. S.; Wong, C.-H. *ChemBioChem* **2005**, *6*, 1167−1169.

(2) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

(3) (a) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565. (b) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 633. (c) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 1−176.

(4) Rostovtsev, H. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(5) Torne, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(6) (a) Srinivas, H.; Sudhir, K. *J. Org. Chem.* **2006**, *71*, 364−367. (b) Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. R.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. *Org. Lett*. **2004**, *6*, 3123−3126. (c) Marmuse, L.; Nepogodiev, S. V.; Field, R. A. *Org. Biomol. Chem.* **2005**, *3*, 2225−2227.

(7) Ryu, E.-H.; Zhao, Y. *Org. Lett*. **2005**, *7*, 1035−1037.

(8) (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928−3932. (b) Scheel, A. J.; Komber, H.; Voit, B. I. *Macromol. Rapid Commun.* **2004**, *25*, 1175−1180. (c) von Steenis, D. J. V. C.; David, O. R. P.; van Srrijdonck, G. P. F.; van Maarseveen, J. H.; Reek, J. N. H. *Chem. Commun*. **2005**, 4333−4335.

(9) (a) Ramachary, D. B.; Barbas, C. F., III *Chem. Eur. J*. **2004**, *10*, 5323−5331. (b) Odlo, K.; André Høydahl, E.; Hansen, T. V. *Tetrahedron Lett*. **2007**, *48*, 2097−2099. (c) Barral, K.; Moorhouse, A. D.; Moses, J. E. *Org. Lett*. **2007**, *9*, 1809−1811.

(10) Prasad, A.; Dehaen, W.; Fokin, V. V.; Eycken, E. V. der *Org. Lett.* **2004**, *6*, 4223−4225.

(11) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331−2336.

(12) Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Kiran, M. U. *J. Org. Chem*. **2006**, *71*, 337−340. (b) Kumaraswamy, G.; Markondaiah, B. *Tetrahedron Lett*. **2007**, *48*, 1707−1709.

(13) (a) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Yadav, J. S. *Org. Lett*. **2002**, *4*, 343−345. (b) Das, B.; Reddy, V. S.; Tehseen, F.; Krishnaiah, M. *Synthesis*, **2007**, 666−668. (c) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1995**, *117*, 5897−5898.

10.1021/jo701724f CCC: $37.00
Published on Web 11/14/2007

SCHEME 1. Cu (I)-Catalyzed Synthesis of Substituted Aryloxy *β*-Hydroxy Triazoles

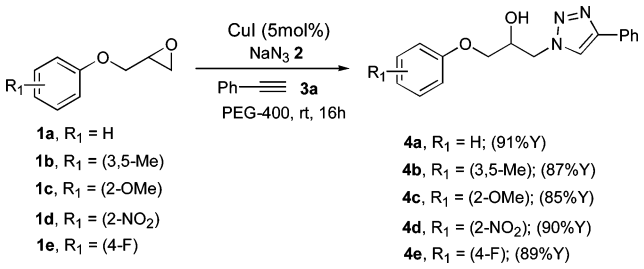


TABLE 1. Study of Solvent Effects on Epoxy−Azide-Cu(I)-Catalyzed Cycloaddition Reaction of 1a, Sodiumazide 2, and Terminal Alkyne 3a[a,b]

entry	solvent	time (h)	% yield of **4a**[c]
1	PEG-200	16	40
2	PEG-400	16	91
3	PEG-600	16	2
4	H_2O:18-crown-6 (15 mol % to **1a**)	48	35
5	H_2O:PEG-400 (8:2)	48	45
6	H_2O	48	0
7	CH_3CN	16	0
8	DMF	16	0
9	DMSO	16	0

[a] All reactions were stirred at room temperature. [b] In all cases 1.1 equiv of NaN_3 and 5 mol % of CuI was used. [c] Isolated yields.

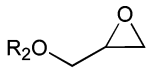
desired product **4a** was obtained in 91% isolated yield (Scheme 1). Next, we examined the catalyst loading and found that 5 mol % of CuI was sufficient to drive the reaction to completion with the same efficacy. Attempts to generate **4a** utilizing $CuSO_4$ with sodium ascorbate in *tert*-butanol:H_2O (8:2) at room temperature failed, while refluxing the same reaction mixture 24 h yielded **4a** in 70% isolated yield.

Among the solvents surveyed, PEG-400 turned out to be the solvent of choice (Table 1). We have also evaluated other reaction media such as PEG-200 and PEG-600 for this transformation. In PEG-200, the product **4a** was obtained in 40% yield, whereas PEG-600 did not yield any trace of product. Other polar solvents like CH_3CN, DMF, and DMSO also were screened at room temperature but the product **4a** was not observed. To our surprise, the reaction in water did not proceed even after prolonged stirring at rt. On the other hand, H_2O:PEG-400 (8:2) as reaction medium provided albeit low yield (45% yield) of product **4a** after 48 h of stirring at rt. The reaction in H_2O:18-crown-6 (15 mol % to **1a**) also yielded product **4a** under identical conditions. These results demonstrate that PEG-400 not only acts as a reaction medium but also presumably activates epoxide and aziridines.

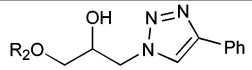
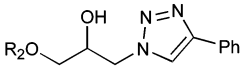
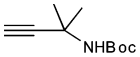
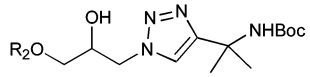
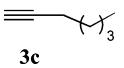
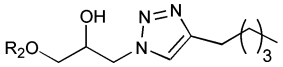
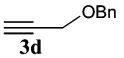
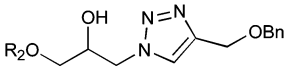
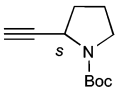
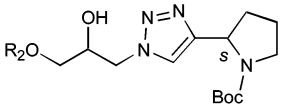
Further, we evaluated the potential of this reaction under optimized conditions and our results are shown in Scheme 1. Regardless of the substitution pattern of the aryl moiety, phenoxyepoxide **1b**−**e** underwent highly regioselective[14] ring opening followed by click reaction to furnish substituted 1,2,3-triazolo *β*-hydroxy products **4b**−**e** in high isolated yields. As can be seen from Table 2, we could extrapolate the epoxy−azide-click reaction using benzyloxy (±)-**1f** and 1-naphthyloxy

(14) No trace of triazole formation was observed between phenylacetylene **3a** and NaN_3 **2** in the presence of 5 mol % of CuI while stirring for 30 h at room temperature in PEG-400. This indicates that the primary step is S_N2 opening of epoxide by azide nucleophile followed by trizole formation leading to the observed product.

TABLE 2. Epoxy−Azide-Cu(I)-Catalyzed [3+2] Huisgen Reaction with Various Acetylenes[a]



(±)-1f, R_2 = Bn
(±)-1g, R_2 = 1-Naphthyl

entry	Acetylene	product[b]
1	**3a**	 **4f** R_2 = Bn (92%Y)
2	**3a**	 **4g** R_2 = 1-Naphthyl (90%Y)
3	 **3b**	 **4h** R_2 = Bn (92%Y)
4	 **3c**	 **4i** R_2 = Bn (88%Y)
5	 **3d**	 **4j** R_2 = 1-Naphthyl (85%Y)
6	 **3e**	 **4k** R_2 = 1-Naphthyl (86%Y)

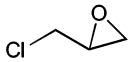
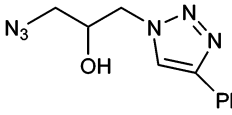
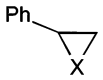
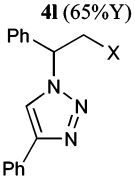
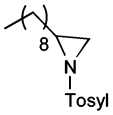
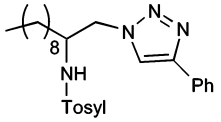
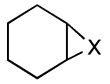
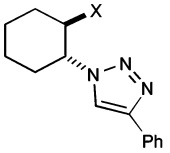
[a] All reactions were carried out at rt with 5 mol % of CuI, 1.1 equiv of NaN_3, in PEG-400 for 16 h. [b] Yield refers to isolated after column chromatography.

epoxide (±)-**1g** and sodium azide **2** with various acetylenes **3a**−**e.** The resulting products of substituted *β*-hydroxy triazoles **4f**−**k** were isolated in good yields. To our delight, epichlorohydrin **1h** underwent S_N2 ring opening with NaN_3 and cycloaddition giving the product ***4l*** with excellent yield (Table 3, entry 1). As predicted, the *meso* epoxide ***1l*** and aziridine **1m** underwent ring opening with NaN_3 concomitant 1,3-dipolar addition with terminal acetylene **3a** to afford the trans-configuration products **4p** and **4q** respectively in good yield (Table 3, entry 4).[13a] In the case of 2-phenyl-*N*-tosylaziridine (±)-**1i,** the product triazole (±)-**4m** was formed exclusively by attack of the azide at benzylic carbon.

Whereas styrene epoxide (±)-**1j** as a substrate yielded the product triazole (±)-**4n** at the benzylic position as the major product (8:2), when 2-*n*-nonyl-*N*-tosylaziridine **1k** was reacted under the same conditions, triazole **4o** was obtained from the attack at the less substituted carbon as exclusive product. A wide array of di- and trivalent aryloxy epoxides as well as acetylenes (Scheme 2) were subjected to the three-component one-pot reaction under standard conditions and the corresponding products **4r**−**u** were obtained with excellent yields.

With the successful formation of the *β*-hydroxy 1,2,3-triazoles from one-pot epoxide−azide−Cu(I)-catalyzed Huisgen [3+2] dipolar cycloaddition, we envisaged to apply the same protocol to enantiomerically pure chiral epoxide and aziridines. Accordingly, the starting materials (*S*)-**1f**, (*S*)-**1g**, (*S*,*S*)-**1p**, and (*S*)-**1i** were prepared[15]and subjected to copper-catalyzed epoxide−azide-click reaction. Gratifyingly, in all cases the corresponding *β*-hydroxy and *N*-tosylamino 1,2,3-triazoles were obtained in

TABLE 3. Cu-Catalyzed Synthesis of *β*-Hydroxy and *N*-Tosyloxyamino 1,2,3-Triazole by Azidation of Epoxides and *N*-Tosylaziridine-"Click" Reaction

Entry	Epoxide	Product [b,c] / Yield[a]
1	 **1h**	 **4l** (65%Y)
2	 **(±)-1i**, X = N-Tosyl; **(±)-1j**, X = O	 **(±)-4m**, X = NH-Tosyl ; (88%Y); **(±)-4n**, X = OH ; (83%Y)[d]
3	 **1k**	 **4o** (90%)
4	 **1l**, X = N-Tosyl; **1m**, X = O	 **4p**, X = NH-Tosyl; (87%Y); **4q**, X = OH ; (88%Y)

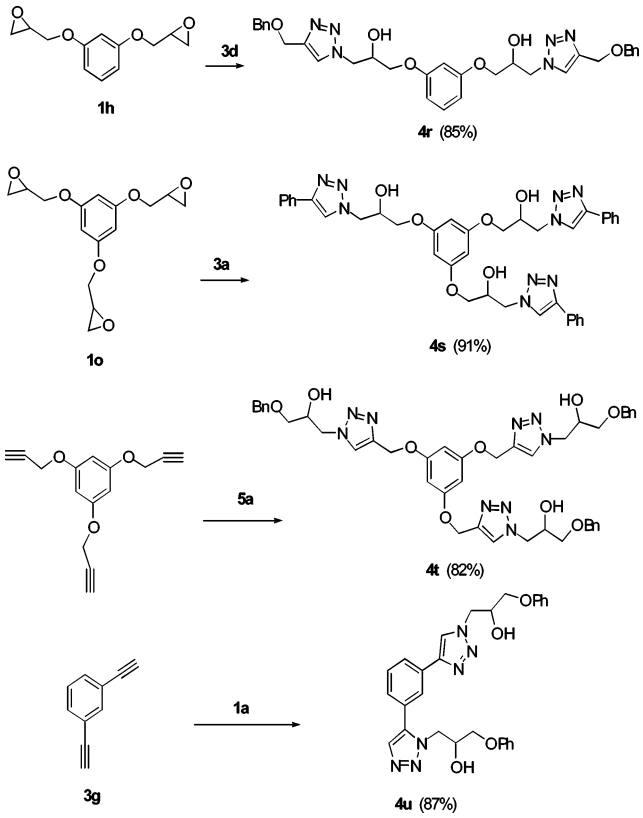
[a] Yield refers to isolated after column chromatography. [b] All reactions were stirred at room temperature for 16 h. [c] In all cases 1.1 equiv of NaN_3 and 5 mol % of CuI was used. [d] Major product isolated yield.

high yields with excellent ee indicating no racemization during the reaction[16] (Scheme 3).

In conclusion, we have developed a novel and practical procedure for the synthesis of small molecules possessing *β*-hydroxy or *N*-tosylamino 1,2,3-triazole motif by azidation of epoxides or *N*-tosylaziridines with sodium azide following "click reaction" using PEG-400 as a reaction medium in the presence of 5 mol % of CuI. This protocol offers the following advantages: (a) use of sodium azide as a low cost raw material when compared to the soluble organic azides for azidolysis under mild reaction conditions, (b) an eco-friendly solvent such as PEG-400 as a reaction medium, and (c) a multicomponent one-pot reaction that is catalyzed by only CuI with a low level of loading.

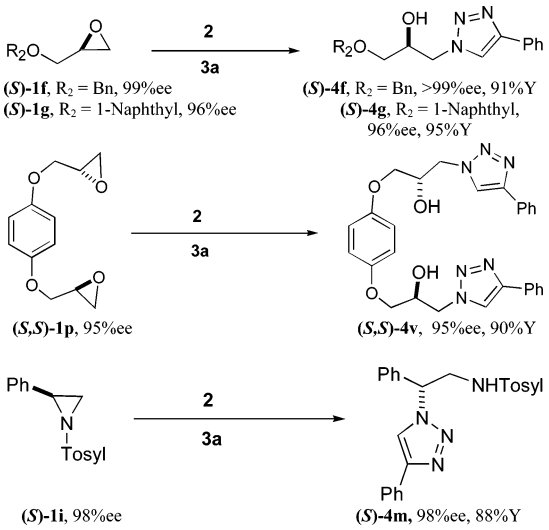
This efficient protocol also facilitates rapid synthesis of small molecules possessing pharmacophores which could be screened for biological activity. Further work is in progress to make use of a chiral catalyst so as to enable the production of enantiomerically pure *β*-hydroxy or *N*-tosylamino 1,2,3-triazoles directly from olefins.

SCHEME 2. Azide-[3+2] Cycloaddition Reaction with Various Epoxides[a,b]



[a] All reactions were carried out at rt with 5 mol % of CuI, 1.1 equiv of NaN_3, in PEG-400 for 16 h. [b]Yields refer to isolated after column chromatography.

SCHEME 3. Enantiopure Epoxide−Azide-[3+2] Cycloaddition Reaction[a,b]



[a] All reactions were carried out at rt with 5 mol % of CuI and 1.1 equiv of NaN_3, in PEG-400 for 16 h. [b]Yields refer to isolated after column chromatography.

(15) (a) Wang, Z. H.; Shen, M. *J. Org. Chem.* **1998**, *63*, 1414−1418. (b) Berry, M. B.; Craig, D. *Synlett* **1992**, 41−44.

(16) (a) The products (*S*)-**4f**, (*S*)-**4g**, and (*S*,*S*)-**4v** were converted to the corresponding (*S*)-MTPA esters. The (*S*)-MTPA esters of (*S*)-**4f** and (*S*)-**4g** were analyzed with reference to their respective racemic (*S*)-MTPA esters on chiral column [Chiral AD-H (220 nm), flow rate = 0.5 mL/min, hexane: 2-propanol (90:10)]. In case of product (*S*,*S*)-**4v**, the ee was estimated by NMR, based on methoxy resonance of (*S*)-MTPA ester, using the recemic (*S*)-MTPA ester as reference. (b) The ee of (*S*)-**4m** was estimated by chiral column [Chiral AD-H (254 nm), flow rate = 1 mL/min, hexane:ethanol: diethylamine (80:20:0.1), see the Supporting Information]. (c) The absolute chemistry of (*S*)-**4f**, (*S*)-**4g**, (*S*,*S*)-**4v**, and (*S*)-**4m** was assigned tentatively.

Experimental Section

Typical Experimental Procedure. Epoxide/aziridine (1 mmol), NaN_3 (1.1 mmol), and CuI (5 mol %) were dissolved in PEG-400 (3 mL). The combined contents were stirred for 5 min at room temperature under argon atmosphere. To this was added acetylene (1.1 mmol) via syringe, and the resultant reaction mixture was allowed to stir at room temperature for a specified period of time. The reaction mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, followed by concentration under reduced pressure resulting in crude product. The crude residue was purified by column chromatography (silica gel 60−120 mesh) with hexane: EtOAc (6:4) elutant to give the triazole product. This was recrystallized with hexane:EtOAc (6:4).

4a: white solid, yield 91%; m p 133−135 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 3.87−4.04 (m, 2H), 4.24−4.38 (m, 1H), 4.45−4.55 (dd, J = 7.1, 13.8 Hz, 1H), 4.76−4.75 (dd, J = 3.6, 13.8 Hz, 1H), 4.51 (d, J = 5.5 Hz, 1H), 6.92−6.95 (m, 3H), 7.21−7.43 (m, 5H), 7.79−7.83 (dd, J = 1.6, 8.3 Hz, 2H), 8.16 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) 52.7, 67.7, 69.3, 114.4, 120.7, 122.2, 125.0, 127.6,128.7, 129.4, 130.7, 145.9, 158.2; IR (KBr) 1466, 1593, 1685, 2916, 3087, 3443 cm^{-1}; ESIMS (*m*/*z*) 296 (M + 1); HRMS calcd for $C_{17}H_{17}N_3O_2Na$ 318.1218, found 318.1220.

Acknowledgment. We are grateful to Dr. J. S. Yadav, Director, IICT, for his constant encouragement. Thanks are also due to Dr. T. K. Chakraborty for his support. K.A. and A.P. are thankful to CSIR & UGC (New Delhi) for awarding the fellowship.

Supporting Information Available: Experimental details and analytical data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701724F