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An Efficient Method for the Synthesis of Nitropiperidones

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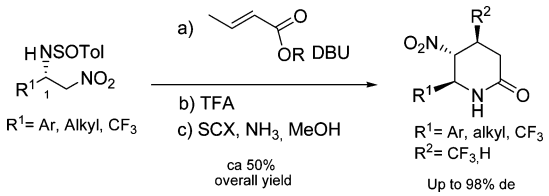
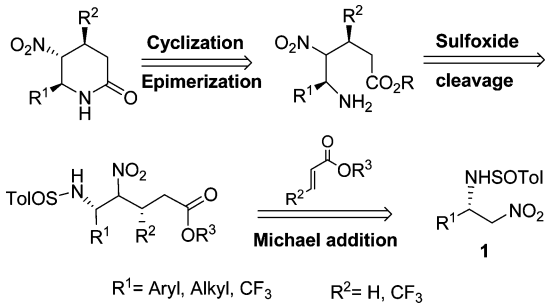


A three step efficient strategy for the synthesis of substituted 5-nitropiperidones in high de, employing Michael addition of N-*p*-tolylsulfinyl β-nitroamines to α,β-unsaturated esters, hydrolysis of the sulfinyl group, and cyclization of the resulting free amines, has been developed. A very simple experimental procedure involving mild conditions and only one chromatographic purification are the main features of the process.

Piperidones are attractive synthetic targets due to their interesting pharmacological properties.[1] They are also used as precursors to the piperidine ring,[1a,2] which is a frequently observed structural feature of many of the biologically important alkaloids and aza sugars. As a consequence, considerable interest is centered on the synthesis of piperidones in general, and nitropiperidones[3] in particular, because the latter are precursors to aminopiperidines, which exhibit a wide range of interesting biological activities.[4] Moreover, in view of the increased biological potential of the fluorinated derivatives,[5] there has been an ever increasing quest for novel routes toward the synthesis of fluorinated piperidones[6] and thus piperidines.[7]

We have recently reported the highly diastereoselective synthesis of nitroamines **1** by the asymmetric aza-Henry reaction

SCHEME 1. Retrosynthetic Analysis of Substituted Piperidones



of nitromethane[8] with a wide variety of *N*-*p*-tolylsulfinylimines derived from aldehydes (aliphatic and aromatic) or ketones,[9] even when they had enolizable protons. We envisioned that enantiomerically pure substituted nitropiperidones could be obtained from the Michael addition of β-nitroamines **1**, followed by sulfoxide removal and cyclization (Scheme 1). Despite of the low diastereoselectivity anticipated for the Michael addition on the basis of our previous results,[10] the strong acidity of the α-proton to nitro group also made predictable an easy epimerization of the final nitropiperidone favoring one diastereoisomer.

A straightforward strategy for the diastereoselective synthesis of substituted nitropiperidones, including fluorinated derivatives, is reported herein.

For optimization of the Michael reaction conditions, *N*-*p*-tolylsulfinylnitroamine **1a** and ethyl acrylate were utilized as reaction partners. Reaction was attempted by using several bases (Et_3N, cinchona alkaloids, BuLi, DBU) and solvents (THF, CH_2Cl_2, MeCN) at different temperatures.[11] Some representative results are presented in the Table 1, which indicate that a fine-tuning of the reaction conditions was necessary to minimize

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(9) *N*-*p*-Tolylsulfinylimines where obtained by condensation of the corresponding aldehydes with (*S*)-*N*-*p*-tolylsulfinylamide following the Ti-$(OEt)_4$ Davis' protocol (a) with slight modifications in the workup (b): (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13 and references cited therein. (b) García Ruano, J. L.; Alemán, J.; Cid, M. B.; Parra, A. *Org. Lett.* **2005**, *7*, 179.

(10) For reaction with nitroethane and transformations, see also: García Ruano, J. L.; López-Cantarero, J.; de Haro, T.; Alemán, J.; Cid, M. B. *Tetrahedron* **2006**, *62*, 12197.

(11) For a review article on the conjugate additions of nitroalkanes, see: Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

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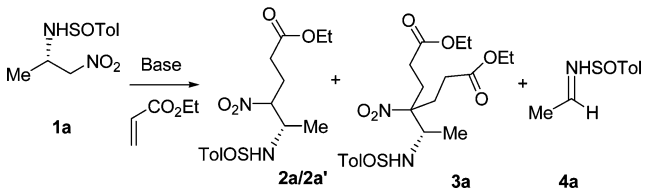
TABLE 1. Optimization of the Reaction Conditions for the Michael Addition



entry	base (equiv), equiv of acrylate	solvent	*t* (h)	*T* (°C)	conv[a] (%)	**2a**/**2a′**/ **3a**/**4a**[a]
1	Et_3N (5), 18	CH_2Cl_2	120	rt	80	31:43:26:0
2	quinine (5), 18	CH_2Cl_2	144	rt	99	30:42:11:17
3	quinidine (5), 20	CH_2Cl_2	15	rt	100	16:22:26:36
4	cinchonidine (5), 20	CH_2Cl_2	168	rt	43	52:38:0:10
5	$(DHQ)_2PHAL$ (5), 20	CH_2Cl_2	168	rt	0	
6	BuLi (0.5), 5	THF	10	−78 to 0	100[b]	44:34:22:0
7	DBU (1.1), 5	CH_2Cl_2	1	rt	100	0:0:0:100
8	DBU (0.4), 5	CH_2Cl_2	1.5	−35	92	50:36:7:7
9	DBU (0.4), 5	MeCN	1.5	−35	100[c]	55:28:17:0

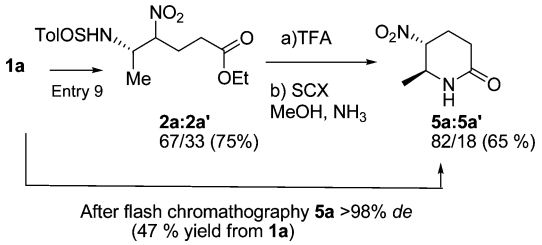
[a] Determined by ^1H NMR. [b] **2a** and **2a′** were isolated in 42% yield after flash chromatography. [c] **2a** and **2a′** were isolated in 75% yield after flash chromatography.

the formation of the double Michael addition (**3a**) and the retro aza-Henry reaction **(4a**) products.[12,13]

When Et_3N was used as base (entry 1), the sluggish reaction afforded a mixture of the mono- and double-Michael addition products **2** and **3**, with a low selectivity at the new chiral center (**2a**/**2a′** = 42:58). The use of chiral bases such as cinchona alkaloids (entries 2−5) neither increased the diastereoselectivity nor suppressed the formation of the retro aza-Henry product **4a**.[14] Under cinchonidine catalysis, **3a** was not formed, but the reactivity was drastically decreased (43% conversion at rt after 168h, entry 4). No reaction was observed with $(DHQ)_2PHAL$ (entry 5). A large excess of ethyl acrylate (18−20 equiv) and a high equivalent of base were used in all the above-mentioned cases. When BuLi (0.5 equiv) was used as base, **2a** and **2a′** were isolated in 42% combined yield (entry 6) and compound **4a** was not formed.

The best results were obtained with substoichiometric amounts of DBU at −35 °C (entries 8 and 9). When acetonitrile was used as solvent, formation of **4a** could not be detected by ^1H NMR, and a 2:1 mixture of the Michael addition products **2a** and **2a′** in good overall yields (entry 9) along with compound **3a** were obtained. When CH_2Cl_2 was used as solvent, a small ratio of **4a** was detected (entry 8) which became the exclusive product when over-stoichiometric amount of DBU was used at room temperature, as a result of the retro aza-Henry reaction (entry 7). Variation in the temperature in these last two reactions (entries 8 and 9) did not improve the results. Although the results shown in entries 8 and 9 are very similar, we have chosen conditions of the entry 9 to extend our investigations on the

SCHEME 2. Synthesis of Piperidone 5a from 2a + 2a′



basis of the slightly higher selectivity observed. The low selectivity (**2a**/**2a′** ratio) obtained under all the conditions, suggests an easy equilibration due to the strongly acidic character of the α-proton to the nitro group. Differences in the **2a**/**2a′** ratio observed in CH_2Cl_2 and CH_3CN indicates the influence of the solvent polarity on the stability of the epimers.

The treatment of a purified **2a**/**2a′** mixture (67:33) with TFA to remove the sulfinyl group[15] resulted in a crude that after loading on a SCX column[16] directly afforded lactams **5a** and **5a′** as a clean 82/18 mixture of diastereoisomers in 65% yield.[17] Cyclization and further isomerization[18] at C5 occurred when the product was being eluted with $MeOH/NH_3$ from the SCX column (Scheme 2).[19]

Further, in order to increase the synthetic as well as practical utility of this method, it was planned to eliminate the chromatographic purification after the Michael addition step. Toward this end, a crude mixture of the Michael addition reaction, obtained under conditions mentioned in Table 1 (entry 9), was subjected to the treatment shown in Scheme 2. To our delight, lactam **5a** was isolated diastereomerically pure after only one final chromatographic purification (**5a′** was not detected by ^1H NMR) in 47% overall yield starting from **1a** (Scheme 2 and entry 1, Table 2). It is noteworthy that this protocol involves three steps (Michael addition/desulfinilation/cyclization to one of the epimers) in a very simple experimental procedure, requiring only one final chromatographic separation, for obtaining a diastereoismerically pure product, despite of the modest diastereoselectivity of the Michael addition step.

With the optimized conditions for the whole process, we examined the scope and limitations of this straightforward approach in the reactions of *N*-sulfinyl nitroamines containing aromatic and more hindered aliphatic groups with ethyl acrylate and methyl β-trifluoromethylacrylate (Table 2). When *N*-sulfinyl β-nitroamines **1b** and **1c** were submitted to the conditions indicated in Table 2, lactams **5b** and **5c** respectively, were obtained in excellent diastereomeric excess and reasonable yields (Table 2, entries 2 and 3).[20]

The (*S*) configuration at C-6 has been assigned on the basis of the well-established stereochemical course of the aza-Henry

(12) We observed a similar behavior when the corresponding *N*-sulfonylnitroamine, obtained by oxidation of the corresponding *N*-sulfinylnitroamine **1a** was subjected to Michael addition conditions.

(13) When we used nitroamine with a phenyl group (**1b**) as starting material, compound obtained from retro aza-Henry reaction turned out to be the main product under most of the conditions used.

(14) For enantioselective Michael addition of nitro derivatives with cinchona alkaloids see for example a review article: Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, 299.

(15) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993.

(16) SCX (Strong cation exchange) resin to effect "catch and release" purification.

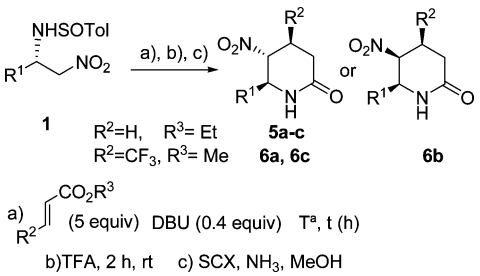
(17) For another example of synthesis of piperidones from sylfinylimines, see: Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *17*, 2623.

(18) **5a** was treated for several hours with DBU (0.4 equiv) in $CHCl_3$ and then filtered through a sort pad of silica gel eluting with EtOAc. The formation of a 87/13 mixture of **5a** and **5a′** supports that epimerization is taking place under these conditions.

(19) A similar strategy that also uses aza-Henry reaction and cyclization has been described to obtained racemic 5-nitro-6-substituted lactames: Bhagwatheeswaran, H; Gaur, S. P.; Jain, P. C. *Synthesis* **1976**, 615.

(20) Although in most of the cases the amine has been previously passed through a SCX column, it has been proven that the yields of the final piperidones are similar when the reaction crudes are directly treated with NH_3 in MeOH (see note b in entry 2 of Table 2 and Scheme 3).

TABLE 2. Preparation of Substituted Piperidones through the Sequence Michael/Desulfuration/ Cyclization/Epimerization



entry	R^1	R^2	step a: T (°C)/t	de[a] **5** or **6**	yield (%) of **5** or **6**
1	Me (**1a**)	H	−35/1h 30 min	>98	47 (**5a**)
2	Ph (**1b**)	H	−15/35 min	>98	49[b] (**5b**)
3	*i*-Pr (**1c**)	H	−10/3 h	>98	54 (**5c**)
4	Me (**1a**)	CF_3	−25/25 min	82[c]	50 (**6a**)
5	Ph (**1b**)	CF_3	−15/20 min	96	54 (**6b**)
6	*i*-Pr (**1c**)	CF_3	−5/15 min	96	44 (**6c**)

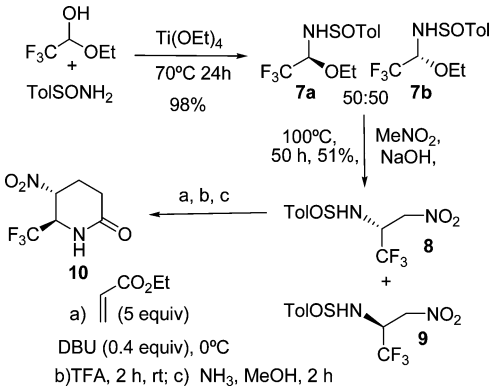
[a] Determined by ^{1}H NMR after flash chromatography. [b] 52% yield was obtained when the crude obtained after treatment with TFA was directly treated with NH_3/MeOH without using the SCX column. [c] Before flash chromatography **6a** was obtained in 60% de.

reaction.[8] The trans arrangement of the substituents R^1 and NO_2 was unequivocally established by X-ray analysis for **5b** (R^1 = Ph) (see the Supporting Information). Identical configuration was assumed for the rest of the disubstituted piperidones **5**.

As the synthesis of (±)-CP-99,994, a highly potent NK1 and substance P nonpeptidic antagonist,[21] has been described from racemic **5b**,[22] the above-described method for preparing enantiomerically pure **5b** (Table 2) can be considered as an efficient formal synthesis of (+)-CP-99,994.[23]

Although reactions of compounds **1a**−**c** with *β*-trifluoromethyl acrylate[24] were expected to be much more complex because of the formation of an additional chiral center, the results were analogously satisfactory (Table 2, entries 4−6) by employing the sequence used for synthesizing lactams **5**. Under very mild conditions,[25] Michael reactions afforded diastereomeric mixtures[26] that were directly transformed into *γ*-trifluoromethyl piperidones **6a**−**c** by the sequence shown in Table 2. Lactam **6a** was obtained with 82% de (entry 4) after chromatographic purification, whereas **6b** and **6c** were obtained in 96% de. The stereochemistry of lactams **6a**−**c** has been determined by analysis of the coupling constants and NOESY experiments.[26]

SCHEME 3. Synthesis of the α-trifluoromethyl Piperidone 10



It is remarkable that the stereochemistry of **6b** (all groups are in a cis arrangement) is different from that observed in case of **6a** and **6c**, which is probably related to the thermodynamic stability of the epimers at C-5.

Due to the electron-withdrawing properties of the CF_3 group, small changes in the strategy used to obtain the starting nitroamine **8**, required for the preparation of the disubstituted piperidone **10,** were necessary (Scheme 3). Compounds **7a** or **7b** were prepared as a 1:1 diastereomeric mixture by reaction of (*S*)-tolylsulfinyl amide with the ethyl hemiacetal of the trifluoroacetaldehyde.[27] The aza-Henry reaction of either **7a**, **7b**, or a mixture of both, with nitromethane using NaOH as base required high temperature to afford the same mixture of nitroamines **8** and **9**, which could be obtained diastereomerically pure in 28 and 23% yield, respectively, after separation by flash chromatography. The application of the previously developed protocol involving three steps to compound **8,** afforded α-trifluormethyl piperidone **10** in an unoptimized 37% yield after flash chromatography (Scheme 3).

In summary, we have developed an efficient three step diastereoconvergent strategy that provides a straightforward access to a number of enantiomerically pure substituted nitropiperidones from nitroamines, using a simple experimental protocol involving only one chromatographic purification. Structural variation can be set up in the substituent appended at C6 including aliphatic, aromatic, and CF_3 groups. Trisubstituted lactams have also been prepared in a highly stereoselective manner with a CF_3 group at C4.

Experimental Section

General Procedure for the Michael Reaction of (*S*)-*N*-Sulfinylnitroamines. DBU (0.05 mmol) was added to a solution of the corresponding *N*-sulfinylnitroamine (0.123 mmol) and the α,*β*-unsaturated compound (0.615mmol) in acetonitrile (1 mL) at the specified temperature. The reaction mixture was stirred at temperature and reaction time indicated in each case. Reactions were monitored by TLC (hexane/EtOAc). After completion, the reaction mixture was filtered through a short pad of silica gel, and the silica gel was thoroughly washed with excess of EtOAc. In all cases, the crude was used for the next step without prior purification. Nevertheless, for some cases

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(22) (a) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831. (b) Desai, M. C.; Lefkowitz, S. L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2083.

(23) For some examples of asymmetric synthesis of CP-99,994, see: (a) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466. (b) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4564. (c) Davis, F. A.; Zhang, Y.; Li, D. *Tetrehedron Lett.* **2007**, *48*, 7838.

(24) For Michael addition of other nitro derivatives on this substrate, see: Miyake, N.; Kitazume, T. *J. Fluorine Chem.* **2003**, *122*, 243.

(25) The CF_3 group increases the reactivity of the acrylate. Other substituted acrylates like 3-phenyl acrylate and *p*-nitrophenyl acrylate do not react under the optimized conditions for ethyl acrylate.

(26) For a discussion of the stereochemical assignment as well as some molecular modeling supporting such assignment, see the Supporting Information.

(27) To prepare **7a** and **7b**, we followed the same procedure described for the synthesis of the corresponding *t*-Bu (Ellman) sulfinimine−ethanol adducts: Kuduk, S. D.; Di Marco, C. Ng.; Pitzenberger, S. M.; Tsou, N. *Tetrahedron Lett.* **2006**, *47*, 2377.

diastereoisomers have been purified by flash chromatography for characterization purpose.

(5*S*,4*R*,(S)*S*)- and (5*S*,4*S*,(S)*S*)-Ethyl-5-phenyl-5-*N*-(*p*-tolylsulfinyl)amino-4-nitropentanate (2b and 2b′). These compounds were obtained as a mixture of diastereoisomers (60:40) following the general procedure for the Michael addition using DBU from **1b** at −15 °C for 35 min. The diasteroisomers were separated by flash chromatography (Hex/EtOAc = 3/1) to give **2b** and **2b′** in >98 % de and 31% and 20% respective yields. Data of the major diasteroisomer **2b**: colorless oil; $[\alpha]^{20}_D$ +136 (*c* 0.45, $CHCl_3$); IR (film): 3228, 3004, 2927, 1723, 1642, 1555, 1089, 1059 cm^{-1}; ^1H NMR (300 MHz) δ: 7.52 (d, J = 8.3 Hz, 2H), 7.42−7.31 (m, 7H), 4.94−4.97 (m, 2H), 4.72 (t, J = 7.6 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 2.40−2.04 (m, 3H), 1.92−1.80 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 171.5, 141.9, 140.9, 136.8, 129.7, 129.3, 129.1, 127.5, 125.5, 91.4, 60.8, 59.8, 29.7, 26.2, 21.4, 14.1; MS (FAB) *m*/*z* 405 (M + 1, 15), 154 (24), 139 (100); HRMS [M + 1] calcd for $C_{20}H_{25}N_2O_5S$ 405.1477, found 405.1474. Data of the minor diasteroisomer **2b′**: yellow oil; $[\alpha]^{20}_D$ +114 (*c* 0.15 $CHCl_3$); IR (film) 3442, 3004, 2925, 1724, 1642, 1552, 1089, 1057 cm^{-1}; ^1H NMR (300 MHz) δ 7.57 (d, J = 8.3 Hz, 2H), 7.42−7.32 (m, 7H), 4.89−4.77 (m, 3H), 4.10 (q, J = 7.3 Hz, 2H), 2.43 (s, 3H), 3.37−2.04 (m, 4H), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz) δ 171.7, 136.6, 129.8, 129.1, 129.0, 128.3, 127.6, 127.4, 125.3, 90.9, 60.9, 59.4, 30.0, 24.8, 21.4, 14.1; MS (FAB) *m*/*z* 405 (M + 1, 46), 154 (56), 139 (100), HRMS [M + 1] calcd for $C_{20}H_{25}N_2O_5S$ 405.1484, found 405.1480.

General Procedure for Removal of Sulfinyl Group, Cyclization, and Epimerization. TFA (trifluoroacetic acid) (0.615 mmol) was added to a solution of the corresponding crude material, obtained from the Michael addition (using 0.123 mmol of the β-nitroamine) in methanol (1 mL) at room temperature, and the reaction mixture stirred for 2 h. The solvent was evaporated under reduced pressure to get a residual mass. The cyclization can be carried out by two different procedures. (A) The crude residual mass was dissolved in 1 mL of a 7 N NH_3/MeOH solution, and the mixture was stirred for 30 min. The solvent was evaporated and the crude was purified by flash chromatography. (B) The crude residual mass was directly loaded onto a SCX column (Varian BondElut, 1000 mg SCX resin/10 mL) and the impurities were eluted with MeOH (2 × 5 mL), the product was eluted with 7 N NH_3/MeOH (2 × 5 mL), and the resulting solution stirred for 30 min. After removal of the solvent, the compounds were purified by flash chromatography.

(5*R*,6*S*)-5-nitro-6-phenylpiperidin-2-one (5b). This compound was obtained in 49% yield following the general method for the hydrolysis of sulfoxide with TFA of a mixture of **2b** and **2b′** and the procedure B for the cyclization process. After flash chromatography (Hex/EtOAc = 1/2), compound **5b** was obtained in a de >98%. Following procedure A, diastereomerically pure **5b** was obtained in 52% yield: white solid; mp 141 °C; $[\alpha]^{20}_D$ −56 (*c* 0.25, $CHCl_3$); IR (film) 3364, 3229, 1662, 1551, 1373, 786, 462, 442 cm^{-1}; ^1H NMR (300 MHz) δ 7.45−7.30 (m, 5H), 6.16 (bs, NH), 5.25 (dd, J = 6.1 Hz, J = 1.8 Hz 1H), 4.74−4.68 (m, 1H), 2.74−2.68 (m, 3H), 2.37−2.27 (m, 1H); ^{13}C NMR (75 MHz) δ 169.7, 137.3, 129.4 (2C), 126.5, 85.1, 58.9, 27.8, 23.3; MS (EI+) *m*/*z* 220 (M^+, 3), 173 (100), 77 (25); HRMS (EI+) calcd for $C_{11}H_{12}N_2O_3$ 220.0839, found 220.0847.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2a**−**c**, **5a**−**c**, **6a**−**c**, **7a**,**b**, and **8**−**10** and some other intermediates as well as X-ray ORTEP of **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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