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Formation of 4*H*-1,2-Benzoxazines by Intramolecular Cyclization of Nitroalkanes. Scope of Aromatic Oxygen-Functionalization Reaction Involving a Nitro Oxygen Atom and Mechanistic Insights

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Abstract: In this paper, we deal with the scope and mechanism of the strong Brønsted acid-catalyzed intramolecular cyclization reaction of methyl 3-aryl-2-nitropropionates to give 4*H*-1,2-benzoxazines. This reaction can be regarded as an oxygen functionalization of the aromatic ring wherein the oxygen atom is derived from the nitro group in the molecule, and it is favored by the presence of electron-withdrawing groups on the benzene ring. The reaction rate is strongly influenced by the acidity of the reaction medium, and the methyl ester group on the α-carbon atom with respect to the nitro group facilitates deprotonation at the α-position to give *aci*-nitro species in situ. Some correlation was found between the electron-withdrawing ability of the substituents on benzene, represented in terms of Hammett's σ_p value of the substituents, and the rate of disappearance of the starting substrate leading to the product in trifluoromethanesulfonic acid (TFSA)/trifluoroacetic acid (TFA) medium. This would be because the acidity of the α-proton with respect to the nitro group is influenced by the substituents on the benzene ring. Experimentally, we excluded the 6π electrocyclization mechanism involving deprotonation of the benzyl proton of the protonated *aci*-nitro species. Alternative cyclization mechanisms involving equilibrating monocationic *aci*-nitro species bearing *O*-protonated ester carbonyl group and *O*-protonated *aci*-nitro species were calculated to be highly energetically unfavorable. Diprotonated or protosolvative species can reduce the activation energy significantly, and this is consistent with the observed acidity-dependent nature of the cyclization.

1. Introduction

Oxygen-containing aromatic structures, such as phenols and anisoles, are key components of both natural and synthetic compounds and are important in many areas of applied chemistry. Many synthetic methods for oxygen-functionalized aromatic compounds have been reported: the cumene−hydroperoxide method,[1] the toluene−benzoic acid method,[2] hydrolysis of aryl diazonium salts or aryl sulfonic acids,[3] Dakin oxidation,[4] Baeyer−Villiger reaction,[5] Claisen rearrangement,[6] aromatic nucleophilic substitution (S_NAr) reaction of aryl halides,[7] direct oxygenation of aryl−metal species,[8] and so on. Friedel−Crafts-type reactions with oxygen-electrophilic species, formally equivalent to ^+OH, have also been reported.[9] In addition, aromatic oxygenation with the aid of various zeolite catalysts has been investigated recently.[10] However, these reported synthetic methods of oxygenated aromatic compounds have various limitations, including harsh reaction conditions, limited substrate applicability, low reaction efficiency, low chemoselectivity, and low regioselectivity. Therefore, the development of efficient oxygenation reactions of aromatic compounds,

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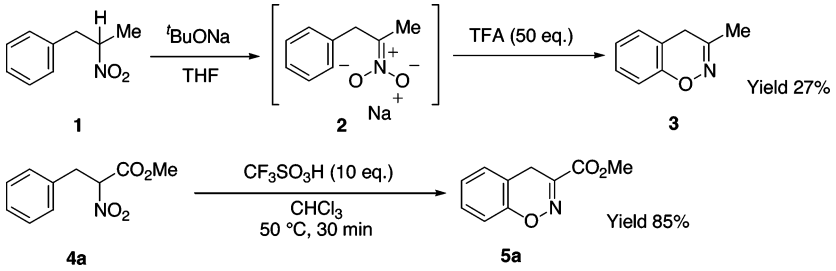
Scheme 1



particularly those with high substrate generality and high chemo- and regioselectivity, is still of great interest.

Direct introduction of an oxygen atom into a C−H bond is a very attractive idea, but its feasibility is still very limited, for both aromatic and aliphatic C−H bonds. In particular, there has been little study of the utilization of an oxygen atom of the nitro group as an oxygen source for aromatic-oxygenation, although aromatic nitrogen-functionalization via reduction of a nitro group is well established.[11]

Acid-catalyzed Friedel−Crafts-type cyclization reaction of nitro olefins in the presence of benzene has been reported to generate 4*H*-1,2-benzoxazine.[12] This reaction could be regarded as the first example of intermolecular oxygen transfer reaction from a nitro group to a benzene ring. However, this reaction turned out to lack generality, because substituted aromatic compounds failed to provide the desired heterocyclic compounds.[12] Thus, oxygen functionalization from a nitro group is still little explored, although it is of great interest because of its singular character. We will report herein several chemical features of the acid-catalyzed intramolecular transfer of an oxygen atom of the nitro group of nitroalkanes to provide cyclized products, 4*H*-1,2-benzoxazines, and the results of a mechanistic study of this aromatic oxygen-functionalization reaction.[13]

2. Results and Discussion

Acid-Catalyzed Cyclization of Nitro Alkanes to 4*H*-1,2-Benzoxazines. Scheme 1 shows the acid-catalyzed cyclization reaction of 2-nitro-3-phenylpropane **1**. Its sodium salt **2** gave 3-methyl-4*H*-1,2-benzoxazine **3** in 27% yield in the presence of TFA as a Brønsted catalyst, while no cyclization reaction of free **1** took place even in the presence of acids such as TFA or trifluoromethanesulfonic acid (CF_3SO_3H, TFSA). These results suggested involvement of an *aci*-nitro species or *O*-protonated *aci*-nitro species in the cyclization reaction. Thus, we studied the reaction of methyl 2-nitro-3-phenylpropionate **4a**, in which the ester group should facilitate enolization to the *aci*-nitro species. When methyl 2-nitro-3-phenylpropionate **4a** was added to 10 equiv of TFSA in $CHCl_3$ as a cosolvent and the mixture was heated at 50 °C for 30 min, 3-methoxycarbonyl-4*H*-1,2-benzoxazine **5a** was obtained in 85% yield. Without the use of the cosolvent, the yield of **5a** was decreased (<58%). The reaction did not proceed at all in TFA even when the solution was heated at reflux for 2 days. The reaction also proceeded in 1,2-dichloroethane (1,2-$(CH_2Cl)_2$) as a cosolvent, while aprotic polar solvents such as acetonitrile or ethers were inappropriate, because they worked as bases to neutralize the high acidity of TFSA. We also examined various Lewis acids, which might promote the present intramolecular cyclization of **4a**. When $TiCl_4$ (2.5 equiv) or $ZrCl_4$ (10 equiv) was employed, the cyclization proceeded, and the cyclized product (**5a**) was obtained in moderate to low yield (41% and 18%, respectively). Other Lewis acids such as $Ti(O^iPr)_4$, $Sc(OTf)_3$, $FeCl_3$, $ZnCl_2$, $AlCl_3$, or $GaCl_3$ did not catalyze the reaction or did not provide a pure product.

Next, similar reactions of methyl 3-aryl-2-nitropropionates bearing various substituents on the benzene ring were investigated (Table 1). Unexpectedly, when the substituent on the benzene ring was an electron-withdrawing group such as a halogen **4b**−**4f**, ester **4g**, amide **4h**, trifluoromethyl **4i**, cyano **4j**, or nitro group **4k**, the reactions proceeded smoothly to give the corresponding 4*H*-1,2-benzoxazines **5** in moderate to good yields. This substituent preference of the substrates is in sharp contrast to the case of 3-aryl-2-nitropropanes (Scheme 1); only unsubstituted **1** (in the form of the salt **2**) gave the cyclized product **3**, while the cyclization of the sodium salt of 3-aryl-2-nitropropanes failed to proceed when the aromatic moiety was substituted with a chloride, cyano, nitro, or methyl group at the *p*-position, or two methyl groups at the *m*,*p*-positions. Furthermore, **4l**, bearing an aromatic nitro group at the *o*- and *p*-positions with respect to the cyclizing carbon atom, also gave the cyclization products, a mixture of *p*-cyclized (**5l**, yield 23%) and *o*-cyclized products (**5l′**, yield 51%) (Table 1, entry 12). It seems unlikely that this regioselectivity of the cyclization was controlled by steric factors; it seems more likely to depend on electronic factors, that is, the electron deficiency of the aromatic carbon atom, because the *o*-cyclization with respect to the nitro group was favored over the *p*-cyclization.

In contrast, the reaction of substrates bearing an electron-donating group on the benzene ring gave the cyclized products, 4*H*-1,2-benzoxazines, in low yields. In the case of methyl (**4m**) and 3,4-dimethyl (**4n**) substituents, the yields were only 16% and 4%, respectively, and the cyclization reaction of the

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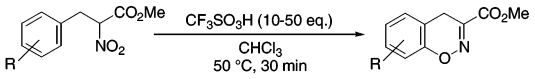
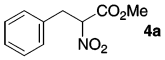
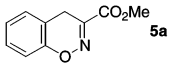
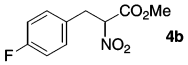
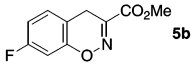
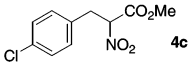
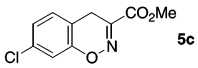
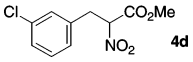
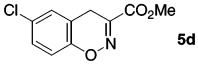
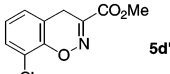
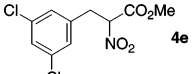
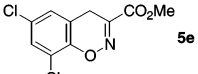
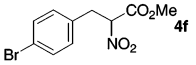
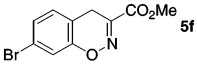
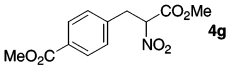
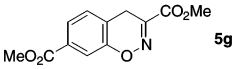
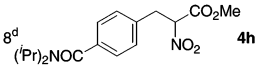
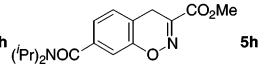
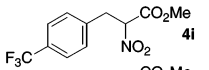
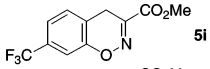
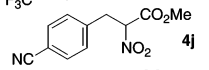
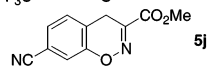
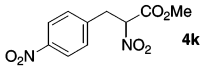
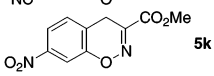
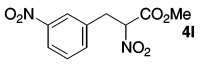
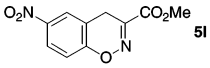
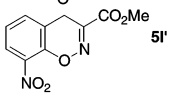
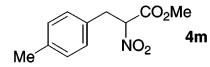
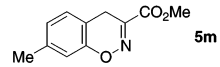
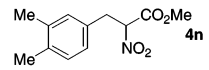
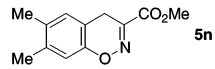
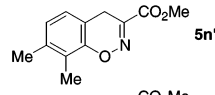
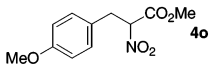
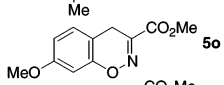
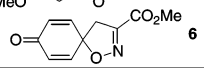
(13) A part of the work was communicated in ref 12.

Table 1. Cyclization of Methyl 3-Aryl-2-nitropropionates to Substituted 4*H*-1,2-Benzoxazines



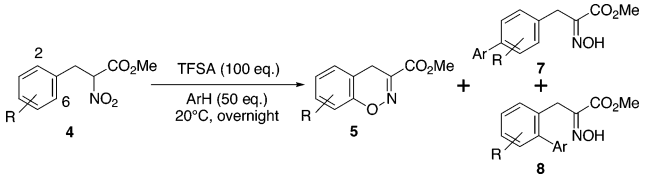
entry[a]	reactant (**4**)	product (**5**)	yield (%)
1	 **4a**	 **5a**	85 45[b] 28[c]
2	 **4b**	 **5b**	75
3	 **4c**	 **5c**	93
4	 **4d**	 **5d**	69
		 **5d′**	9
5	 **4e**	 **5e**	38
6	 **4f**	 **5f**	88
7[d]	 **4g**	 **5g**	85
8[d]	 **4h**	 **5h**	98
9	 **4i**	 **5i**	88
10[d]	 **4j**	 **5j**	59
11	 **4k**	 **5k**	81
12	 **4l**	 **5l**	23
		 **5l′**	51
13	 **4m**	 **5m**	16
14	 **4n**	 **5n**	1[e]
		 **5n′**	3[e]
15	 **4o**	 **5o**	trace
		 **6**	55

[a] Typical reaction conditions: A solution of the substrate (1.0 mmol) in $CHCl_3$ (10 mL) was added to 10 equiv of TFSA (0.89 mL) at 0 °C. The mixture was heated at 50 °C for 30 min. [b] With 2.5 equiv of $TiCl_4$ instead of TFSA, and the reaction was run for 3 h. [c] With 10 equiv of $ZrCl_4$ instead of TFSA. [d] With 50 equiv of TFSA. [e] Determined by ^1H NMR.

substrates with a naphthalene or indole skeleton failed to proceed. In particular, the reaction of the substrate (**4o**) with a methoxy group at the *p*-position gave the spiro compound as a major product **6** (55%), together with a trace amount of the corresponding 4*H*-1,2-benzoxazine (**5o**) (Table 1, entry 15). The low yield of the 4*H*-1,2-benzoxazines bearing electron-donating groups does not result from instability of the products under the reaction conditions. When the isolated cyclized products, **5a** (H), **5i** (*p*-CF_3), and **5m** (*p*-Me), were exposed to these reaction conditions (excess amount of TFSA/$CHCl_3$ at 50 °C for 30 min), the recoveries were 94%, 90%, and 85%, respectively. It should be noted that even **5m** was recovered in good yield, despite the low yield of the cyclization reaction.

Interestingly, when an excess amount of benzene was used as a cosolvent, the biphenyloxime derivatives **7a** and **8a** were formed in addition to the cyclized product **5a** (Table 2, entry 1). The yields of **7a** and **8a** were increased when a large excess of TFSA (50 equiv) and a low reaction temperature (20 °C) were employed. The biphenyl products would likely be formed by electrophilic substitution of benzene onto the aromatic moiety of the starting substrate **4a**. The corresponding biaryl derivatives were obtained, even though in low yields, when *p*-xylene (entry 2) or mesitylene (entry 3) was employed instead of benzene. In addition, a similar reaction proceeded with *o*-dihalo-substituted substrates **4q**, **4r**, and **4s** to afford the corresponding biaryl compounds **7q**, **7r**, and **7s** in moderate yields (42%, 41%, and 43%, respectively) (Table 2). Under these reaction conditions, the corresponding 4*H*-1,2-benzoxazines were not formed.

Table 2. Superacid-Catalyzed Reaction of Methyl 3-Aryl-2-nitropropionates with Aromatic Solvents

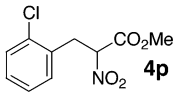
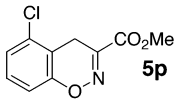
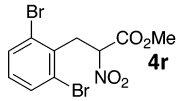
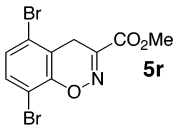
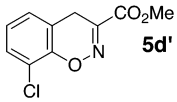
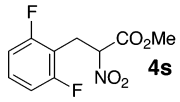
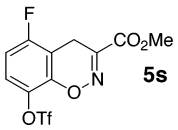
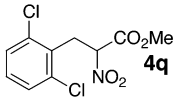
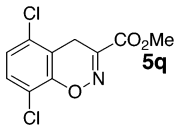


			yield (%)		
entry[a]	R	ArH	**5**	**7**	**8**
1	H (**4a**)	benzene	67	total **26** (**7a**:**8a** = 12:1[c])	
2[b]	H (**4a**)	*p*-xylene	41	trace	
3[b]	H (**4a**)	mesitylene	50	10 (**7a-mes**)	0
4	2,6-Cl_2 (**4q**)	benzene	n.d.[d]	42 (**7q**)	0
5	2,6-Br_2 (**4r**)	benzene	n.d.[d]	41 (**7r**)	0
6	2,6-F_2 (**4s**)	benzene	n.d.[d]	43 (**7s**)	0

[a] Typical reaction conditions: To a solution of the substrate (1.0 mmol) in 50 equiv of aromatic solvent was added 100 equiv of TFSA (8.9 mL) at 0 °C. The mixture was stirred at 20 °C overnight. [b] With 10 equiv of TFSA. [c] Determined by ^1H NMR. [d] n.d. = not detected.

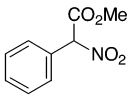
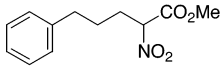
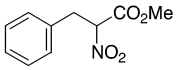
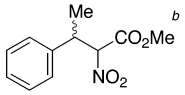
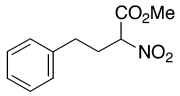
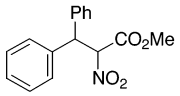
Shifts of *ortho*-Halogen Substituents. To study the regioselectivity of the cyclization, we further investigated the substrate bearing halogen groups at the *o*-position (Table 3). While halogen atoms on the aromatic ring usually deactivate the aromatic electrophilic substitution reaction and enhance nucleophilic substitution, the *o*-monochloro-substituted substrate **4p** readily underwent cyclization at 50 °C to give 5-chloro-4*H*-1,2-benzoxazine **5p** as a major product (41%) together with 8-chloro-4*H*-1,2-benzoxazine **5d′** (27%, Table 3, entry 1). The former product was formed by the normal cyclization reaction,

Table 3. Cyclization of Methyl-3-aryl-2-nitropropionates with Halogen Groups at the *o*-Position

entry[a]	reactant	product	yield (%)	entry[a]	reactant	product	yield (%)
1[b]	 **4p**	 **5p**	41	3[c]	 **4r**	 **5r**	68
		 **5d'**	27	4	 **4s**	 **5s**	46
2[c]	 **4q**	 **5q**	50				

[a] Typical reaction conditions: A solution of the substrate (1.0 mmol) in $CHCl_3$ (10 mL) was added to 10 equiv of TFSA (0.89 mL) at 0 °C. The mixture was heated at 50 °C for 30 min. [b] 50 equiv of TFSA was used, and the reaction mixture was heated for 1.5 h. [c] 50 equiv of TFSA was used, and the reaction mixture was heated for 2.5 h.

Table 4. Investigation of the Cyclization Reaction of Various Methyl Arylnitroalkylates[a]

entry	substrate		expected ring size	yield (%)	entry	substrate		expected ring size	yield (%)
1		**9**	5	0	4		**11**	8	0
2		**4a**	6	85	5		**12**	6	trace[c]
3		**10**	7	0	6		**13**	6	0

[a] Reaction conditions: To $CHCl_3$ (10 mL) were added 1.0 mmol of the substrate and 10 equiv of TFSA (0.89 mL), and the reaction mixture was stirred for 30 min at 50 °C. [b] Mixture of the diastereomers. [c] Detected in the ^1H NMR spectrum, but could not be isolated.

occurring at the less sterically hindered aromatic position. However, the formation of the latter product indicated that a shift of the chloride atom occurred upon ipso attack of the oxygen group. A similar shift of the halogen atom occurred even in the case of the *o*,*o*′-dichloro-substituted substrate **4q**, where both of the *o*-positions are blocked for cyclization. However, **4q** gave the chloride-rearranged and cyclized product **5q** (entry 2, 50% yield). Furthermore, this halogen-shift cyclization is general; the *o*,*o*′-dibromo-substituted substrate **4r** gave **5r** (entry 3, 68% yield). In the case of the *o*,*o*′-difluoro-substituted substrate **4s** (entry 4), the cyclization occurred to give **5s**, but one of the two fluoride atoms was replaced with a triflate group. It seems likely that in the process of cyclization, the ipso position of the halogen atom on the aromatic moiety was attacked by the oxygen atom of the nitro group, followed by migration or replacement of the fluoride atom with a triflate anion in the reaction medium. Migration of a halogen atom in an aromatic system, which is known as halogen dance, has been intensively studied.[14] Usually, the halogen dance occurs in a metalated aromatic group bearing a halogen atom under strongly basic conditions. The mechanism of the halogen migration in the present work seems quite different from that of base-catalyzed halogen shift, because an anionic aromatic species could not be generated under these highly acidic reaction conditions. Few reports have appeared about halogen shift on an aromatic ring under acidic conditions, and they have been practically limited to bromide and iodide.[15] In those cases, attack of an electrophile at the ipso-carbon atom bearing the halogen atom gives a cationic *σ*-complex, which can undergo a 1,2-shift of the halogen atom. It is noteworthy that the chloride atom migrated in this reaction and that nucleophilic replacement of a triflate occurred in the case of the fluoride atom.[15h]

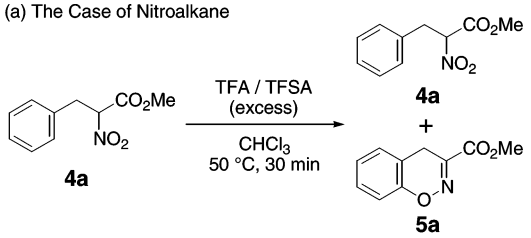
Size Effect in Ring Formation. We found that the cyclization is extremely sensitive to the length and substituents of the

(14) For recent reports on halogen dance, see: (a) Stanetty, P.; Schnurch, M.; Mereiter, K.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 567−574. (b) Stangeland, E. L.; Sammakia, T. *J. Org. Chem.* **2004**, *69*, 2381−2385. (c) Saitton, S.; Kihlberg, J.; Luthman, K. *Tetrahedron* **2004**, *60*, 6113−6120. (d) Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. *Org. Lett.* **2002**, *4*, 2385−2388. (e) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1999**, *55*, 12149−12156. (f) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Heterocycles* **1999**, *50*, 215−226. (g) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron Lett.* **1998**, *39*, 6465−6466. For reviews, see: Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3975−3984 and references therein.

(15) Acid-promoted halogen migrations. For bromine, see: (a) Giles, R. G. F.; Green, I. R.; Knight, L. S.; Son, V. R. L.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 865−873. (b) Giles, R. G. F.; Green, I. R.; Knight, L. S.; Son, V. R. L.; Mitchell, P. R. K.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 853−857. (c) Jacquesy, J. C.; Jouannetaud, M. P.; *Tetrahedron Lett.* **1982**, *23*, 1673−1676. (d) Press, J. B.; Eudy, N. H. *J. Heterocycl. Chem.* **1981**, *18*, 1261−1262. (e) Brittain, J. M.; Mare, P. B. D. D. L.; Newman, P. A. *Tetrahedron Lett.* **1980**, *21*, 4111−4112. For iodine, see: (f) Muramoto, Y.; Asakura, H.; Suzuki, H. *Nippon Kagaku Kaishi* **1992**, *1*, 172−178. (g) Butler, A. R.; Sanderson, A. P. *J. Chem. Soc., Perkin Trans. 2* **1972**, 989−992. Removal of the fluorine atom on the benzene ring accompanied by introduction of the chloride atom in $ZrCl_4$-catalyzed electrophilic amination of 4-fluorophenol has been reported: (h) Bombek, S.; Pozgan, F.; Kocevar, M.; Polanc, S. *J. Org. Chem.* **2004**, *69*, 2224−2227.

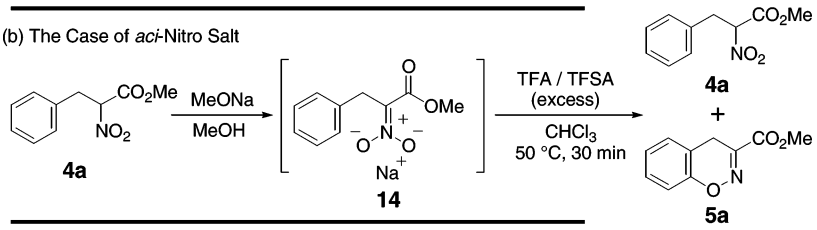
Table 5. Acidity Dependence of the Cyclization Reaction

(a) The Case of Nitroalkane



entry	acid	recovery of **4a** (%)	yield of **5a** (%)
1	TFSA	0	85
2	TFSA : TFA = 1:1 (w/w)	4	80
3	TFSA : TFA = 1:9 (w/w)	48	42
4	TFSA : TFA = 1:99 (w/w)	85	4
5	TFA	95	0

(b) The Case of *aci*-Nitro Salt



entry	acid	recovery of **4a** (%)	yield of **5a** (%)
1	TFSA	0	84
2	TFSA : TFA = 1 : 1 (w/w)	0	71
3	TFSA : TFA = 1 : 9 (w/w)	10	73
4	TFSA : TFA = 1 : 99 (w/w)	42	27
5	TFA	81	3

connecting alkyl chain between the aromatic moiety and the nitro group (Table 4). Only the phenylnitropropionate derivative **4a** afforded the cyclized product (entry 2), while the corresponding derivatives of phenylnitroacetate **9** (entry 1), phenylnitrobutanate **10** (entry 3), and phenylnitroheptanate **11** (entry 4) gave neither the cyclized products nor recovery of the starting material; that is, formation of only a six-membered ring was observed. Substitution of a methyl (**12**) or a phenyl group (**13**) at the benzyl position of the phenylnitropropionate system significantly retarded the cyclization reaction (entry 5 and entry 6).

Acidity Dependence of the Reaction. The reaction proceeds efficiently with an excess amount of TFSA ($H_0 = -14.1$), whereas no cyclized product can be obtained with TFA ($H_0 = -2.7$).[12] To investigate the effect of the acidity of the medium on the cyclization, we used a mixed acid of TFSA and TFA. The acidity function (H_0) of mixtures of TFSA and TFA has been reported in detail, and such mixtures are frequently applied to investigate the acidity dependence of organic reactions.[16−18] The ratio of the cyclized product/substrate was examined when an excess amount of the mixed acid was used in the reaction (Table 5). It was found that the progress of the reaction was strongly influenced by the acidity of the reaction medium when neutral **4a** was used as a substrate (Table 5a). In TFA, cyclization did not occur at all (entry 5, $H_0 = -2.7$). As the acidity of the system was increased by addition of TFSA, the reaction started to occur. When TFSA (entry 1, $H_0 = -14.1$) itself or TFSA:TFA = 1:1 (w/w) (entry 2, $H_0 = -11.2$) was employed as the acid catalyst, the reaction proceeded quite efficiently, although the reaction rates were extremely small in the case of TFSA:TFA = 1:99 (w/w) (entry 4, $H_0 = -7.7$). In the case of TFSA:TFA = 1:9 (w/w) (entry 3, $H_0 = -9.5$), the yield of the cyclized product was found to be moderate. In TFSA:TFA = 1:9 (w/w), only the methyl ester group would be substantially protonated, while the nitro group would be almost unprotonated (Table 6), judging from the reported acidities of the conjugate acid of an aliphatic ester group ($pK_{BH+,ester} \approx -6.5$) and that of an aliphatic nitro group ($pK_{BH+,nitro} = -11$).[19,20] The fact that the reaction proceeds in highly acidic media, more acidic than TFSA:TFA = 9:1 (w/w) ($H_0 = -9.5$), therefore, can be interpreted in terms of activation by protonation of the methyl ester group.[21]

The acidity dependence of the reactions was investigated similarly with the sodium salt of the substrate **14**, which was prepared by treatment of the substrate with MeONa in THF.

(16) (a) Hammett, L. P.; Deyrup, A. J. *J. Am. Chem. Soc.* **1932**, *54*, 2721−2739. (b) Paul, M. A.; Long, F. A. *Chem. Rev.* **1957**, *57*, 1−45. (c) Jorgenson, M. J.; Hartter, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 878−883. (d) Ryabova, R. S. *Zh. Fiz. Khim.* **1966**, *40*, 339−345.

(17) (a) Saito, S.; Saito, S.; Ohwada, T.; Shudo, K. *Chem. Pharm. Bull.* **1991**, *39*, 2718−2720. (b) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312−2317.

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(20) Greig, C. C.; Johnson, C. D. *J. Am. Chem. Soc.* **1968**, *90*, 6453−6457.

(21) Protonation of the ester group of ethyl nitroacetate was confirmed previously: Ohwada, T.; Yamagata, N.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 1364−1373.

Table 6. Approximate Ratio of Protonation in the TFSA/TFA System[a]

			C_{BH^+}/C_B	
TFSA	TFA	H_0	aliphatic ester ($pK_{BH^+} = -6.5$)[b]	aliphatic nitro ($pK_{BH^+} = -11$)[b]
100	0	−14.1	3.2×10^7	1.0×10^3
50	50	−11.2	3.2×10^4	1
10	90	−9.5	1.0×10^3	3.2×10^{-2}
1	99	−7.7	16	5.0×10^{-4}
0	100	−2.7	1.6×10^{-4}	5.0×10^{-9}

[a] On the hypothesis that these substrates can be regarded as Hammett bases. See reference 19. [b] Reference 20.

As compared to that of the neutral form, the reaction rate was increased in terms of the yield of the product as the acidity was increased (Table 5b), while in this case the neutral nitro species would also be recovered by *C*-protonation of the salt. It should be noted that the cyclized product was obtained in moderate yield even in TFSA:TFA = 99:1 (w/w), while under the same conditions the cyclization reaction did not proceed efficiently with the neutral substrate (**4a**) (Table 5). This observation strongly supports the postulate that the reaction starts with α-deprotonation to form an *aci*-nitro species in situ, facilitated by *O*-protonation of the ester group.

The rate-determining step of the cyclization reaction seems to be removal of the α-proton with respect to the nitro group. When **4a** was added to 10 equiv of TFSA-*d* (CF_3SO_3D) in $CDCl_3$ and the mixture was stirred for 30 min at 30 °C, a lower temperature than the original conditions, followed by aqueous (D_2O) workup, the cyclization proceeded to give **5a** (42%) together with recovery of **4a** (55%). In this case, only 11% of the α-proton of the recovered **4a** was deuterated. This result is in sharp contrast to the case of methyl nitroacetate; when methyl nitroacetate was added to an excess amount of TFSA-*d*, the active methylene protons were completely exchanged with deuterium under gentle heating conditions (30 min, 30 °C). These results are consistent with the view that acid-catalyzed α-deprotonation of **4a** is practically not in equilibrium, that the rate of the deprotonation is so slow as to be rate-determining, and that the following cyclization proceeds very rapidly after formation of the *aci*-nitro species.

Effects of Aromatic Substituents on the Reaction Rate. The effects of aromatic substituents on the reaction rate were also studied by means of rate measurements with ^{1}H NMR spectroscopy. The unsubstituted substrate (**4a**) and *p*-F, *p*-Cl, *p*-CO_2Me, *p*-CF_3, *p*-CN, and *p*-NO_2 substituted substrates were subjected to the reaction at 30 °C in the presence of a large excess of TFSA:TFA (1:1 (w/w)), and the relative ratio of the starting material was monitored in terms of the ^{1}H NMR spectrum based on the signal of acetone as an external standard in a capillary tube. In all cases, disappearance of the starting substrate followed first-order kinetics under these reaction conditions. The rate constants did not differ significantly among all of the examined substrates, which means that electron-withdrawing groups do not retard the reaction. The rate constants of the reaction were plotted against Hammett's σ_p constants,[22] and an apparent relationship was found, except for the ester group (Table 7). An extraordinarily large rate constant was obtained in the case of the methyl ester substituent, probably because the basicity of the carbonyl oxygen atom of the methyl ester group is strong enough to allow protonation to occur in this strongly acidic reaction medium, thereby affording a much more strongly electron-withdrawing substituent (i.e., a larger σ_p value) than the neutral form.[23]

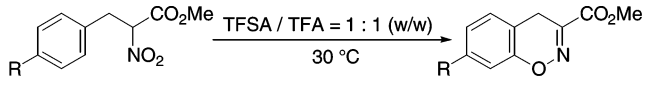
The difference in the disappearance rates of the starting substrates can be mainly attributed to the difference of the acidities of the α-protons with respect to the nitro group. To investigate the effect of aromatic substituents on the acidity of α-protons with respect to the nitro group, the chemical shifts of the α-carbons in the ^{13}C NMR spectra were compared in TFA as a solvent (see Supporting Information, Table S1). The peak of the α-carbon atom with respect to the nitro group was found to be more shielded, although only slightly so, with increasing electron-withdrawing ability of the substituent group on the benzene ring. The acidity of the α-proton was also estimated theoretically in terms of natural population charges and proton affinities (PAs) (see Supporting Information, Table S1).[24] The natural population charge of the α-proton was found to be more positive, that is, more acidic, as the group substituted on the benzene ring became more electron-withdrawing. Moreover, it has already been reported that the PAs of active C−H bonds of organic compounds show a good correlation with the experimental standard ionization energy.[24] PAs of the CH group of some of the substrates **4** (*p*-H, *p*-Cl, *p*-CN, and *p*-NO_2) were calculated and showed an apparent correlation with the electron-withdrawing ability of the substituents (Supporting Information, Table S1). The stronger electron-withdrawing groups gave smaller PAs, which means higher acidity of the C−H moiety.

Mechanistic Insights into the Reactions. Revisit of Proposed 6π Electrocyclization Mechanism and Deuterium Labeling Experiment. To account for the formation of 4*H*-1,2-benzoxazines via acid-catalyzed cyclization of nitroolefins, a 6π electrocyclization mechanism has been proposed.[25] A similar electrocyclization mechanism was subsequently proposed for the reaction of nitrostyrene derivatives to give 4*H*-1,2-benzoxazines.[26] It would be appropriate to consider the involvement of the *aci*-nitro species of the present nitroalkanes (**4**), generated in situ by α-deprotonation, as an intermediate of the cyclization reaction. In the case of the corresponding 6π electrocyclization of the present nitroalkane, one of the benzyl protons should be removed from the protonated *aci*-nitro species **15** to give the "nitrososstyrene" **16** (Scheme 2a). The 6π electrocyclization will result in C−O bond formation between the aromatic carbon and the oxygen atoms, and the resultant intermediate recovers aromaticity via elimination of the proton and uptake of an external proton at the benzylic position.

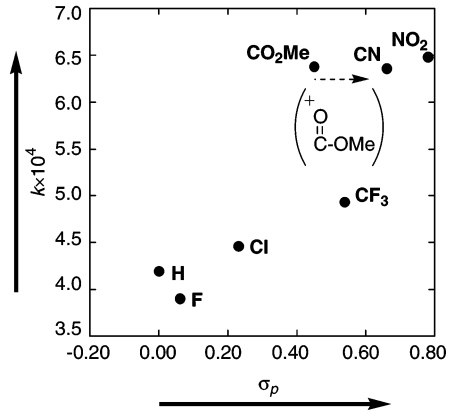
We carried out deuterium exchange experiments to test this mechanism (Scheme 3). When the substrate (**4a**) was subjected to the reaction in deuterated TFSA (CF_3SO_3D) and $CDCl_3$, we found no deuterium incorporation at the benzyl position of the obtained cyclized product (**5a**). A similar result was observed even in the case of the halogen-substituted substrate; no

(22) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(23) Protonation of the ester group in superacid has been thoroughly investigated. For reviews, see: Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767−788.
(24) Nakamura, S.; Hirao, H.; Ohwada, T. *J. Org. Chem.* **2004**, *69*, 4309−4316.
(25) Ohwada, T.; Okabe, K.; Ohta, T.; Shudo, K. *Tetrahedron* **1990**, *46*, 7539−7555.
(26) Hirotani, S.; Zen, S. *Yakugaku Zasshi* **1994**, *114*, 272−276.

Table 7. Correlation between the Pseudo First-Order Rate Constants and Hammett σ_p

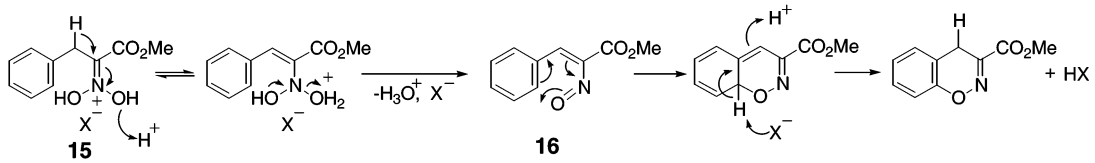


entry	R	σ_p	$k\times10^4$ (1/s)
1	H	0	4.20
2	F	0.06	3.90
3	Cl	0.23	4.46
4	CO_2Me	0.45	6.38
5	CF_3	0.54	4.93
6	CN	0.66	6.36
7	NO_2	0.78	6.48

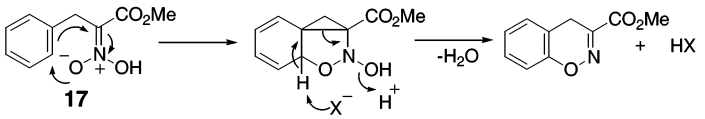


Scheme 2. Plausible Cyclization Mechanisms

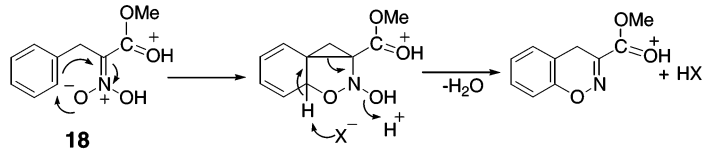
(a) 6π electrocyclization reaction via deprotonation of the benzyl proton



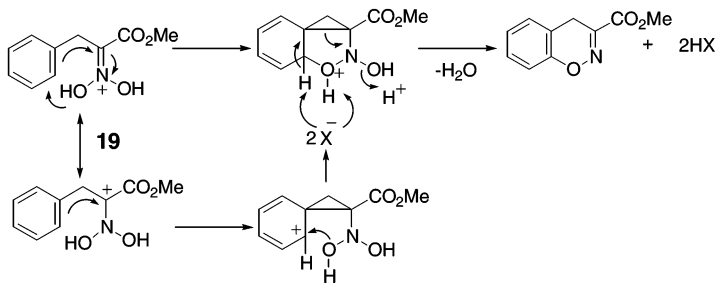
(b) 1,3-dipolar addition of *aci*-nitro species



(c) 1,3-dipolar addition of *aci*-nitro species activated by *O*-protonation of an ester



(d) 1,3-dipolar addition or Friedel-Crafts type reaction of *O*-protonated *aci*-nitro species

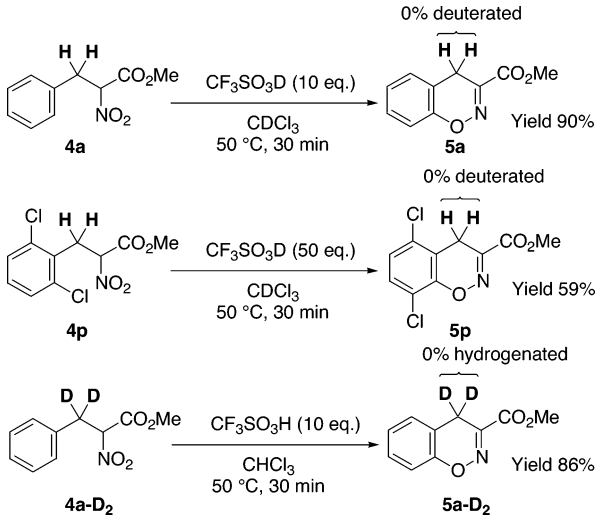


deuterium was incorporated even in the halogen atom shift in the cyclization of 2,6-dichloro-substituted **4q**. We also synthesized the α,α-dideuterated substrate (**4a-D$_2$**). The cyclization of **4a-D$_2$** in TFSA (CF_3SO_3H) in $CHCl_3$ yielded the cylized product (**5a-D$_2$**) with no loss of deuterium (Scheme 3). These results indicated that no proton elimination occurred at the benzylic position. Therefore, the 6π electrocyclization mechanism can be ruled out in this case.

Alternative Possible Reaction Mechanisms. In addition to the 6π electrocyclization mechanism, there are other plausible mechanisms, as shown in Scheme 2: that is, cyclization of *aci*-nitro ((b) and (c)) or *O*-protonated *aci*-nitro species (d). An aromatic intramolecular 1,3-dipolar cyclization mechanism is plausible because of the 1,3-dipolar nature of the *aci*-nitro moiety, as represented by **17** (Scheme 2b).[27] The tricyclic [3+2] cycloadduct would generate the 4*H*-1,2-benzoxazine structure

(27) Although [3+2]-cycloaddition of *aci*-nitro species with aromatic ring has not been reported to our knowledge, that of *aci*-nitro species with aliphatic olefins has been well investigated. See: Denmark, S. E.; Cottell, J. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley and Sons: Hoboken, NJ, 2003; Chapter 2, pp 86−159 and references therein.

Scheme 3. Cyclization Reactions in Deuterated TFSA and $CDCl_3$ or with the Deuterated Substrate



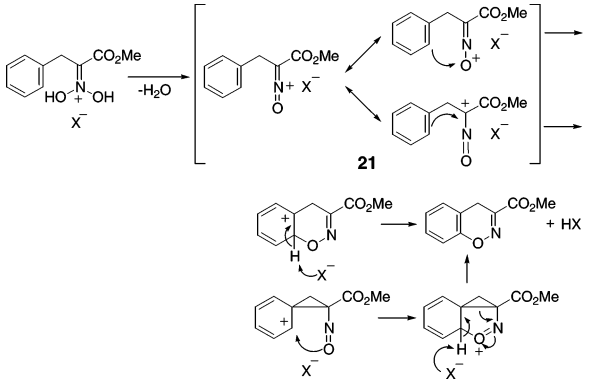
after re-aromatization, accompanied with C−H and C−C bond cleavage. On the other hand, because of the basicity of the oxygen atom of the ester carbonyl group and the strength of the acid catalyst, there should be an equilibrium between the *aci*-nitro species (**17**) and the *O*-protonated *aci*-nitro species (**19**) (Scheme 4a). There would also be an equilibrium between the *aci*-nitro species bearing an *O*-protonated ester group (**18**) and the *O*-protonated *aci*-nitro species (**19**) (Scheme 4a).[28] To investigate the feasibility of these pathways, we evaluated the chemical features of these possible reaction mechanisms by means of theoretical calculations (see Supporting Information, Figures S2−S4 and Table S2).[29,30] In the bond-forming process of aromatic 1,3-dipolar cycloaddition of neutral *aci*-nitro species (**17-TS**), the activation energy is high (43.8 kcal/mol (MP2/6-311G**//B3LYP/6-31+G*), Scheme 4). Two transition structures (**18-TS** and **19-TS**, Scheme 4b) are also conceivable in the cyclization of the monocationic species, but their activation energies were found to be extraordinarily large (**18**, 47.4 kcal/mol; **19**, 46.2 kcal/mol, respectively). On the other hand, the requirement of an excess amount of TFSA and involvement of *O*-protonation of the ester carbonyl group in the acidity−rate profile (Table 5) suggest the contribution of a highly reactive dicationic species such as **20** (Scheme 4a).[31] The relevant dication, a kind of ethylene dication, has been observed spectroscopically.[21,32] Intramolecular hydrogen-bonding interaction between the ester carbonyl moiety and *aci*-nitro moiety would stabilize the high-energy dicationic species (see Scheme 4). We found that the activation energy of **20-TS** was significantly reduced (28.7 kcal/mol) as compared to those of monocationic species. In the vibrational frequency analysis of the dicationic transition structure (**20-TS**), it seemed likely that the C−C bond formation preceded the C−O bond formation, indicating a partial asynchronous nature of the cyclization.[33,34]

3. Conclusion

In this paper, we have discussed the scope and the mechanism of the strong Brønsted acid-catalyzed intramolecular cyclization reaction of methyl 3-aryl-2-nitropropionates to give 4*H*-1,2-benzoxazines. This reaction can be regarded as an oxygen functionalization of the aromatic ring wherein the oxygen atom is derived from a nitro group in the molecule. This reaction is favored by the presence of electron-withdrawing substituents on the benzene ring. The reaction rate is strongly influenced by the acidity of the reaction medium, and the methyl ester group on the α-carbon atom with respect to the nitro group facilitates α-deprotonation to give *aci*-nitro species in situ. Some correlation was found between the electron-withdrawing ability of the substituent on benzene, which is represented by the Hammett σ_p value of the substituent, and the rate of consumption of the starting substrate leading to the product in TFSA/TFA medium. This would be because the acidity of the α-proton with respect to the nitro group is influenced by the nature of the substituent on the benzene ring.

We experimentally excluded the 6π electrocyclization mechanism, which involves deprotonation of the benzyl proton of the protonated *aci*-nitro species. Alternative cyclization mechanisms, such as aromatic 1,3-dipolar cycloaddition and/or Friedel−Crafts-type reaction of the *O*-protonated *aci*-nitro species, were calculated to be high-energy-demand processes.

(28) Elimination of water from protonated *aci*-nitro species generates **21**, which has an oxonium cation character, and intramolecular aromatic electrophilic substitution would afford 4*H*-1,2-benzoxazine through a Friedel−Crafts-type cyclization mechanism. See Supporting Information.



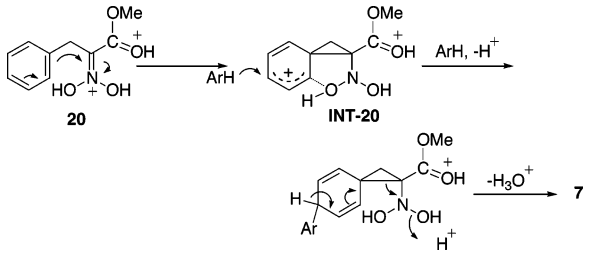
(29) (a) Pople; et al. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998. (b) Pople; et al. *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2003. See Supporting Information.

(30) We also carried out the calculations in the presence of a model acid (HCl). The magnitudes of the activation energies were not altered significantly (see Supporting Information).

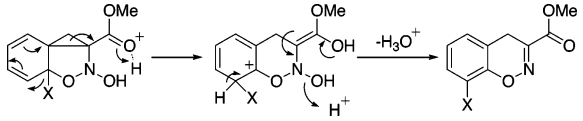
(31) Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211−220. For the reviews on dicationic species, also see ref 23.

(32) See refs 18d and e.

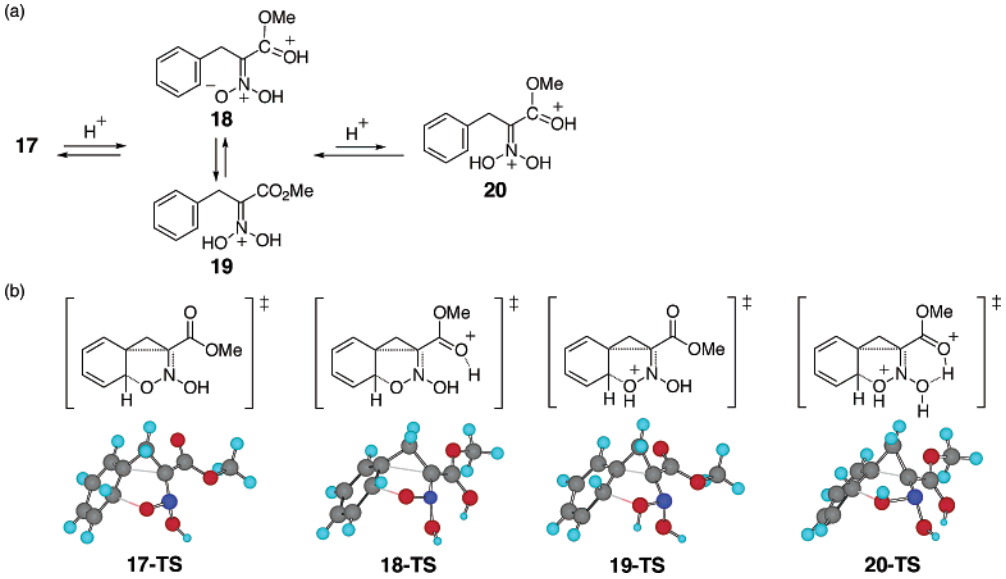
(33) Generation of biaryl oxime derivatives (see Table 2) can be attributed to nucleophilic attack of the aromatic compound on the cationic benzene ring of the intermediate (**INT-20**), due to the partially asynchronous nature of intramolecular attack of the benzene ring on the protonated *aci*-nitro moiety of **20**, as shown below.



(34) Halogen migration (see Table 3) could be interpreted in terms of the following mechanism:



Scheme 4. (a) Equilibria between the Neutral, Monocationic, and Dicationic Species; and (b) the Calculated Transition Structures of the Cyclization[a]



[a] All of the structures were obtained at the B3LYP/6-31+G* level. A gray-colored sphere represents a carbon, light blue is hydrogen, blue is nitrogen, and red is oxygen.

Diprotonated or protosolvative[31] species can reduce the activation energies significantly, which is consistent with the observed acidity-dependent nature of the cyclization. From the viewpoint of synthetic chemistry, the present oxygen-functionalization reactions, involving a transfer of the oxygen atom of the nitro group, will widen the scope of the chemistry of functionalization of aromatic compounds.[35] The mechanistic insights afforded by the reactions described in this paper are of considerable interest, and we are currently further exploring this kind of cyclization.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, to T.O. and by a Japan Society for the Promotion of Science (JSPS) Research Fellowship to S.N. Some of the calculations were carried out at the Computer Center, the Institute for Molecular Science. We thank the computational facility for generous allotments of computer time.

Supporting Information Available: Spectroscopic and analytical data, experimental procedures, Cartesian coordinates, and energetic values of calculated species. Theoretical calculation of the reaction mechanism is also described. This material is available free of charge via the Internet at http://pubs.acs.org.

JA067682W

(35) [3+2]-Cycloaddition reaction between nitrones and alkenes, especially asymmetric, is still of great interest in organic synthesis. For reviews, see: (a) Jones, R. C. F.; Martin, J. N. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley and Sons: Hoboken, NJ, 2003; Chapter 1, pp 1−81. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−910. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449−1458. (d) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley−VCH: Weinheim, Germany, 2002; Chapter 6, pp 211−247. (e) Kanemasa, S. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley−VCH: Weinheim, Germany, 2002; Chapter 7, pp 249−300.