DOI: 10.1002/ejoc.200800369

DFT Study of Brønsted Acid Catalyzed Nitroso Aldol Reaction Between Achiral Enamines and Nitrosobenzene: The Reason for Regio- and Enantioselectivity

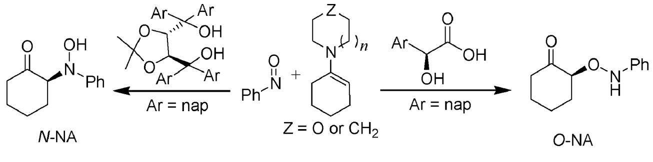
Matsujiro Akakura,*[a] Masanori Kawasaki,[b] and Hisashi Yamamoto*[b]

Keywords: Density functional calculations / Nitroso aldol reaction / Regioselectivity / Enantioselectivity

The regio- and enantioselectivity of the nitroso aldol reaction between achiral enamines and nitrosobenzene catalyzed by chiral Brønsted acid catalysts (TADDOL or 1-naphthylglycolic acid) were investigated in experimental and theoretical studies. The use of a model involving a simple organic acid (MeOH or AcOH) revealed that the reaction was catalyzed by two or more molecules of the organic acid and that the transition-state structure encompassed several hydrogen bonds. The role of hydrogen bonding in the regioselectivity was also examined carefully. The enantioselectivity in the reaction catalyzed by chiral organic acids (*S*,*S*)-TADDOL and (*S*)-1-naphthylglycolic acid was also confirmed through computational study.

Introduction

The nitroso aldol (NA) reaction is one of the most powerful tools in organic synthesis to introduce hydroxy or amino groups at the α position of the carbonyl group.[1] We recently reported regio- and enantioselective nitroso aldol reactions between achiral enamines and nitrosobenzene (PhNO) by using chiral Brønsted acid catalysts.[2] Organic acids with an alcohol group promotes C–N bond-forming reactions (*N*-NA reactions), whereas organic acids with a carboxylic acid group promote C–O bond-forming reactions (*O*-NA reactions) (Scheme 1). Although we succeeded in finding good reactions through control of the selectivity of the nitroso aldol reaction, the mechanism of the reaction, and especially the origin of the selectivity, was unclear until now.



Scheme 1. Brønsted acid catalyzed nitroso aldol reaction between achiral enamines and nitrosobenzene (PhNO).

Houk et al. offered an explanation of stereoselectivity in proline-catalyzed *O*-NA reactions of ketones with PhNO. They proposed a mechanism in which the chiral enamine was included (diastereoselective mechanism).[3] However, their explanation did not cover our observation of regioselective nitroso aldol processes. We herein report an investigation on the origin of the regio- and enantioselectivity of the reaction on the basis of experimental and theoretical factors.

Results and Discussion

At the beginning of this work, our experimental results seemed to show an isotope effect in the organic acid catalyzed nitroso aldol reaction (organic acid = MeOH or AcOH) (Figure 1). Although the difference in the reaction rates was not large, the Ph group of PhNO clearly had an isotope effect: 56:44 and 57:43 (ratio of products). These results suggest that the effect of this Ph group is a secondary isotope effect, which means that the Ph group *indirectly*

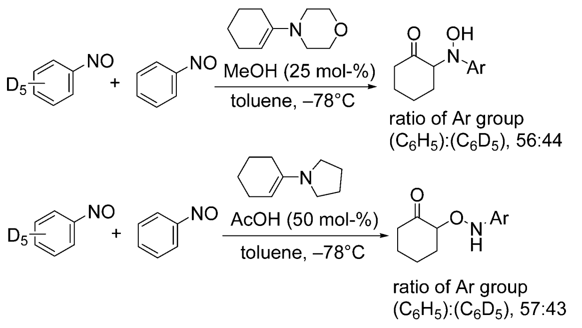


Figure 1. Experimental results of isotope effect in nitroso aldol reaction catalyzed organic acids.

---

[a] Department of Chemistry, Aichi University of Education,
Igaya-cho, Kariya, Aichi 448-8542, Japan
Fax: +81-566-26-2638
E-mail: makakura@auecc.aichi-edu.ac.jp
[b] Department of Chemistry, The University of Chicago,
5735 South Ellis Avenue, Chicago, Illinois 60637, USA

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

takes part in the reaction and influences the reaction rate. The essence of this isotope effect could not be understood from the experiments, so we decided to investigate factors of the reaction rate by using theoretical calculations.

We first studied the complex formed between the organic acid and PhNO. Optimized structures of the complexes indicate an interaction between the *ortho* hydrogen atom of PhNO and the oxygen atom of the organic acid in the equilibrium structures (Figure 2): Acid-N[4] (Acid = MeOH or AcOH), Acid-O-Z, and Acid-O-E. Acid-N was more stable than Acid-O. The energy difference between AcOH-N and AcOH-O (1.9 kcal/mol) was larger than that between MeOH-N and MeOH-O (1.1 kcal/mol). The relative energy levels of the complexes (the values in square brackets in Figure 2) were reflected in the two H-bonds as follows: (1) the H-bond between the hydrogen atom of the –OH group in the organic acid and the –N=O group in PhNO and (2) the H-bond between the oxygen atom of the organic acid and the *ortho* hydrogen atom in PhNO. The former H-bond depends on the acidity of the organic acid and the basicity of the coordination site in the –N=O group. The basicity of the nitrogen atom is larger than the basicity of the oxygen atom in the –N=O group.[3,5] The latter H-bond depends on the acidity of the *ortho* hydrogen atom in PhNO and the basicity of the oxygen atom in the organic acid. The acidity of PhNO is considered to be more than minimal and to be almost the same as that of PhCN.[6] The structures in Figure 2 indicate that the two H-bonds of AcOH-X (X = N or O) are stronger than those of MeOH-X; AcOH-Xs have shorter atom distances [$R(\mathrm{H_{OH}},\mathrm{X})$ and $R(\mathrm{O_{C=O}},\mathrm{H}_{ortho})$] and larger angles [$A(\mathrm{X},\mathrm{H_{OH}},\mathrm{O_{OH}})$] than those of MeOH-Xs [$R(\mathrm{H_{OH}},\mathrm{X})$, $R(\mathrm{O_{OH}},\mathrm{H}_{ortho})$, and $A(\mathrm{X},\mathrm{H_{OH}},\mathrm{O_{OH}})$]; this results from the acidity of the organic acid and the *ortho* hydrogen atom in PhNO and the basicity of the oxygen atom in the organic acid. The cooperative effect[7,8] of the two H-bonds would also contribute to the structure and the energy level of these complexes.

Next, we looked at the nitroso aldol reaction in terms of the structures and energy levels of the TS (transition state). We tried to explain the regioselectivity of nitroso aldol reaction (*N*-NA reaction vs. *O*-NA reaction)[2] by the simplest reaction model, that is, the reaction catalyzed by one molecule of an organic acid, and one molecule of the organic acid (MeOH or AcOH) worked as a catalyst in the model. The relative energy levels at the TS (E_{TS}) of the *N*-NA path were lower than those of the *O*-NA path in both catalytic reactions. Moreover, all the E_{TS} values were too high for the reaction to proceed smoothly.[9] These results indicated that the model incorporating one molecule of an organic acid catalyst was not appropriate to explain our results.

The results from the above experiment suggest that two or more organic acid molecules might act as an active catalyst in the reaction system, as the TADDOL derivative can be regarded as two organic acids. On the basis of this hypothesis, the model incorporating two molecules of an organic acid catalyst was used for further investigations (Figures 3 and 4).[11] Gratifyingly, the E_{TS} values of the *N*-NA and *O*-NA paths were nicely correlated with regioselectivity: TS **1m-i** of the *N*-NA path was the most stable in the four TSs of the $(\mathrm{MeOH})_2$ catalyst model, but TS **2a-o** of the *O*-NA path was the most stable in the four TSs of the $(\mathrm{AcOH})_2$ catalyst model. In fact, three H-bonds in the TSs play an important role in the interactions: (1) the H-bond between the most acidic hydrogen atom of the organic acid and the –N=O group (*HB A*), (2) the H-bond between the *ortho* hydrogen atom in PhNO and the oxygen atom of the organic acid (*HB B*), and (3) the H-bond between hydrogen of the *N*-$\mathrm{CH_3}$ part in the enamine and the oxygen atom of the organic acid (*HB C*).

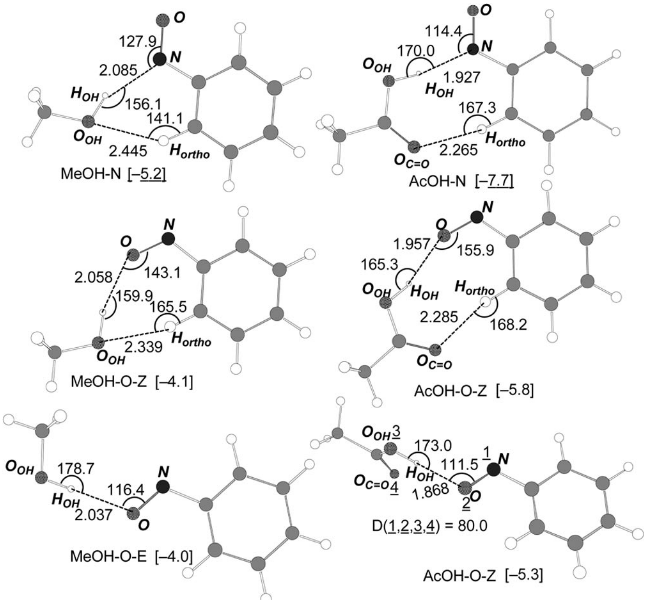


Figure 2. The equilibrium structures and relative energy levels of the complex of PhNO and one organic acid (MeOH or AcOH) molecule calculated at the B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p) level. Relative energy levels [kcal/mol] are in square brackets. The total value of the energies of enamine, PhNO, and one organic acid molecule was used as the standard for relative energy levels.

The organic acid has a higher affinity for the nitrogen atom than for the oxygen atom of the –N=O group, as nitrogen is more basic than oxygen in this group. The basicity of the –N=O group and the acidity of the organic acid seem to correlate with *HB A*, so that the interaction between the nitrogen atom of the –N=O group and the hydrogen atom of AcOH in TSs **2a-i** or **2a-o** was larger than that in the other TSs.

All of the important TSs had *HB B*. We found that this interaction is very important for the regioselectivity of the reaction. The values of the related distances [$R(\mathrm{O_{OH}},\mathrm{H}_{ortho})$ or $R(\mathrm{O_{C=O}},\mathrm{H}_{ortho})$] are also related to the regioselectivity. In the model involving two molecules of MeOH, the value of $R(\mathrm{O_{OH}},\mathrm{H}_{ortho})$ in the most-stable TS in the *N*-NA path (**1m-i**; 2.715 Å) indicates that *HB B* is stronger in this path than in the *O*-NA path (**2m-o**; 3.196 Å). In contrast, in the model involving two molecules of AcOH, the value of $R(\mathrm{O_{C=O}},\mathrm{H}_{ortho})$ in the most-stable TS in the *N*-NA path (**1a-i**; 3.051 Å) indicates that *HB B* is weaker in this path than

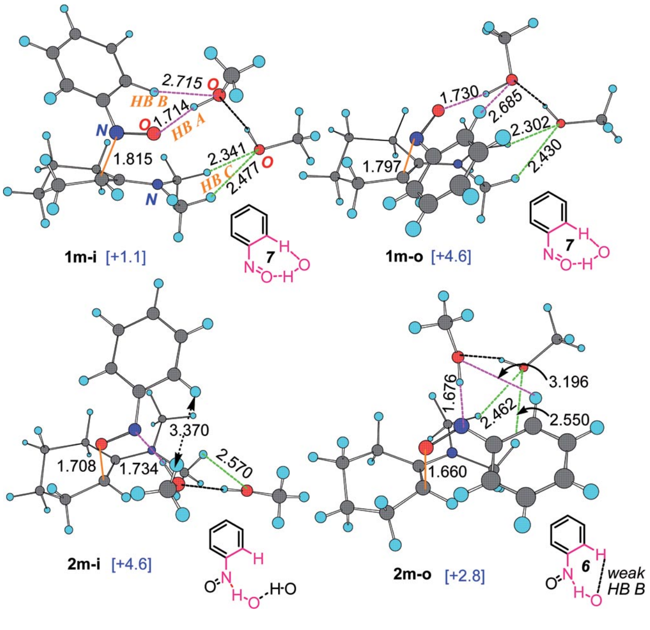


Figure 3. B3LYP-optimized transition-state structures and relative energy levels[10] [kcal/mol] for the nitroso aldol reaction of *N*,*N*-dimethylcyclohexylenamine with PhNO catalyzed by two molecules of MeOH [$(MeOH)_2$]. Distances are in Å. Relative energy levels (E_{TS}) are in square brackets.

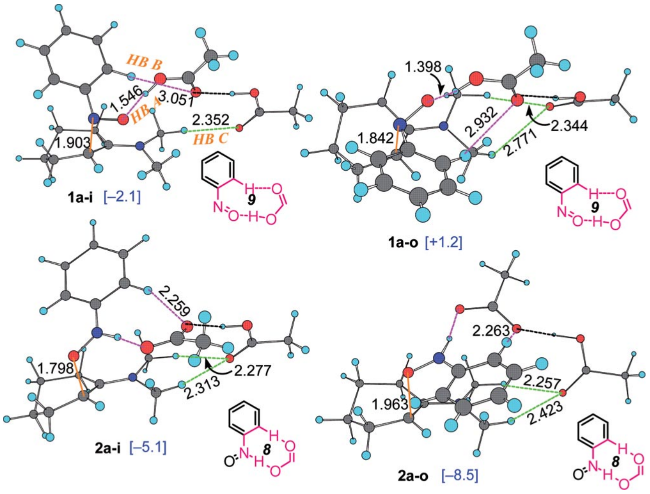


Figure 4. B3LYP-optimized transition-state structures and relative energy levels[10] [kcal/mol] for the nitroso aldol reaction of *N*,*N*-dimethylcyclohexylenamine with PhNO catalyzed by two molecules of AcOH [$(AcOH)_2$]. Distances are in Å. Relative energy levels (E_{TS}) are in square brackets.

in the *O*-NA path (**2a-o**; 2.263 Å). These results suggested that *HB B* is one of the important factors for E_{TS}. The strength of *HC C* was also correlated to E_{TS}. This interaction will construct the TS structure (a cluster-like structure for the stability of the multiorganic acid form). TSs **1m-i** and **2a-o** have strong *HB C*. The reaction path with a suitable TS structure will have a greater importance. Thus, the three H-bonds and E_{TS} values were correlated, allowing us to understand that the three H-bonds played an important role in the regioselectivity.

To put it briefly, the reason that an alcohol catalyst promotes C–N bond formation (nitrogen attack) is that a more-stable seven-membered ring structure is formed when an alcohol catalyst coordinates the oxygen atom of the –N=O group, so the nitrogen atom is activated and attacked. In contrast, the reason a carboxylic acid catalyst promotes C–O bond formation (oxygen attack) is that a more-stable eight-membered ring structure is formed when the carboxylic acid catalyst coordinates the nitrogen atom of the –N=O group, so the oxygen atom is activated and attacked.

Finally, we confirmed the enantioselectivity of the nitroso aldol reaction catalyzed by optically active organic acids [organic acid = (*S*,*S*)-TADDOL or (*S*)-1-naphthylglycolic acid]. The most important TS structures of the TADDOL and (*S*)-1-naphthylglycolic acid catalyzed reactions are shown in Figures 5 and 6, respectively. In these TSs, the H-bonds described above were also important. *HB B* plays a role in fixing PhNO in the TS structure. Calculated E_{TS} values were suitable for enantioselectivity in both organic acid catalyzed reactions. The energy gaps between the TSs for the (*S*) and (*R*) products were 0.9 kcal/mol in the TADDOL-catalyzed reaction and 1.6 kcal/mol in the 1-naphthylglycolic acid catalyzed reaction.[12] The TSs on the way

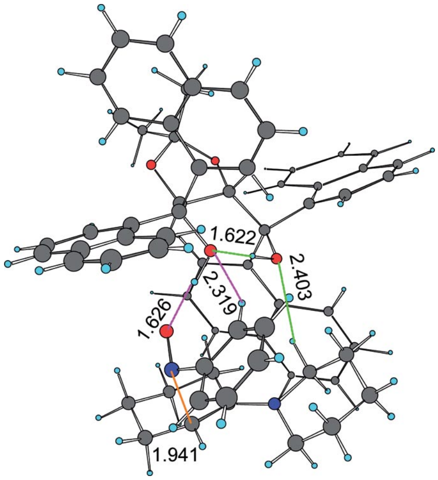


Figure 5. Transition-state structure for the (*S*) product in the (*S*,*S*)-TADDOL-catalyzed nitroso aldol reaction between cyclohexylenamine and PhNO. Distances are in Å.

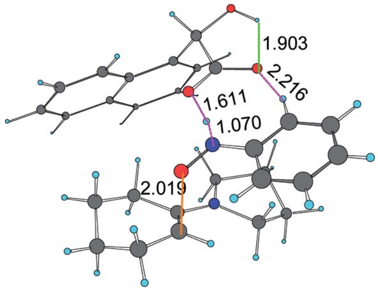


Figure 6. Transition-state structure for the (*S*) product in the (*S*)-1-naphthylglycolic acid catalyzed nitroso aldol reaction between cyclohexylenamine and PhNO. Distances are in Å.

to the (*S*) product were more stable than those of the (*R*) product in both reactions. These calculation results also agree with the facts of the experiment. The hydrogen bonds allowed the catalysts to have effective stereocontrol in the enantioselective reaction, and one important reason is that the hydrogen bonds fix the substrates to the catalyst tightly.

Conclusions

We studied the origins of the regio- and enantioselectivity in the nitroso aldol reaction between achiral enamines and PhNO by using chiral Brønsted acid catalysts. We chose the nitroso aldol reaction catalyzed by simple organic acids for investigation of the regioselectivity. The TS structure comprised the enamine, PhNO, and two or more molecules of organic acid and formed a cluster-like structure. The key points of the regioselectivity were the three H-bonds in the TS structure: (1) the H-bond between the most acidic hydrogen atom of the organic acid and the –N=O group, (2) the H-bond between the *ortho* hydrogen atom in PhNO and the oxygen atom of the organic acid, and (3) the H-bond between the hydrogen atom of the *N*-CH_3 part of the enamine and the oxygen atom of the organic acid. The importance of the H-bonds was confirmed by comparison of the strengths of the H-bonds and the energy levels of the TSs. After understanding the factors for the regioselectivity, we confirmed the enantioselectivity of the reactions, which were catalyzed by (*S*,*S*)-TADDOL or (*S*)-1-naphthylglycolic acid. In this case, the H-bonds were also important in determining the TS structure and the values of E_{TS}.

Experimental Section

Computational Methods: Theoretical calculations were performed by using the Gaussian 98[13] and 03[14] programs. Optimization of the geometries of the complex of the organic acid and PhNO, the calculations for binding energy between *p*-substituted benzene and chloride (Cl^-) ion, and the exploration of the potential energy hypersurface to determine the transition state of the organic acid (except TADDOL and 1-naphthylglycolic acid) catalyzed reactions were carried out by gradient-corrected density functional theory (DFT) calculations with Becke's three-parameter exchange with the Lee, Yang, and Parr correlation functional (B3LYP)[15] by using the 6-31+G(d,p) basis set. The stationary points were characterized by a frequency analysis at the B3LYP level. Single-point calculations for the optimized geometries were then performed by using the 6-311++G(d,p) basic set. In the TADDOL-catalyzed reaction, the ONIOM hybrid method with the use of the B3LYP/6-31+(d,p) level for the high layer (TADDOL framework, PhNO and CH=C–N part of enamine), B3LYP/6-31G(d,p) level for the middle layer (O–C–O part of TADDOL and CH_2 chain of enamine), and UFF for the low layer (naphthyl groups, CH_3 part) was applied for geometrical optimization of transition states; thereafter, single-point calculations of the optimized geometries were performed at the B3LYP/6-311++G(d,p) level. In the case of the 1-naphthylglycolic acid catalyzed reaction, the ONIOM hybrid method with the use of the B3LYP/6-31+G(d,p) level for the high layer (glycolic acid part, PhNO and CH=C–N part of enamine) and B3LYP/6-31G(d,p) level for the low layer (CH_2 chain of enamine and naphthyl group) was applied for geometry optimization of transition states and then single-point calculations of the optimized geometries were made at the B3LYP/6-311++G(d,p) level. The basis set superposition error (BSSE) was computed by optimization and single-point calculation, except that optimization used the ONIOM hybrid method for the TADDOL-catalyzed reaction and the 1-naphthylglycolic acid catalyzed reaction used the counterpoise corrected method.[16] In the case of the TADDOL-catalyzed reaction and the 1-naphthylglycolic acid catalyzed reaction, the counterpoise corrected method was used only in the single-point calculation. The total value of the reactants was used when the relative energies of the complexes and the stationary points were calculated. All the energies reported are in kcal/mol.

Supporting Information (see footnote on the first page of this article): Binding energy between *p*-substituted benzene and the chloride (Cl^-) ion; results for the nitroso aldol reaction catalyzed by one molecule of organic acid; NPA charges of the complex; transition-state structure and E_{TS} values of the reactions catalyzed by TADDOL or 1-naphthylglycolic acid.

Acknowledgments

The authors are grateful to the Research Center for Computational Science (RCCS), Okazaki, for the use of their Fujitsu PRIMEQUEST instrument.

---

[1] For reviews o nitroso compounds, see: a) P. Zuman, P. Shah, *Chem. Rev.* **1994**, *94*, 1621–1641; b) P. F. Vogt, M. J. Miller, *Tetrahedron* **1998**, *54*, 1317–1348; for examples of (*R*)-aminoxylation and (*R*)-hydroxyamination to carbonyl compounds, see: c) T. Sasaki, K. Mori, M. Ohno, *Synthesis* **1985**, 279; d) T. Sasaki, K. Mori, M. Ohno, *Synthesis* **1985**, 280; e) W. Oppolzer, O. Tamura, G. Sundarababu, M. Signer, *J. Am. Chem. Soc.* **1992**, *114*, 5900–5902; f) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809; g) G. Zhong, *Angew. Chem. Int. Ed.* **2003**, *42*, 4247–4250; h) Y. Hayashi, J. Yamaguchi, K. Hibino, M. Shoji, *Tetrahedron Lett.* **2003**, *44*, 8293–8296; i) G. Zhong, Y. Yu, *Org. Lett.* **2004**, *6*, 1637–1639; j) Y. Hayashi, J. Yamaguchi, T. Sumiya, M. Shoji, *Angew. Chem. Int. Ed.* **2004**, *43*, 1112–1115; k) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem. Int. Ed.* **2004**, *43*, 1109–1112; l) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 6038–6039; m) N. Momiyama, H. Yamamoto, *Angew. Chem. Int. Ed.* **2002**, *41*, 2986–2986; n) N. Momiyama, H. Yamamoto, *Org. Lett.* **2002**, *4*, 3579–3582; o) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5374; p) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673–3684; q) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5360–5361.

[2] N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080–1081; also see the Supporting Information.

[3] Paul Ha-Yeon Cheong, K. N. Houk, *J. Am. Chem. Soc.* **2004**, *126*, 13912–13913.

[4] Acid-N was used for a complex in which the organic acid coordinates the nitrogen atom of the –N=O group and Acid-O-Z was used for a complex in which the organic acid coordinates the oxygen atom with a *Z* conformation. The *Z* conformation means that the Ph group and the organic acid part are on the same side relative to the N=O axis of the C–N=O plane. Acid-O-Z was more stable than Acid-O-E.

[5] The complex coordinating to the nitrogen atom was 2.3 kcal/mol more stable than that coordinating to the oxygen atom in the PhNO–H^+ complexes.

[6] The affinity of the *ortho* hydrogen to a Lewis base can be briefly estimated from calculations of binding energy between *p*-substituted benzene and chloride (Cl^-) ion. See the Supporting Information.

[7] Y. Chen, J. J. Dannenberg, *J. Am. Chem. Soc.* **2006**, *128*, 8100–8101.

[8] The NPA charges of Acid-O-E suggest that a cooperative effect acts in the complexes arising from organic acids and PhNO. Detailed results of Acid-O-E are described in the Supporting Information.

[9] The TS structures and E_{TS} values of the reaction catalyzed by one molecule of an organic acid are described in the Supporting Information.

[10] The total value of the energies of the enamine, PhNO, and two molecules of the organic acid was used as the standard for the relative energy level.

[11] The nomenclature used for the TSs is as follows: the number indicates the type of bond forming (**1** is C–N bond forming and **2** is C–O bond forming). The second character (**m** or **a**) refers to the catalyst (**m** is MeOH and **a** is AcOH). The third character (**i** or **o**) means the direction of the Ph group (**i** is inside and **o** is outside).

[12] The energy gap written here is the one between the (*R*) and (*S*) TSs that is most stable among the reaction paths for each product. The other structures and relative energy levels are indicated in the Supporting Information.

[13] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, *Gaussian 98*, Gaussian, Inc., Pittsburgh, PA, **1998**.

[14] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J., J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, K. Nakajima, Y. Honda, O. Kitao, H. Nakai, Li. X. Klene, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov; G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, revision C02, Gaussian, Inc., Pittsburgh, PA, **2003**.

[15] a) A. D. Becke, *J. Chem. Phys.* **1993**, *96*, 5648; b) P. J. Stevens, J. F. Devlin, C. F. Chablowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.

[16] S. F. Boys, F. Bernardi, *Mol. Phys.* **1970**, *19*, 553.

Received: April 11, 2008