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TRIPEPTIDE-CATALYZED ASYMMETRIC ALDOL REACTION OF TRIFLUOROMETHYLATED AROMATIC KETONES WITH ACETONE

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Abstract – The development of H-Pro-Gly-Ala-OH (**3d**) to realize an inexpensive and simple organocatalytic system for the direct asymmetric aldol reaction of trifluoromethylated aromatic ketone **1** with acetone was achieved. The **3d**-catalyzed aldol reaction of **1a**–**1j** provided various aldol adducts **4a**–**4j** with up to 81% yield and 77% *ee*. An investigation of the transition state via DFT calculations revealed that hydrogen bonding was important for the revelation of the enantioselectivity.

The direct asymmetric aldol reaction is one of the most useful carbon-carbon bond forming reactions.[1] In particular, the direct asymmetric aldol reaction of trifluoromethyl ketones is an especially helpful synthetic method, as this reaction yields a trifluoromethylated optically active tertiary alcohol that is a partial structure in various biologically active compounds.[2] On the other hand, organocatalysts for asymmetric reactions receive attention in synthetic chemistry since these catalysts are environment-friendly and easy to use.[3] Owing to these reasons, the development of organocatalysts for the direct asymmetric aldol reaction of trifluoromethyl ketones is actively carried out.[4] However, almost all the organocatalysts for the direct asymmetric aldol reaction of trifluoromethyl ketones contain expensive chiral scaffolds and require acidic co-catalysts; therefore, more inexpensive and simpler organocatalytic systems, i.e., organocatalysts with inexpensive chiral scaffolds that do not require acidic co-catalysts, are awaited. Zhang and Yuan reported that a secondary amine catalyst with the inexpensive proline as the chiral scaffold catalyzed the asymmetric aldol reaction between α,β-unsaturated trifluoromethyl ketones and acetone, with up to 91% *ee*.[5a] Suri et al., and Landge and Török reported the proline-catalyzed asymmetric aldol reaction of ethyl trifluoropyruvate with cyclic and acyclic ketones.[5b,5c]

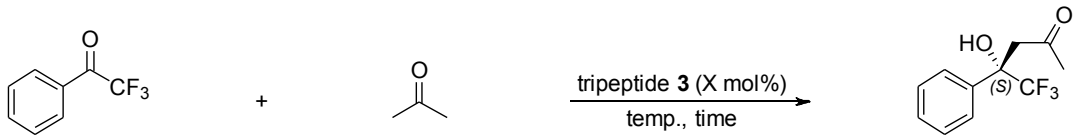
Bøgevig et al. disclosed the proline-catalyzed direct asymmetric aldol reaction between ethyl trifluoropyruvate and aldehydes, with up to 90% *ee*.[5d] As described above those in these reports, simple and inexpensive organocatalytic systems have been developed for the direct asymmetric aldol reaction, using α,β-unsaturated trifluoromethyl ketones and trifluoropyruvates as substrates. However, in the direct asymmetric aldol reaction using trifluoromethylated aromatic ketones as substrates, simple and inexpensive organocatalytic system is limited. For representative example of organocatalytic system for this reaction, Hara et al. have reported proline-derived sulfonamide and trifluoroacetic acid organocatalytic system for this reaction, with up to 96% *ee*.[4n] Furthermore, Kokotos and Duangdee et al. have developed highly enantioselective prolinamide catalyst for this reaction, independently.[4l,4m] But, these catalytic system have faults such as requiring acidic co-catalysts and having expensive chiral scaffolds. As simple and inexpensive organocatalytic systems, although Qiu et al. described the proline-catalyzed direct asymmetric aldol reaction of trifluoromethylated aromatic ketones with up to 64% *ee*, enantioselectivity and reaction rate of this method depend on substrate structure.[5e]

To realize a simple and inexpensive organocatalytic system for the direct asymmetric aldol reaction of trifluoromethylated aromatic ketones, we focused on a tripeptide catalyst. This catalyst is composed of a generally inexpensive α-amino acid; hence it is expected to not only be an organocatalyst with an inexpensive chiral scaffold, but also exhibit a higher enantioselectivity than that of the proline-catalyzed reaction, by the optimization of the amino acid sequence. Moreover, this catalyst has a carboxyl group as the C-terminal functional group, and a secondary amino group as the *N*-terminal functional group; therefore, it is not expected to require an acidic co-catalyst. In this work, we developed a tripeptide catalyst with inexpensive chiral scaffold as an organocatalyst that does not require an acidic co-catalyst.

We investigated the effect of the catalytic structure on the reaction rate and enantioselectivity, with the reaction of 2,2,2-trifluoroacetophenone (**1a)** with acetone (**2**) as the model reaction (Table 1, entries 1-9). To reveal the usefulness of tripeptide catalyst for this reaction, H-Pro-OH-, H-Pro-Gly-OH-, and H-Pro-Gly-Gly-OH (**3a**)-catalyzed reaction were carried out (Table 1, entry 1-3). Tripeptide **3a** was displayed the highest enantioselectivity, and **3a**-catalyzed reaction gave an aldol adduct (*S*)-**4a**, with 18% chemical yield and 45% *ee* (Table 1, entry 3). To reveal the effect of introducing a methyl group into the amino acid residue adjacent to proline, as *N*-terminal amino acid residue, H-Pro-Ala-Gly-OH (**3b**)- and H-Pro-D-Ala-Gly-OH (**3c**)-catalyzed reactions were carried out. However, these reactions did not progress (Table 1, entries 4 and 5). To investigate the effect of introducing of a methyl group into the C-terminal amino acid residue, H-Pro-Gly-Ala-OH (**3d**)- and H-Pro-Gly-D-Ala-OH (**3e**)-catalyzed reactions were carried out (Table 1, entries 6 and 7). The chemical yields of both the reactions improved, compared with that of **3a**-catalyzed reaction. For the **3d**-catalyzed reaction, the enantioselectivity also improved compared with that of reaction catalyzed by **3a** (Table 1, entry 6). The reaction rate and

enantioselectivity of the aldol reactions catalyzed by H-Pro-Gly-Val-OH (**3f**) with a bulky ^{i}Pr group and H-Pro-Gly-Phg-OH (**3g**) with a plane Ph group did not improved (Table 1, entries 8 and 9).

Table 1. Optimization of the catalytic structure and the reaction conditions



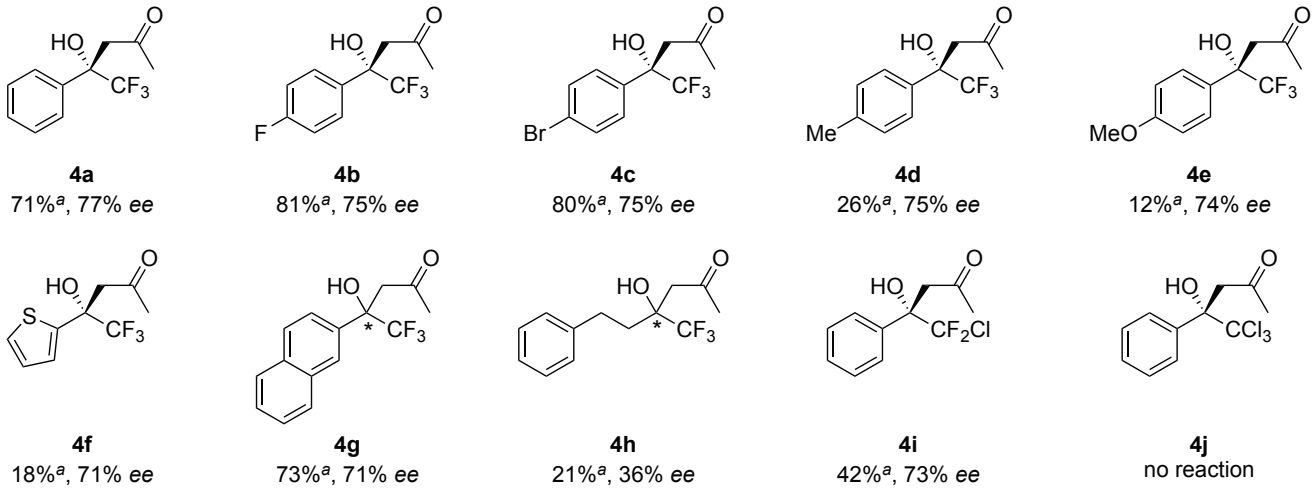
1a **2** (Y equiv) **4a**

Entry	Temp. (°C)	Time (h)	tripeptide **3** (mol%)	**2** (equiv.)	Yield (%)[a]	*ee* (%)[b]
1	20	3	H-Pro-OH(10)	20	95	28
2	20	3	H-Pro-Gly-OH(10)	20	<5	44
3	20	3	H-Pro-Gly-Gly-OH **3a**(10)	20	18	45
4	20	3	H-Pro-Ala-Gly-OH **3b**(10)	20	N.R.[c]	N.D.[d]
5	20	3	H-Pro-D-Ala-Gly-OH **3c**(10)	20	N.R.	N.D.
6	20	3	H-Pro-Gly-Ala-OH **3d**(10)	20	97	53
7	20	3	H-Pro-Gly-D-Ala-OH **3e**(10)	20	83	36
8	20	3	H-Pro-Gly-Val-OH **3f**(10)	20	91	45
9	20	3	H-Pro-Gly-Phg-OH **3g**(10)	20	95	41
10	0	12	H-Pro-Gly-Ala-OH **3d**(10)	20	96	63
11	-40	36	H-Pro-Gly-Ala-OH **3d**(10)	20	72(71)[e]	77
12	-60	72	H-Pro-Gly-Ala-OH **3d**(10)	20	13	74
13	-40	36	H-Pro-Gly-Ala-OH **3d**(5)	20	21	69
14	-40	36	H-Pro-Gly-Ala-OH **3d**(20)	20	82	67
15	-40	36	H-Pro-Gly-Ala-OH **3d**(10)	10	34	72
16	-40	36	H-Pro-Gly-Ala-OH **3d**(10)	50	92	65

[a] Determined by ^{1}H NMR using internal standard technique. [b] Determined by HPLC analysis using DAICEL CHIRALPAK OD-H. [c] N.R. is no reaction. [d] N.D. is not determined. [e] Isolated yield after preparative thin layer chromatography.

These investigation revealed that optimized catalyst was **3d**. Using **3d** as the optimum catalyst, the effect of the reaction conditions on the reaction rate and enantioselectivity was investigated (Table 1, entries 7 and 10-16). The reaction temperatures, catalytic amounts and amounts of acetone revealed that the highest enantioselectivity was obtained in the reaction using **3d** of 10 mol% and acetone of 20 equiv. at -40 °C (Table 1, entry 11).

The reactions of various trifluoromethylated aromatic ketones under optimized reaction condition were investigated (Scheme 1). The use of trifluoromethylated aromatic ketones substituted with electron-withdrawing groups at *para* position gave the corresponding aldol adducts **4b** and **4c** with a good chemical yield and enantioselectivity. The reactions of **1d** and **1e** having electron-donating groups at *para* position progressed at a low reaction rate and with good enantioselectivity. The reason for the lower reaction rate than that of reaction using **1a** as substrate might be the improvement in the electron density of the carbonyl carbon compared with that of **1a**, due to the introduction of electron-donating groups at *para* porition on phenyl group.



4a 71%[a], 77% *ee*
4b 81%[a], 75% *ee*
4c 80%[a], 75% *ee*
4d 26%[a], 75% *ee*
4e 12%[a], 74% *ee*
4f 18%[a], 71% *ee*
4g 73%[a], 71% *ee*
4h 21%[a], 36% *ee*
4i 42%[a], 73% *ee*
4j no reaction

Scheme 1. Products of **3d**-catalyzed aldol reactions of **1b–1j** under optimized reaction conditions

The reaction of **1f** that have 2-thienyl group as heteroaromatic ring reacted at low yield and good enantioselectivity. **4g** with naphthalene ring as polycyclic aromatic ring was obtained by the reaction of **1g**, with good yield and enantioselectivity. **1h** containing methylene chain reacted with acetone, with low yield and enantioselectivity. To expand the substrate scope of this method to other trihalomethyl ketones, reactions of **1i** and **1j** were carried out. The reaction of chlorodifluoromethyl phenyl ketone **1i** progressed at medium yield and good enantioselectivity. However, trichloromethyl phenyl ketone **1j** did not give corresponding aldol adduct **4j**. Qiu et al. reported that the proline-catalyzed reactions between trifluoromethylated aromatic ketones substituted with electron-withdrawing groups at the *para* position, and **2**, achieved up to 56% *ee*, whereas those between trifluoromethylated aromatic ketones having electron-donating groups at the *para* position, and **2**, did not progress.[5e] In contrast, the **3d**-catalyzed reaction between both types of trifluoromethylated aromatic ketones and **2** gave the corresponding aldol adducts, with good enantioselectivity.

It was assumed that the catalytic cycle of this reaction was similar to that of the proline-catalyzed asymmetric aldol reaction of aldehydes (Figure 1a).[6] Therefore, **2** was activated by enamine formation

due to the reaction between the amino group of **3d**, and **2**. The C–C bond was then formed by nucleophilic addition to the trifluoromethylated aromatic ketone **1** of enamine as nucleophile. Finally, the aldol adduct was produced by the hydrolysis of the iminium cation generated by nucleophilic addition to the trifluoromethylated aromatic ketones **1** of enamine. In this reaction, the absolute configuration of the aldol adduct **4** was determined at this C–C bond formation step. To elucidate the mechanism of revelation of enantioselectivity in this reaction, the transition state structure of the C–C bond formation step was investigated via DFT calculations.[7,8]

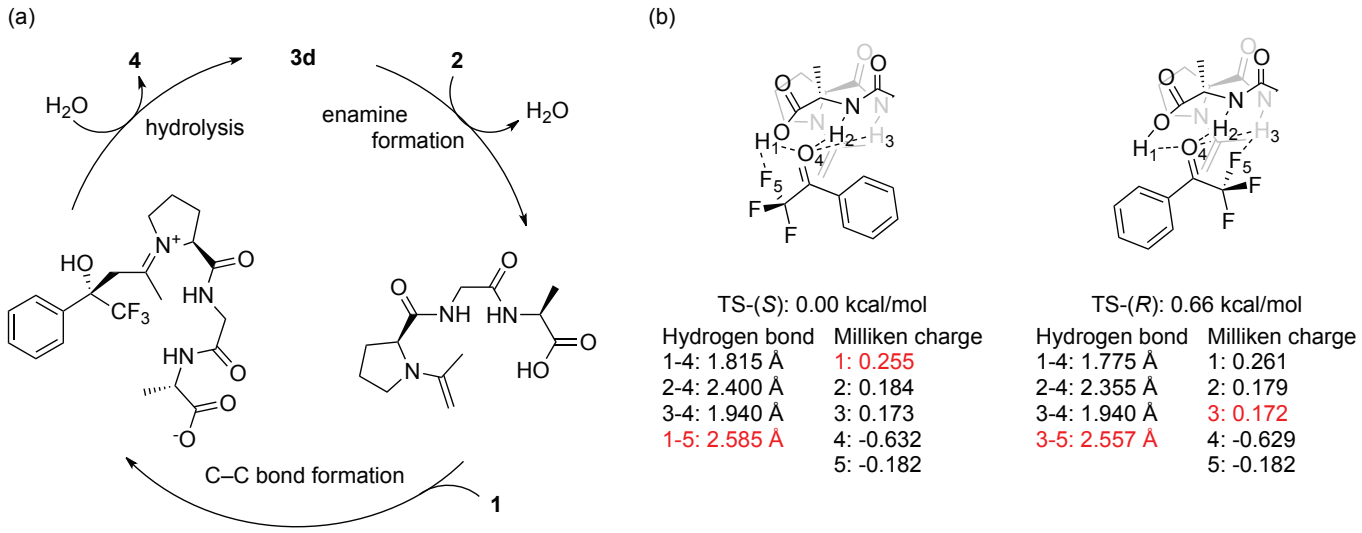


Figure 1. (a) Plausible catalytic cycle and (b) transition state of C–C bond forming step

The **3d**-catalyzed aldol reaction between 2,2,2-trifluoroacetophenone (**1a**) and acetone (**2**) was selected as the model reaction. The investigation of transition state via DFT calculations revealed that (*S*)-**4a** and (*R*)-**4a** were respectively provided through TS-(*S*) and TS-(*R*) (Figure 1b). A comparison of the Gibbs energies of TS-(*S*) and TS-(*R*) revealed that TS-(*S*) was 0.66 kcal/mol more stable than TS-(*R*). The relationship between the Gibbs energies of TS-(*S*) and TS-(*R*) was elucidated by the difference in stabilization efficacy of the transition state, caused by hydrogen bonds. There were multiple hydrogen bonds such as 1-4, 2-4, and 3-4 in both the transition states. However, the 1-5 and 3-5 hydrogen bonds were found only in TS-(*S*) and TS-(*R*), respectively. H1 in TS-(*S*) was more electron deficient than H3 in TS-(*R*); therefore, the stabilization efficacy of TS-(*S*) by hydrogen bond 1-5 might have been stronger than that of TS-(*R*) by hydrogen bond 3-5. We surmise that (*S*)-**4a** was preferentially given through TS-(*S*) due to this difference in stabilization efficacy of the transition state by hydrogen bonds.

In conclusion, we successfully developed of H-Pro-Gly-Ala-OH (**3d**) as an organocatalyst with inexpensive chiral scaffold that does not require an acidic co-catalyst, for the direct asymmetric aldol reaction of trifluoromethylated aromatic ketones. The **3d**-catalyzed reactions of various

trifluoromethylated aromatic ketones gave the aldol adducts **4a**–**4e**, with up to 81% chemical yield and 75% *ee*. The investigation of the transition state structure via DFT calculations revealed that the enantioselectivity was controlled by hydrogen bonds.

REFERENCES AND NOTES

1. B. M. Trost and C. S. Brindlea, *Chem. Soc. Rev.*, 2010, **39**, 1600.
2. (a) J. Ren, J. Milton, K. L. Weaver, S. A. Short, D. I. Stuart, and D. K. Stammers, *Structure*, 2000, **8**, 1089; (b) M. L. Brown, H. A. Eidam, M. Paige, P. J. Jones, and M. K. Patel, *Bioorg. Med. Chem.*, 2009, **17**, 7056; (c) Y. Rew, M. DeGraffenreid, X. He, J. C. Jaen, D. L. McMinn, D. Sun, H. Tu, S. Ursu, and J. P. Powers, *Bioorg. Med. Chem.*, 2012, **22**, 3786.
3. R. R. Torres, 'Stereoselective Organocatalyst', Wiley-VCH: Weinheim, 2013.
4. (a) I. Vlasserou, M. Sfetsa, D. T. Gerokonstantis, C. G. Kokotos, and P. Moutevelis-Minakakis, *Tetrahedron*, 2018, **74**, 2338; (b) J. Duan, Y. Cheng, J. Cheng, R. Li, and P. Li, *Chem. Eur. J.*, 2017, **23**, 519; (c) P. Wang, H. F. Li, J. Z. Zhao, Z. H. Du, and C. S. Da, *Org. Lett.*, 2017, **19**, 2634; (d) X. Hou, Z. Jing, X. Bai, and Z. Jing, *Molecules*, 2016, **21**, 842; (e) L. M. Lutete, T. Miyamoto, and T. Ikemoto, *Tetrahedron Lett.*, 2016, **57**, 1220; (f) Z. Jing, X. Bai, W. Chen, G. Zhang, B. Zhu, and Z. Jing, *Org. Lett.*, 2016, **18**, 260; (g) W. Yamg, Y. M. Cui, W. Zhou, L. Li, K. F. Yang, Z. J. Zheng, Y. Lu, and L. W. Xu, *Synlett*, 2014, **25**, 1461; (h) H. Zong, H. Hung, G. Bian, and L. Song, *J. Org. Chem.*, 2014, **79**, 11768; (i) W. Guo, J. Wei, Y. Liu, and C. Li, *Tetrahedron*, 2014, **70**, 6561; (j) J. Lin, T. Kang, Q. Liu, and L. He, *Tetrahedron: Asymmetry*, 2014, **25**, 949; (k) Y. H. Deng, J. Q. Chen, L. He, T. R. Kang, Q. Z. Liu, S. W. Luo, and W. C. Yuan, *Chem. Eur. J.*, 2013, **19**, 7143; (l) N. Duangdee, W. Harnying, G. Rulli, J. M. Neudorfl, H. Groger, and A. Berkessel, *J. Am. Chem. Soc.*, 2012, **134**, 11196; (m) C. G. Kokotos, *J. Org. Chem.*, 2012, **77**, 1131; (n) N. Hara, R. Tamura, Y. Funahashi, and S. Nakamura, *Org. Lett.*, 2011, **13**, 1662; (o) X. J. Wang, Y. Zhao, and J. T. Liu, *Org. Lett.*, 2007, **9**, 1343.
5. (a) D. Zhang and C. Yuan, *Tetrahedron*, 2008, **64**, 2480; (b) J. T. Suri, S. Mitsumori, K. Albertshofer, F. Tanaka, and F. Barbas III, *J. Org. Chem.*, 2006, **71**, 3822; (c) S. M. Landge and B. Török, *Catal. Lett.*, 2009, **131**, 432; (d) A. Bøgevig, N. Kumaragurubaran, and K. A. Jørgensen, *Chem. Commun.*, 2002, 620; (e) L. H. Qiu, Z. X. Shen, C. Q. Shi, Y. H. Liu, and Y. W. Zhang, *Chin. J. Chem.*, 2005, **23**, 584.
6. B. List, C. F. Lerner, and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395.
7. Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., 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.

Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. 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, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

8. Gaussian 09, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.