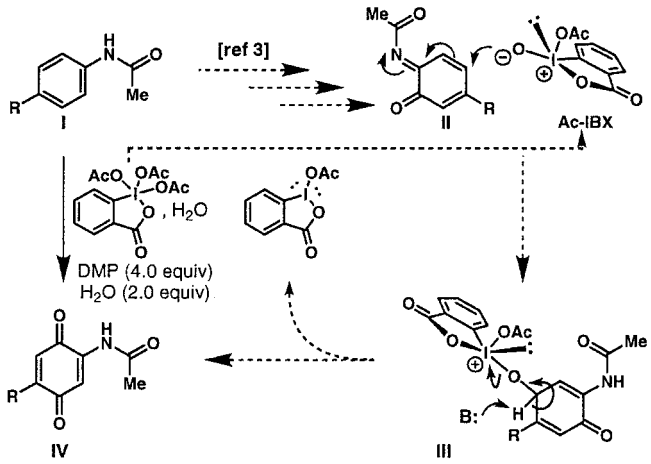
New Synthetic Technology for the Construction of N-Containing Quinones and Derivatives Thereof: Total Synthesis of Epoxyquinomycin B**

K. C. Nicolaou,* Kazuyuki Sugita, Phil S. Baran, and Yong-Li Zhong

Possessing both reactive carbonyl and olefinic bonds, quinones are powerful intermediates for organic synthesis, and also occur frequently within structures of natural products.[1] The inclusion of a nitrogen functionality within these unique systems, as in aminoquinone derivatives, enhances their versatility as building blocks for the construction of biologically relevant compound libraries and qualifies them as potential precursors to numerous naturally occurring substances.[2] Herein we report a facile process by which N-substituted *p*-quinones and *o*-azaquinones can be obtained regioselectively and in one step from readily available anilides by double functionalization of the aromatic nucleus (Scheme 1), and describe various applications of the resulting products including a short and efficient total synthesis of the naturally occurring anti-inflammatory agent epoxyquinomycin B (**20**, Scheme 4).

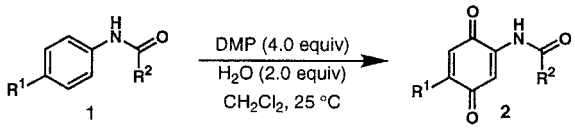
Based on mechanistic insights gained during the study of the reaction of anilides with DMP (for abbreviations of reagents and protecting groups, see legends to schemes) described in the preceding communication,[3] we contemplated the possibility of an Ac-IBX molecule attacking intermediate **II** (Scheme 1) to give complex **III**, whose collapse in the presence of base was expected to form *p*-quinones (**IV**). Indeed, a small amount of ^{18}O-labeled *p*-quinone was detected upon exposure of a substituted anilide to two equivalents each of DMP and Ac-IBX-^{18}O. Encouraged by these results we set out to explore the generality and scope of this one-step entry into quinones and to study the potential utility of the resulting products in organic synthesis. Thus a systematic investigation of the reaction of DMP with *p*-, *m*-, and *o*-substituted anilides was undertaken.

Under the optimal conditions described in Scheme 1, *p*-substituted anilides are converted into *p*-quinones (Table 1). A range of substituents, with the exception of the nitro group,



Scheme 1. Postulated mechanistic rationale for the one-pot cascade synthesis of 4-substituted N-containing quinones from simple anilides through a double oxygenation of the aromatic nucleus. The two equivalents of H_2O convert two of the four equivalents of DMP to two equivalents of Ac-IBX, thus providing the opportunity for a second oxidation of the aromatic nucleus. DMP = Dess–Martin periodinane; IBX = *o*-iodoxybenzoic acid (1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide).

Table 1. Synthesis of *p*-quinones from 4-substituted anilides.



Entry	Substrate	R^1	R^2	*t* [h]	Product	Yield [%]
1	**1a**	H	Me	4	**2a**	52
2	**1b**	Et	Me	2	**2b**	53
3	**1c**	*t*Bu	Me	4	**2c**	36
4	**1d**	Ph	Me	4	**2d**	44
5	**1e**	OMe	Me	1.5	**2e**	46
6	**1f**	F	Me	24	**2f**	27
7	**1g**	Cl	Me	24	**2g**	30
8	**1h**	Br	Me	24	**2h**	25
9	**1i**	I	Me	24	**2i**	22
10	**1j**	NO_2	Me	72	**2j**	< 1
11	**1k**	H	Ph	12	**2k**	40
12	**1l**	H	*t*Bu	280	**2l**	41
13	**1m**	H	*i*Pr	12	**2m**	43

on the aromatic nucleus and the amide side chain are well tolerated. The products of these reactions are rather reactive species and, most likely, the yields reported in Table 1 represent minimum values, since some decomposition is observed during the isolation procedures. The reactivity of these N-containing quinones was demonstrated in both intermolecular and intramolecular Diels–Alder reactions, which proceeded regio- and stereoselectively to furnish products of considerable molecular diversity and complexity. Thus, reaction of *p*-quinone **2a** with Danishefsky's diene **3**[4] in toluene at 95 °C furnished **4** in quantitative yield (Scheme 2). Compound **5a** was formed in 86% yield upon exposure of **4** to silica gel in air.[5] Compound **5a** was converted into phenol **5b** (95%) by treatment with TBAF in THF.[5] The same conditions proved effective in directly converting compound **4** into phenol **5b** (68%). An intramolecular version of the Diels–Alder elaboration of these compounds is shown in

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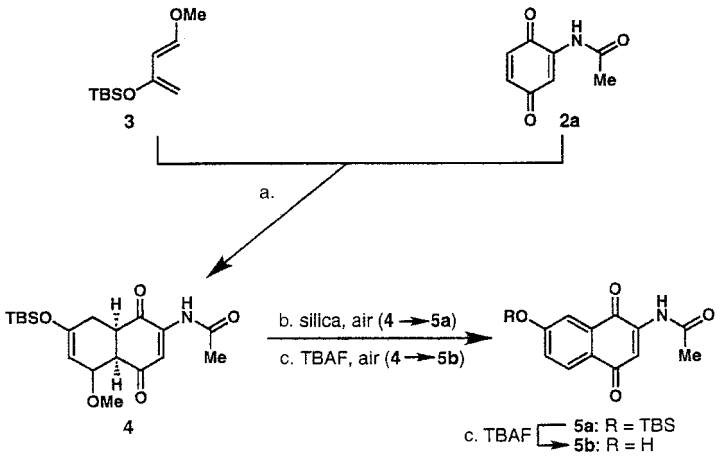
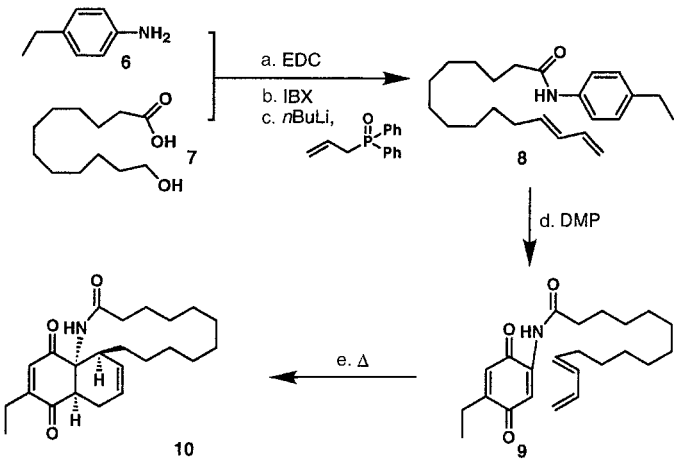


Scheme 2. Diels–Alder reaction of **2a** and Danishefsky's diene **3** leading to *cis*-fused quinone and benzoquinone systems. Reagents and conditions: a) **3** (1.5 equiv), toluene, 95 °C, 3 h, 100 %; b) silica gel, air, CH_2Cl_2, 25 °C, 12 h, 86 %; c) TBAF (1.5 equiv, 1 M solution in THF), THF, 25 °C, air, 3 h, **4** → **5b**: 68 %; **5a** → **5b**: 95 %. TBAF = tetra-*n*-butylammonium fluoride.

Scheme 3. This sequence, which leads to the complex macrocyclic system **10**, began by a coupling of aniline **6** with the hydroxycarboxylic acid **7** and proceeded through diene anilide **8** (obtained by oxidation and olefination as summarized in Scheme 3) and *p*-quinone diene **9**,[6] whose conversion



Scheme 3. Synthesis of tricycle **10**. Reagents and conditions: a) EDC (1.5 equiv), DMAP (0.5 equiv), aniline (5.0 equiv), CH_2Cl_2, 0 → 25 °C, 12 h, 97 %; b) IBX (2.0 equiv), DMSO, 25 °C, 12 h, 100 %; $Ph_2P(O)CH_2CH{=}CH_2$ (3.0 equiv), *n*BuLi (2.5 equiv), HMPA (6.0 equiv), THF, −78 °C, 20 min; then add aldehyde, −78 → 25 °C, 12 h, 72 %; d) DMP (3.5 equiv), H_2O (2.3 equiv), CH_2Cl_2, 0 °C, 22 h, 29 %; e) xylene, 145 °C, 24 h, 63 %. EDC = 3-(3-dimethylaminopropyl)-1-carbodiimide; DMAP = 4-dimethylaminopyridine; DMSO = dimethyl sulfoxide; HMPA = hexamethyl phosphoramide.

into the final product (**10**; Table 2) required heating in refluxing xylenes (145 °C). Presumably diene **9** reacted this time at the less reactive, N-substituted site of the quinone residue as a result of a conformational effect (Figure 1). This mode of capture leaves open the other side of the quinone for further elaboration.

The DMP oxidation of *m*-substituted anilides proved to be more complex and led to multiple products and decomposition. For example, 3-fluoro- and 3-methoxy-(methylanilide) led to, among other products, *p*-quinone **2a** (Table 1) in low yield, whereas 3-ethyl-(methylanilide) gave several products whose structures were not assigned.

Interestingly, however, when the same oxidation was attempted with *o*-substituted anilides only *o*-azaquinones were obtained (Table 3). Not surprisingly, these rarely encountered compounds[7] proved to be willing partners in inverse electron demand Diels–Alder reactions with electron-rich olefins. Table 4 demonstrates the molecular diversity

Table 2. Selected data for compounds **10** and **19**.

10: colorless needles; m.p. 233–235 °C (decomp; ethyl acetate); $R_f = 0.55$ (silica gel, hexane/EtOAc 2/1); IR (film): $\tilde{\nu}_{max} = 3256, 2931, 2858, 1705, 1687, 1639, 1547, 1538, 1456, 1441, 1375, 1350, 1259, 1210, 1038\,cm^{-1}$; ^1H NMR ($CDCl_3$, 600 MHz): $\delta = 6.56$ (t, $J = 1.3$ Hz, 1H), 5.96 (s, 1H), 5.77 (ddd, $^1J = 10.1$ Hz, $^2J = 5.2$ Hz, $^3J = 3.4$ Hz, 1H), 5.56–5.52 (m, 1H), 3.02 (dd, $^1J = 10.1$ Hz, $^2J = 6.6$ Hz, 1H), 2.45–2.39 (m, 1H), 2.31–2.20 (m, 3H), 2.19–2.11 (m, 1H), 2.05–1.98 (m, 2H), 1.94–1.87 (m, 1H), 1.83–1.64 (m, 4H), 1.54–1.11 (m, 20H), 1.03 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 200.4, 192.4, 172.9, 146.0, 135.1, 128.2, 121.6, 66.5, 55.8, 45.4, 35.3, 28.4, 26.3, 25.7, 25.5, 25.3, 24.8, 24.0, 23.6, 23.1, 22.3, 21.9, 12.0$; HR-MS (matrix-assisted laser desorption/ionization (MALDI)) *m*/*z*: calcd for $C_{23}H_{34}NO_3$ $[M+H^+]$: 372.2533, found: 372.2527.

19: white powder; $R_f = 0.43$ (silica gel, hexane/EtOAc 2/1); IR (film): $\tilde{\nu}_{max} = 3195, 2928, 2855, 1712, 1643, 1614, 1550, 1456, 1362, 1258, 1227, 1143, 1095, 1055, 837, 482\,cm^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 8.86$ (s, 1H), 7.63 (s, 1H), 7.55–7.47 (m, 2H), 7.05 (d, $J = 8.2$ Hz, 1H), 6.98 (t, $J = 7.4$ Hz, 1H), 4.34 (d, $J = 12.7$ Hz, 1H), 4.20 (d, $J = 12.7$ Hz, 1H), 4.11 (s, 1H), 0.90 (s, 9H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 192.1, 189.3, 169.0, 161.9, 138.1, 136.1, 126.0, 119.6, 119.2, 116.8, 113.8, 61.6, 56.9, 54.1, 25.7$ (3C), 1.0, −5.4 (2C); HR-MS (MALDI) *m*/*z*: calcd for $C_{20}H_{26}NO_6Si$ $[M+H^+]$: 404.1524, found: 404.1531.

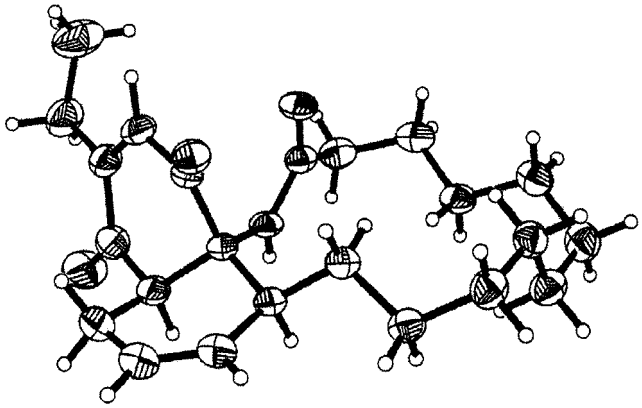
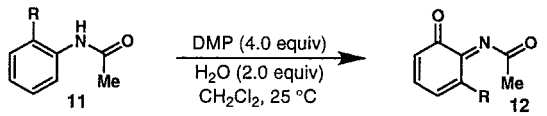


Figure 1. X-ray crystal structure of macrocycle **10**.[12]

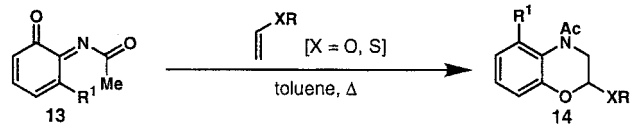
Table 3. Synthesis of *o*-azaquinones from 2-substituted anilides.



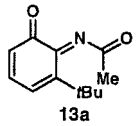
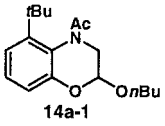
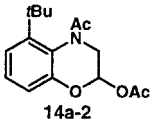
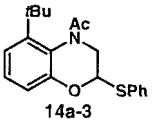
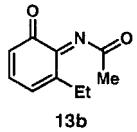
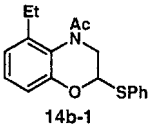
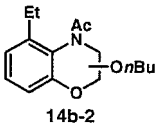
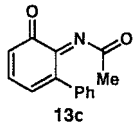
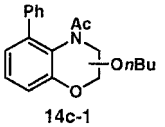
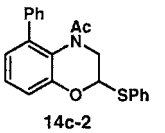
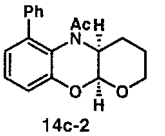
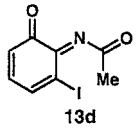
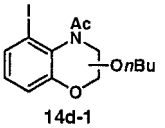
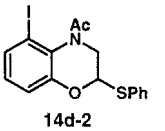
Entry	R	*t* [h]	Product	Yield [%]
1	**11a**: Br	6	**12a**	32
2	**11b**: *t*Bu	4	**12b**	88
3	**11c**: Ph	6	**12c**	41
4	**11d**: I	6	**12d**	44
5	**11e**: Et	4	**12e**	64
6	**11f**: Cl	6	**12f**	71

  0044-8249/01/11301-0214 $ 17.50+.50/0

Table 4. Inverse Diels–Alder reactions of 2-substituted *o*-azaquinones with electron-rich olefins.



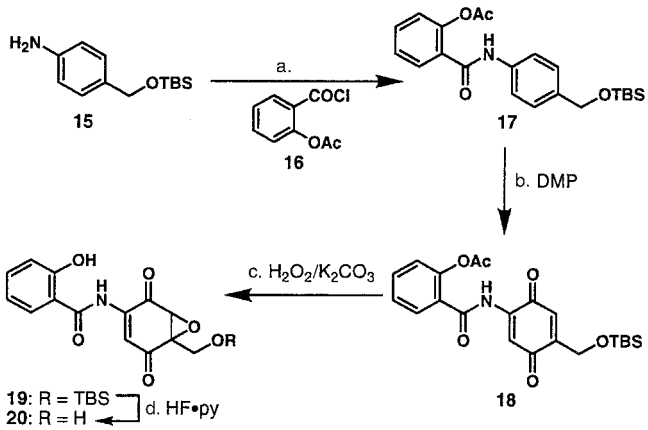
13 14

Entry	Substrate	Dienophile	Product	Yield [%]
1	 **13a**		 **14a-1**	95
2	**13a**		 **14a-2**	83
3	**13a**		 **14a-3**	95
4	 **13b**		 **14b-1**	95
5	**13b**		 **14b-2**	90[a]
6	 **13c**		 **14c-1**	95[a]
7	**13c**		 **14c-2**	95
8	**13c**		 **14c-2**	71
9	 **13d**		 **14d-1**	95[a]
10	**13d**		 **14d-2**	95

[a] This product was obtained as a mixture of unassigned regioisomers (ca. 1–1.5:1 ratio).

accessible through this chemistry, including compounds equipped with handles (for example, iodide, anomeric position *N*-acetyl) for further elaboration.

Finally, an expeditious entry into the epoxyquinomycin class of natural products was developed as demonstrated by a short total synthesis of epoxyquinomycin B (**20**, Scheme 4). The epoxyquinomycins are a class of structurally related,



Scheme 4. Total synthesis of epoxyquinomycin B (**20**). Reagents and conditions: a) **15** (1.0 equiv), **16** (1.0 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 25 °C, 20 min, 100 %; b) DMP (3.0 equiv), H_2O (2.0 equiv), CH_2Cl_2, 25 °C, 3 h, 43 %; c) H_2O_2 (30 % solution in H_2O, 3.0 equiv), K_2CO_3 (1.0 equiv), THF, 25 °C, 30 min, 95 %; d) HF · py (5.0 equiv), THF, 10 min, 95 %. Ac = acetyl; py = pyridine; TBS = *tert*-butyldimethylsilyl.

naturally occurring substances initially isolated from *Amycolatopsis sp.* MK299-95F4 as weak antibiotics.[8] These compounds were subsequently shown to inhibit type II collagen-induced arthritis in vivo with low associated toxicity.[8] More recently,[9] they have been demonstrated to be potent inhibitors of rat embryo histidine decarboxylase, an enzyme implicated in inflammation. Epoxyquinomycins and related compounds have recently been the focus of considerable synthetic activity because of their potential as anti-inflammatory agents and for the treatment of rheumatoid arthritis.[10] The total synthesis reported herein for the most potent member of the class, epoxyquinomycin B (**20**), represents the shortest route to these compounds, featuring only four steps from simple and readily available starting materials and proceeding in 38 % overall yield.[11] Thus, coupling of anilide derivative **15** with carboxylic acid chloride **16** in the presence of triethylamine led to amide **17**, whose exposure to DMP (CH_2Cl_2, 25 °C) furnished quinone **18** in good yield. Regioselective epoxidation of **18** with hydrogen peroxide in the presence of K_2CO_3 in aqueous THF was accompanied by concomitant acetate cleavage to give, after desilylation with HF · py, epoxyquinomycin B (**20** via **19**), whose spectral data matched those reported for the natural product.[8]

In conclusion, we have described a new method for the tandem oxidation of anilides to *p*-quinones or *o*-azaquinones and demonstrated its synthetic utility through the construction of a variety of complex structures, including a short and efficient total synthesis of the anti-inflammatory agent epoxyquinomycin B. The extension of the principles involved in the design of this process to the fashioning of other reactions, as well as further applications of the described technology to synthetic and combinatorial chemistry, are envisioned.

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[1] *Naturally Occurring Quinones IV: Recent Advances*, 4th Edition (Ed.: R. H. Thomson), Blackie, London, **1997**, p. 746.

[2] For a recent review on the synthesis of quinones, see W. M. Owton, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2409, and references therein.

[3] K. C. Nicolaou P. S. Baran, R. Kranich, Y.-L. Zhong, K. Sugita, N. Zou, *Angew. Chem.* **2001**, *113*, 208; *Angew. Chem. Int. Ed.* **2001**, *40*, 202.
[4] S. J. Danishefsky, T. Kitahara, C. F. Yan, J. Morris, *J. Am. Chem. Soc.* **1979**, *101*, 6996.
[5] S. J. Danishefsky, C. F. Yan, R. K. Singh, R. B. Gammill, P. McCurry, N. Fritsch, J. C. Clardy, *J. Am. Chem. Soc.* **1979**, *101*, 7001.
[6] The DMP-mediated conversion of **8** into quinone **9** was accompanied by the formation of an epoxide product whose structure was consistent with epoxidation of the inner diene bond of **9**.
[7] A multistep route to this type of diene is known; however, the reaction requires the presence of chlorine substituents on the aryl ring, see H. W. Heine, B. J. Barchiesi, E. A. Williams, *J. Org. Chem* **1984**, *49*, 2560.
[8] N. Matsumoto, T. Tsuchida, M. Umekita, N. Kinoshita, H. Iinuma, T. Sawa, M. Hamada, T. Takeuchi, *J. Antibiot.* **1997**, *50*, 900; N. Matsumoto, H. Iinuma, T. Sawa, T. Takeuchi, S. Hirano, T. Yoshioka, M. Ishizuka, *J. Antibiot.* **1997**, *50*, 906.
[9] N. Matsumoto, N. Agata, H. Kuboki, H. Iinuma, T. Sawa, T. Takeuchi, K. Umezawa, *J. Antibiot.* **2000**, *53*, 637.
[10] N. Matsumoto, A. Ariga, S. To-E, H. Nakamura, N. Agata, S.-I. Hirano, J.-I. Inoue, K. Umezawa, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 865; O. Block, G. Klein, H.-J. Altenbach, D. J. Brauer, *J. Org. Chem.* **2000**, *65*, 716; P. Wipf, P. D. G. Coish, *J. Org. Chem.* **1999**, *64*, 5053; L. Alcaraz, G. Macdonald, J. Ragot, N. J. Lewis, R. J. K. Taylor, *Tetrahedron* **1999**, *55*, 3707.
[11] For a previous total synthesis, see N. Matsumoto, H. Iinuma, T. Sawa, T. Takeuchi, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2945.
[12] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-148280. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Structure and Base Catalysis of Supercritical Water in the Noncatalytic Benzaldehyde Disproportionation Using Water at High Temperatures and Pressures**

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The physicochemical characteristics of water are greatly changeable by varying the pressure or temperature under supercritical conditions,[1] and supercritical water (scH_2O) offers exiting possibilities for the development of new chemical processes.[2] Furthermore, scH_2O is a suitable medium in connection with "green" (environmentally friendly) technology because water is the most environmentally acceptable and naturally abundant solvent. However, the microscopic characteristics of scH_2O, including the structure which is closely related to chemical reactivity in scH_2O, are not sufficiently well understood. Hence a better understanding of the structure and nature of scH_2O leads to marked improvements in practical applications such as in the mechanical, chemical, and geothermal industries.

Currently in organic synthesis, a matter of primary interest is the promotion of reaction rates by more "green" chemical processes. Recently we reported an interesting finding that scH_2O itself successfully functions as an acid in accelerating pinacol/Beckmann rearrangements.[3] Bröll et al. have briefly reported a base-catalyzed Cannizzaro-type disproportionation of formaldehyde in scH_2O carried out without a base catalyst.[4] In addition, our in situ Raman spectroscopy measurements have indicated that the extent and strength of hydrogen bonding of scH_2O are very different to those in heated and ambient H_2O.[5] This suggests a pronounced stimulation of the breakdown of monomeric water molecules under supercritical conditions, which would account for the acid and base difunctionality of scH_2O. We have further studied the base function of scH_2O by conducting a base-catalyzed disproportionation of benzaldehyde in the absence of any base catalysts. The rate of such a noncatalytic disproportionation in scH_2O has been found to be several-hundred-fold larger than in the conventional catalytic reactions, whereas the rates of these reactions in hot water (below 300 °C), even at high pressures, are extremely small. In addition, the participation of the OH^- ion, the not $OH^\bullet$ radical, in the reaction is strongly suggested from GC-MS and NMR spectroscopic analysis of the benzyl alcohol product in the disproportionation using [D6]benzaldehyde as a reactant.

We first demonstrate that the reaction of benzaldehyde to benzyl alcohol and benzoic acid proceeds in scH_2O even in the absence of any base catalysts. Figure 1 shows the background corrected IR spectra for reaction mixtures in scH_2O (397 °C) and hot water (277 °C) at a constant pressure of 25 MPa along with those for ordinary benzyl alcohol and benzaldehyde aqueous solutions. These measurements were performed by real time, in situ FT-IR spectroscopy for benzaldehyde in H_2O introduced into a high-pressure, high-temperature, flow reactor at a constant residence time of 105.0 s. The spectrum obtained in scH_2O (trace D),shows a new intense band at 1002 cm^{-1}, not present in that of the benzaldehyde solution (trace A). This strong band can be assigned to the CO stretching vibration(ν_1) of the benzyl alcohol formed, and is not observed in the hot water (trace C) or ordinary water (trace A) phases. We have further analyzed the absorption bands around 1700 cm^{-1} (not shown) can be assigned to the CO stretching vibrations of benzaldehyde and benzoic acid, in which the ν_1 frequency of benzoic acid is somewhat higher than that of benzaldehyde. In the scH_2O an intense band at 1702 cm^{-1} nearly coincides with that of the authentic benzoic acid sample, showing unambiguously that benzoic acid is produced in addition to benzyl alcohol. Detailed analysis of

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