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Novel and potent Lewis acid catalyst: Br₂-catalyzed Friedel–Crafts reactions of naphthols with aldehydes

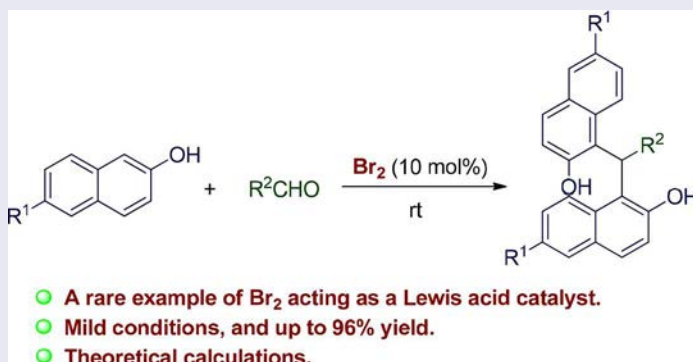
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ABSTRACT

A discovery that the inexpensive Br₂ can serve as a potent Lewis acid catalyst for bis(2-hydroxy-1-naphthyl)methanes synthesis is presented. Under the catalysis of Br₂ at room temperature, naphthols reacted smoothly with various aldehydes with high efficiency and broad substrate scope. This reaction used to require highly acidic conditions and/or high temperature and/or pressure, and sometimes featured poor yields. Moreover, theoretical calculations suggested that Br₂ is a potent Lewis acid to activate the carbonyl group, yet it was not the primary cause for the remarkable activity of Br₂ in the current communication.

GRAPHICAL ABSTRACT



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Alkylation; bromine effect; C–C coupling; homogeneous catalysis

Introduction

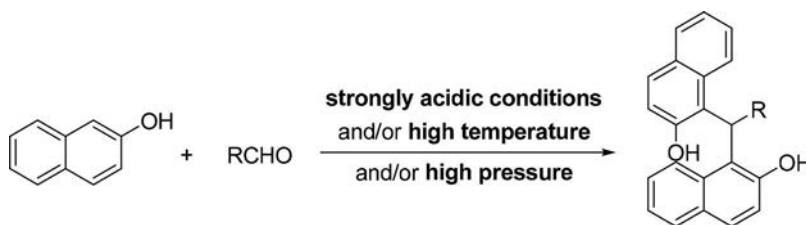
Halogens are of critical importance and have been well studied.^[1] In this regard, expensive molecular iodine is much safer than other halogens, is convenient to use, and has wide applications as a catalyst in modern synthetic chemistry.^[1,2] Elemental bromine is cheap but more volatile and corrosive. In sharp contrast, though, there is an increasing tendency to explore the utility of *N*-bromosuccinimide (NBS)^[3] and other solid alternatives to Br₂.^[4–6] Br₂ itself has rarely been used in a catalytic manner except as an oxidant.^[7–9]

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Scheme 1. Previously reported bis(2-hydroxy-1-naphthyl)methanes synthesis.

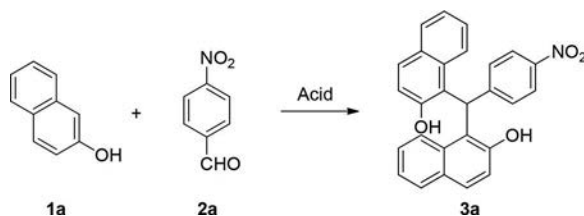
Those alternatives are associated with higher costs and/or tedious steps of preparations, and yet are no match for Br_2 in many cases.

We believe that chemists' distaste for Br_2 hinders the development of science. Not long ago, the abnormal catalytic performances of HBr in some C–C coupling processes was surprising, and some attributed it to the counterion effect.^[10,11] On the other hand, Jamison et al. reported a *N*-bromosuccinimide (NBS)– or Br_2 -catalyzed synthesis of cyclic carbonates from epoxides and CO_2 , and they pointed out that the epoxides were activated by electrophilic bromine.^[12] Although in this work the catalytic activity of Br_2 was not unique, we suggest that Br_2 might serve as a novel and potent Lewis acid, which was subsequently confirmed by the extremely high efficiency of Br_2 in activating carbonyl compounds.^[13,14] Nevertheless, the curious bromine effect is far from well understood and further inquiries are needed.

Friedel–Crafts alkylation is one of the most important and fundamental tools for the construction of aromatic C–C bonds and was found to be acidity dependent.^[15] In this field, the synthesis of xanthenes from electron-rich β -naphthols and aldehydes was well established.^[16–18] In comparison, bis(2-hydroxy-1-naphthyl)methane derivatives are biologically important and exhibit a broad range of bioactivities,^[19–21] but from the same materials their synthesis was seldom reported (Scheme 1).^[22–24] Moreover, these reactions featured harsh conditions, such as strongly acidic conditions^[22,23] and high temperature^[22,24] and/or pressure,^[24] and sometimes featured poor yields.^[23] Very recently, Wang et al. achieved this transformation at ambient temperature by using only 10 mol% of HBr as the catalyst.^[10] Despite this contribution, the development of more mild protocols still remains highly important and challenging. Inspired by the aforementioned curious bromine effect,^[10–14] and in an effort to gain further insights into it, we examined the catalytic power of Br_2 in this transformation. Herein, we present a mild and efficient Br_2 -catalyzed synthesis of bis(2-hydroxy-1-naphthyl)methane derivatives (Scheme 1), and while theoretical calculations proved that Br_2 as a novel Lewis acid possesses significant acidity, it might not be the primary cause of the unique performance of Br_2 .

Results and discussion

We began our study with β -naphthol **1a** and 4-nitrobenzaldehyde **2a** as model substrates (Table 1). Preliminary results showed that in the presence of 5 mol% of Br_2 in MeCN at room temperature, this Friedel–Crafts reaction did not reach completion after 24 h, affording expected benzylidene biphenol **3a** in only 72% yield, which was, however, much greater than the one achieved in the case of 5 mol% HBr as catalyst (entry 1).^[10] When

Table 1. Optimization of reaction conditions^a.

| Entry | Acid (mol%) | Solvent | Time (h) | Yield of 3a ^b (%) |
|-------|---|---------------------------------|----------------------|--|
| 1 | Br ₂ (5) | MeCN | 24 | 72 (36) ^c |
| 2 | Br ₂ (10) | MeCN | 7.0 | 81 (76) ^c |
| 3 | Br ₂ (10) | MeCN | 24 | 97 (95) ^d (90) ^e |
| 4 | BF ₃ ·Et ₂ O (10) | MeCN | 24 | Trace |
| 5 | FeCl ₃ (10) | MeCN | 24 | Nr |
| 6 | SnCl ₄ (10) | MeCN | 24 | Nr |
| 7 | Br ₂ (10) | CH ₂ Cl ₂ | 12 (24) ^f | 96 (Nr) ^c (43) ^f |
| 8 | Br ₂ (10) | EtOAc | 24 | 38 |
| 9 | Br ₂ (10) | THF | 24 | Trace |
| 10 | Br ₂ (10) | DMF | 24 | Trace |
| 11 | Br ₂ (10) | EtOH | 24 | Nr |

^aUnless otherwise noted, all reactions were run using 1.0 mmol of **1a** and 0.55 mmol of **2a** in 5.0 mL of solvent at room temperature.

^bIsolated yields.

^cResults from Wang et al.,^[10] wherein the same loading of HBr (40% aqueous) was used instead of Br₂.

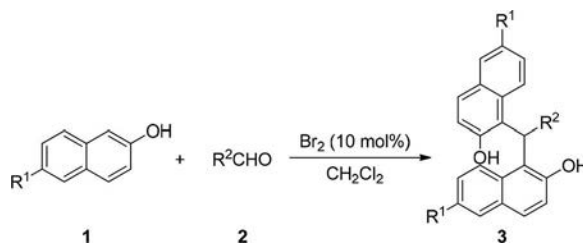
^d0.012 mL of H₂O was additionally added under otherwise identical conditions.

^eThe reaction was run under otherwise identical conditions except that 10 mol% of HBr (40% aqueous) was used as catalyst instead of Br₂.

^fThe reaction was run under otherwise identical conditions except that 10 mol% of anhydrous HBr (33% solution in acetic acid) was used instead of Br₂.

the catalyst loading was increased to 10 mol%, thin-layer chromatography (TLC) revealed that after 7 h **1a** was mostly consumed, and **3a** was isolated in 81% yield (entry 2). To our delight, by prolonging the reaction time to 24 h, nearly quantitative yield of **3a** could be obtained (90% yield with Wang's catalyst, entry 3). Notably, when the same amount of water contained in aqueous HBr at the same loading was additionally added, the reaction was hardly affected (note d, entry 3). An evaluation of some typical Lewis acids demonstrated that, at the loading of 10 mol%, BF₃·Et₂O (entry 4), FeCl₃ (entry 5), and SnCl₄ (entry 6) all showed little or no activity. So did CuBr₂, Bu₄NBr, and a series of Brønsted acids, including HCl, HI, HBF₄, HPF₆, trifluoroacetic acid (TFA), TsOH, H₂SO₄, and TfOH.^[10] Next, other solvents were screened. Somewhat surprisingly, CH₂Cl₂, the use of which led to totally retarded reaction in Wang's work and provided only a moderate yield after 24 h with anhydrous HBr as the catalyst, was superior to MeCN in the present study and within 12 h bis(2-hydroxy-1-naphthyl)methane **3a** was generated in 96% yield (entry 7). While the reaction run in ethyl acetate was sluggish, producing product **3a** in only 38% yield after 24 h (entry 8), employment of tetrahydrofuran (THF, entry 9), *N,N*-dimethylformamide (DMF, entry 10), or ethanol (entry 11) proved fruitless.

Under the optimized reaction conditions (entry 7, Table 1), a variety of bis(2-hydroxy-1-naphthyl)methane derivatives **3** were synthesized from β-naphthols **1** and aldehydes **2**. As summarized in Table 2, aromatic aldehydes **2a–e** bearing electron-withdrawing substituents, such as the nitro group (entries 1 and 2) and halogen atoms (entries 3–5), at the *para*, *meta*, or *ortho* positions all reacted efficiently with β-naphthol **1a** to furnish the desired

Table 2. Scope of the Br₂-catalyzed bis(2-hydroxy-1-naphthyl)methanes synthesis^a.

| Entry | 1 | R ¹ | 2 | R ² | t (h) | 3 | Yield of 3 ^b (%) |
|-----------------|----|----------------|----|----------------------|-------|----|-----------------------------|
| 1 | 1a | H | 2a | 4-NO ₂ Ph | 12 | 3a | 96 |
| 2 | 1a | H | 2b | 3-NO ₂ Ph | 12 | 3b | 90 |
| 3 | 1a | H | 2c | 4-ClPh | 12 | 3c | 92 |
| 4 | 1a | H | 2d | 2-ClPh | 6.0 | 3d | 91 |
| 5 | 1a | H | 2e | 4-BrPh | 12 | 3e | 94 |
| 6 | 1a | H | 2f | Ph | 24 | 3f | 86 |
| 7 ^c | 1a | H | 2g | 4-MePh | 24 | 3g | 83 |
| 8 ^c | 1a | H | 2h | 4-MeOPh | 24 | 3h | 70 |
| 9 | 1a | H | 2i | 2-Furyl | 1.0 | | Complex |
| 10 | 1a | H | 2j | H | 6.0 | 3i | 92 |
| 11 ^c | 1b | Br | 2a | 4-NO ₂ Ph | 24 | 3j | 77 |
| 12 ^c | 1b | Br | 2c | 4-ClPh | 24 | 3k | 45 |
| 13 | 1b | Br | 2j | H | 24 | 3l | 84 |

^aUnless otherwise noted, all reactions were run using 1.0 mmol of 1, 0.55 mmol of 2, and 0.1 mmol of Br₂ in 5.0 mL of solvent at room temperature.

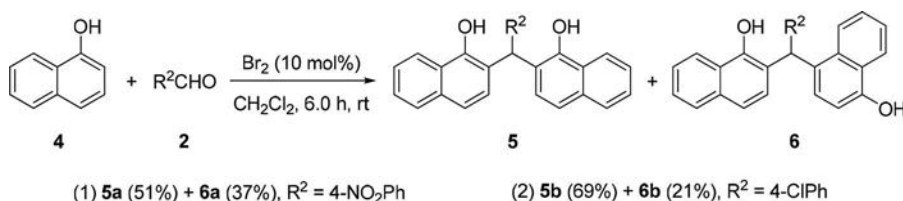
^bIsolated yields.

^cThe reaction was run at 40 °C.

biphenols **3a–e** in excellent yields. The reaction of electron-neutral benzaldehyde **2f** with **1a** gave corresponding product **3f** in 86% yield (entry 6), whereas in the cases of aromatic aldehydes **2g** and **h** with electron-donating substituents, a little greater temperature of 40 °C was required to obtain products **3g** and **h** in good yields (entries 7 and 8). Even this was remarkable, considering that electron-rich aromatic aldehydes were challenging substrates and they did not participate in Wang's reactions to yield the desired products.^[10] It thus represented a significant advantage of the current method. Unfortunately, the use of the heteroaromatic aldehyde **2i** resulted in a complex mixture (entry 9). It is worthy of notice that aliphatic paraformaldehyde **2j** was also adept in efficiently furnishing the related product **3i** in 92% yield within 6 h (entry 10). Then, the reaction was extended to 6-bromonaphthalen-2-ol **1b**, and the desired biphenols **3j–l** were synthesized from **1b** and various aldehydes in moderate to good yields (entries 11–13), though in the cases concerning aromatic aldehydes, a slightly elevated temperature was required. These aryl bromides (entries 5 and 11–13) and chlorides (entries 3, 4, and 12) could facilitate further elaboration to more interesting molecules.

α-Naphthol **4** could also participate in this Br₂-catalyzed Friedel–Crafts reaction (Scheme 2). 4-Nitrobenzaldehyde **2a** and 4-chlorobenzaldehyde **2c** were selected to react with **4**, and the corresponding biphenol products **5a** and **b** and their isomers **6a** and **b** were produced in high to excellent overall yields, though poor *ortho/para* selectivities were observed.

Although in many cases, trace amounts of brominated by-products^[25] were observed, in the present protocol the possibility that HBr generated in situ was the true catalyst could be ruled out, since with CH₂Cl₂ as solvent aqueous HBr was totally inactive and anhydrous



Scheme 2. Reactions of α -naphthol with aldehydes.

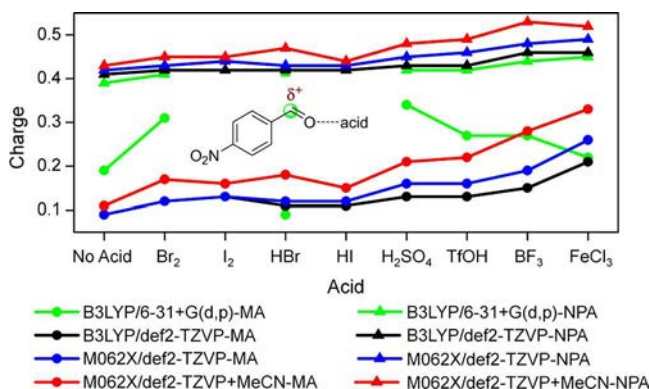


Figure 1. Charge calculations for acid-activated carbonyl carbon of 4-nitrobenzaldehyde.

HBr in AcOH was far less active (notes c and f, entry 7, Table 1), whereas the catalytic activity of Br_2 was not affected by a minute quantity of water (note d, entry 3, Table 1).

In an effort to gain insight into the extraordinary performance of Br_2 , theoretical calculations of the power of a range of Brønsted and Lewis acids in activating the carbonyl group were carried out (Fig. 1; for details see Table S1). 4-Nitrobenzaldehyde **2a** was used as the model substrate. Upon coordination of the carbonyl oxygen atom to acids, the positivity of the carbonyl carbon was enhanced. Various theoretical methods, including B3LYP^[26]/6-31 + G(d,p),^[27] B3LYP/def2-TZVP,^[28] and M062X^[29]/def2-TZVP, confirmed that the positive charge on the carbonyl carbon activated by Br_2 was more or less on par with the ones with other strong acids as activator. This might be related to the high electronegativity in combination with high polarizability of the element of bromine. Be that as it may, Br_2 seemed not to be so superior, and when the solvent effect of MeCN was considered (acids were all compared in MeCN as solvent; see Table 1 and Wang's work^[10]), the trend was basically unaffected (M062X/def2-TZVP+MeCN^[30]). These results suggested that Br_2 , similar to I_2 , was indeed a potent Lewis acid; however, in the present reaction acidity might not be the primary cause of the unique activity of Br_2 , the origin of which remains unclear at this stage. Further exploration still needs to be carried out.

Conclusion

In conclusion, we have demonstrated that Br_2 could act as a novel and potent Lewis acid catalyst in Friedel–Crafts reactions of naphthols, and have developed a mild and efficient synthesis of biologically important bis(2-hydroxy-1-naphthyl)methane derivatives.

Theoretical calculations suggested that Br₂ did possess the significant power to activate the carbonyl group, yet it might not be the primary cause for the remarkable activity of Br₂ presented here. This work might inspire more novel Br₂-catalyzed reactions and provide further clues for the understanding the curious bromine effect, further studies toward which are under way in our laboratory.

Experimental

Chemicals were all purchased from commercial sources and used without treatment. TLC was carried out using silica-gel GF254 plates. Products were purified by column chromatography over silica gel. ¹H NMR and ¹³C NMR spectra were recorded at 25 °C on a Bruker AscendTM 400 spectrometer in CDCl₃/DMSO using tetramethylsilane (TMS) as internal standard. High-resolution mass spectra (HRMS) were obtained using a Bruker microTOF II Focus spectrometer (ESI). Products **3a**, **3c**, **3f**, **3i**, **3j**, **5a**, **5b**, **6a**, and **6b** are known compounds and their spectral data can be found in the literature.^[10]

Optimization of all molecular geometries, vibrational analyses, and Mulliken atomic (MA) charges were calculated at B3LYP and M06-2X functions with the 6-31 + G(d,p) and def2TZVP basis sets by using Gaussian 09 program. A natural bonding orbital (NBO) analysis for structures was also performed to determine the natural population atomic (NPA) charges by using the NBO 3.1 package implemented in Gaussian 09. All calculated structures were true minima (i.e., no imaginary frequencies). Solvent effect at M06-2X/def2TZVP level was calculated using the solvent model density (SMD) approach.^[30]

General procedure (taking the synthesis of **3b** as an example)

A solution of Br₂ (0.0051 mL) in CH₂Cl₂ (1.0 mL) was added to a stirred solution of β-naphthol **1a** (144 mg, 1.0 mmol) and 3-nitrobenzaldehyde **2b** (83 mg, 0.55 mmol) in CH₂Cl₂ (4.0 mL), and the mixture was stirred for 12 h at ambient temperature. After **1a** was consumed, as indicated by TLC, the reaction mixture was quenched with saturated aqueous Na₂S₂O₃ (0.5 mL) and water (20.0 mL), and extracted with CH₂Cl₂ four times. The residue obtained after evaporation of the solvent was purified by column chromatography on silica gel (petroleum ether–ethyl acetate = 12:1, v/v) to afford benzylidene biphenol **3b** as an off-white solid (202 mg, 96% yield).

1,1'-((3-Nitrophenyl)methylene)dinaphthalen-2-ol (**3b**)

Off-white solid: mp 174–175 °C (dec.). ¹H NMR (400 MHz, DMSO) δ = 7.10–7.25 (m, 7H), 7.48 (d, *J* = 4.9 Hz, 2H), 7.70 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.83 (s, 1H), 8.00–8.03 (m, 1H), 8.13 (d, *J* = 8.5 Hz, 2H), 10.39 (bs, 2H); ¹³C NMR (100 MHz, DMSO) δ = 154.0, 148.0, 147.7, 135.5, 134.5, 129.4, 128.93, 128.86, 126.5, 123.7, 123.0, 122.5, 120.5, 119.9, 119.5, 41.7. HRMS (ESI-TOF) calcd. for C₂₇H₂₀NO₄⁺ ([M+H]⁺) 422.1387; found 422.1393.

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References

- [1] Sanderson, R. T. *J. Chem. Educ.* **1964**, *41*, 361.
- [2] Küpper, F. C.; Feiters, M. C.; Olofsson, B.; Kaiho, T.; Yanagida, S.; Zimmermann, M. B.; Carpenter, L. J.; Luther, III, G. W.; Lu, Z.; Jonsson, M.; Kloo, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 11598.
- [3] Koval', I. V. *Russ. J. Org. Chem.* **2002**, *38*, 301.
- [4] Teimouri, M. B.; Akbari-Moghaddam, P.; Motaghinezhad, M. *Tetrahedron* **2013**, *69*, 6804.
- [5] Ganesh, V.; Sureshkumar, D.; Chanda, D.; Chandrasekaran, S. *Chem. Eur. J.* **2012**, *18*, 12498.
- [6] Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303.
- [7] Yuan, Y.; Shi, X.; Liu, W. *Synlett* **2011**, 559.
- [8] Uyanik, M.; Fukatsu, R.; Ishihara, K. *Chem. Asian J.* **2010**, *5*, 456.
- [9] Mu, R.; Liu, Z.; Yang, Z.; Liu, Z.; Wu, L.; Liu, Z. *Adv. Synth. Catal.* **2005**, *347*, 1333.
- [10] Xu, C.; Yuan, H.; Liu, Y.; Wang, M.; Liu, Q. *RSC Adv.* **2014**, *4*, 1559.
- [11] Yuan, H.; Wang, M.; Liu, Y.; Wang, L.; Liu, J.; Liu, Q. *Chem. Eur. J.* **2010**, *16*, 13450.
- [12] Kozak, J. A.; Wu, J.; Su, X.; Simeon, F.; Hatton, T. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2013**, *135*, 18497.
- [13] Liang, D.; Huang, W.; Yuan, L.; Ma, Y.; Ma, J.; Ning, D. *Catal. Commun.* **2014**, *55*, 11.
- [14] Huang, W.; Nang, L.; Li, X.; Yuan, L.; Ma, Y.; Liang, D. *Chin. J. Chem.* **2015**, *33*, 1167.
- [15] Olah, G. A. In *Friedel-Crafts and Related Reactions*; Wiley: New York, 1963.
- [16] Khaligh, N. G.; Shirini, F. *Ultrason. Sonochem.* **2015**, *22*, 397.
- [17] Naeimi, H.; Nazifi, Z. S. *Appl. Catal. A: Gen.* **2014**, *477*, 132.
- [18] Mokhtary, M.; Refahati, S. *Dyes Pigm.* **2013**, *99*, 378.
- [19] Du, F.; Li, X.; Song, J.; Li, C.; Wang, B. *Helv. Chim. Acta* **2014**, *97*, 973.
- [20] Thimm, D.; Funke, M.; Meyer, A.; Müller, C. E. *J. Med. Chem.* **2013**, *56*, 7084.
- [21] Elam, C.; Lape, M.; Deye, J.; Zultowsky, J.; Stanton, D. T.; Paul, S. *Eur. J. Med. Chem.* **2011**, *46*, 1512.
- [22] Kharasch, M. S.; Porsche, J. *J. Org. Chem.* **1936**, *1*, 265.
- [23] Selvam, N. P.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2972.
- [24] Ohishi, T.; Kojima, T.; Matsuoka, T.; Shiro, M.; Kotsuki, H. *Tetrahedron Lett.* **2001**, *42*, 2493.
- [25] Song, S.; Sun, X.; Li, X.; Yuan, Y.; Jiao, N. *Org. Lett.* **2015**, *17*, 2886.
- [26] Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.
- [27] Petersson, G. A.; Bennett, A.; Tensfeldt, T. G.; Al-Laham, M. A.; Shirley, W. A.; Mantzaris, J. *J. Chem. Phys.* **1988**, *89*, 2193.
- [28] Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297.
- [29] Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
- [30] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.