A Rational Approach towards the Nucleophilic Substitutions of Alcohols "on Water"**

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Heterogeneous Reactions

When water, which is unquestionably cheap, safe, and environmentally benign,^[1] is used as a solvent,^[2] the reactivity and selectivity observed are different from those of the same reactions conducted in standard organic solvents.^[3] Although coupling reactions between benzylic halides and nucleophiles are possible in water,^[4] in general, alcohols are not reactive substrates under these conditions.^[5] In fact, the reaction between benzhydrol and the strong π nucleophile 1-methylindole is not promoted in water, and common Brønsted acids (AcOH, trifluoroacetic acid, trifluoromethanesulfonic acid) are also ineffective catalysts for this reaction in water.^[6] Nevertheless, a number of methods for the promotion of direct catalytic nucleophilic substitution of alcohols in organic solvents have been reported.^[7] Kobayashi and Shirakawa have recently found that dodecylbenzenesulfonic acid (DBSA), a Brønsted acidic surfactant, efficiently catalyzes dehydrative nucleophilic substitution of benzylic alcohols with various carbon nucleophiles in water.^[6] We report herein that the direct substitution of alcohols "on water"^[2,8] without added Brønsted or Lewis acid is possible; the reaction is related to the stability of the corresponding carbocation.

Recently, we have demonstrated the direct substitution of optically active ferrocenyl alcohols "on water"^[9] with indole, pyrrole, and thiophenols, which proceeds in good to moderate yield.^[10] Electrophilicity parameters were introduced by Mayr et al., and they demonstrated that one parameter for the electrophile (E) and two parameters for the nucleophiles are sufficient for a quantitative description of the rates of a large variety of electrophile–nucleophile combinations.^[11] We realized that in all attempts to react alcohols in water, alcohols that can form carbocations at the top of Mayr's list (see the Supporting Information) were always selected. In aqueous solution such carbocations tend to have very short lifetimes as a result of their rapid reactions with water.^[12] However, the lifetimes of carbocations can be increased substantially by the

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introduction of electron-donating substituents on the aryl ring.^[13] Ferrocenylcarbenium ions are characterized by an *E* value of -2.57;^[11b] therefore we decided to explore the reactivity "on water" of alcohols that can generate carbocations with a similar or lower *E* value. We examined the reactions of the alcohols depicted in Figure 1 and the nucleophiles shown in Figure 2.^[14] All the reactions were



Figure 1. Alcohols selected for the reaction "on water".

carried out in deionized water (pH 6.52) at 80 °C without inert gas protection and with vigorous stirring. Under these conditions the reactants float on the water emulsion surfaces owing to their low solubility.^[15]



Figure 2. Nucleophiles **a**–**j** employed in the direct nucleophilic substitution of the alcohols **1–8** "on water".



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Electrophiles with E values close to 0 are simply too reactive for the direct substitution of their alcohol precursors "on water". (In fact, alcohols **5** and **8** were isolated unchanged after prolonged reaction time). For the other alcohols tested, the generation of a more stabilized electrophile in water is possible. The E values for the corresponding carbocations in Mayr's scale range from -8.5 (for the carbocation generated from **6**) to -2.5 (for the carbocation generated from **1**). We were pleased to see our prediction confirmed by the experimental results (Table 1). It is worth noting that C, N, and S nucleophiles could be employed in water and the products were isolated in good to excellent yields. Various ketoesters, diketones, and nitroacetates can react smoothly with the selected alcohols in water without the requirement for Lewis or Brønsted acids.

The preparation of a series of substituted benzhydrols, which are key intermediates for the preparation of drugs, $^{\left[16\right] }$

highlights the applicability of this methodology; the products are readily obtained from a clean reaction in water.^[17] To the best of our knowledge, this is the first report of general and direct substitution reactions of alcohols "on water". The unsatisfactory results obtained with alcohol **6** could be explained by the higher stabilization of the generated carbocation in water.^[18]

To compare the reactivity of alcohols "on water" with that under other conditions, we carried examined the reactions of alcohols **1** and **4** with indole at room temperature and 80°C using a range of solvents (see Table 1 in the Supporting Information). Alcohol **1** does not react in the absence of solvent or in a range of solvents at either room temperature or at 80°C. The more reactive **4** gives the product in good yield, in both the presence and absence of solvent. However, the conversions were significantly lower than those of the corresponding reaction "on water". In practical terms,

Nu

Table 1:	Reactions	of ferrocenyl	alcohols	1-10 with	the nucleo	philes a	i−j "on wate	er".
					OH			
					1		water, 80	°C
					- ^-1	+ NIII		-

					R'	R' 'Nu			R∕⊂R ¹			
Entry ^[a]	<i>t</i> [h]	Alcohol ^[b]	Nu	Product		Yield [%] ^[c]	Entry ^[a]	<i>t</i> [h]	Alcohol ^[b]	Nu	Product	Yield [%] ^[c]
1	24	1	a	HN HN HN Me Fe 1a		85	16 ^[e]	72	3	b	NH 3b	65
2 ^[d]	72	1	b			68	17 ^[f]	72	3	b		80
3	24	1	c	NMe N S Fe Tc		65	18	24	3	c		90
4	24	1	h	O O Fe Th		90	19	16	3	e	N ₃ 3e	95
5	24	1	i	O O He Fe 1i		48	20	14	4	a		98
6	24	1	j	O ₂ N OEt Fe Fe J		78	21	24	4	c		79
7	24	2	а	HN- 2a		82	22	24	4	e	Me ₂ N 4e NMe ₂	85 ^[g]

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Table 1: (Continued)											
Entry ^[a]	<i>t</i> [h]	Alcohol ^[b]	Nu	Product	Yield [%] ^[c]	Entry ^[a]	t [h]	Alcohol ^[b]	Nu	Product	Yield [%] ^[c]
8	12	2	e	N ₃ 2e S	68	23	24	4	h		92
9	48	2	f	_	0	24	24	4	i		88
10	24	2	c	MeN S N 2c	90	25	24	4	j		91
11	24	2	d	S S S S Me	85	26	48	5	а	-	0
12	48	2	g		0	27	48	6	а	- NH	[h]
13	24	2	i		83	28	16	7	Ь	Ph Fe Tb	60
14	24	2	j		91	29	16	7	e	N ₃ Ph Fe 7e	95
15	16	3	а	HN	82	30	48	8	а	_	0

[a] All reactions were carried out in air. The alcohol (0.2–0.4 mmol) and the nucleophile (0.4–0.8 mmol) were suspended in of water (2.0–4.0 mL) at 80 °C and stirred for the time indicated. [b] The alcohols are commercially available or were prepared as described in the Supporting Information. Alcohols 1 and 7 were used as racemic mixtures. [c] Yield of purified product. [d] The reaction was performed with 10 equiv of pyrrole. [e] The reaction was performed with 4 equiv of pyrrole. [f] The reaction was performed with 8 equiv of pyrrole. [g] The product decomposed on attempted purification on silica gel. The yield was determined based on the crude reaction mixture. [h] The desired compound was detected by HPLC MS in less than 10% estimated yield.

reactions of 4 (a solid) with indole in aqueous suspensions are more reproducible and convenient than in the absence of solvent, as water provides for the efficient mixing of the reactants.

The direct generation of carbocations in water from alcohols is probably driven by the formation of hydrogen bonds between water and the hydroxy group of the alcohol. Marcus and Jung recently proposed that the formation of hydrogen bonds on the interface between water and oil is responsible for the acceleration of the reactions "on water".^[19] On the other hand, a templated, water-promoted epoxide-opening cascade was recently reported by Jamison and Vilotijevic,^[20] who suggested the concomitant activation

of the nucleophile (OH) and electrophile (epoxide) mediated by a cooperative network of hydrogen bonds.

Although benzylic alcohol **5** and ferrocenyl alcohol **6** are not reactive in water, we took into account the *N* parameter for solvents studied by Mayr et al.^[21] and used the less nucleophilic 2,2,2-trifluoroethanol as the reaction solvent (Scheme 1).^[22] Remarkably, the reaction with indole provided the desired product, showing that other possible combinations of solvents able to form hydrogen bonds with alcohols are suitable for direct alcohol substitutions, without the need of Brønsted or Lewis acid.

In summary, we have described examples of the direct nucleophilic substitution of alcohol "on water", without the



Scheme 1. Direct substitution of the alcohols **6** and **8** in 2,2,2-trifluoroethanol.

use of Lewis or Brønsted acids or surfactants. Mayr's electrophilicity parameters enabled us to predict that many different alcohols bearing metal π complexes will react with nucleophiles "on water" and Nicholas-type reactions may also be possible.^[23]

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- S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* 2005, 117, 3339–3343; *Angew. Chem. Int. Ed.* 2005, 44, 3275–3279.
- [2] a) C.-J. Li, T.-H. Chan, Organic Reactions in Aqueous Media, Wiley, New York, 1997; b) Organic Synthesis in Water (Ed.: P. A. Grieco), Blackie Academic and Professional, London, 1998; c) C.-J. Li, Chem. Rev. 2005, 105, 3095-3166; C.-J. Li, L. Chen, Chem. Soc. Rev. 2006, 35, 68-82; d) Organic Reactions in Water (Ed.: U. M. Lindström), Blackwell Publishing, Oxford, 2007.
- [3] a) U. M. Lindström, F. Andersson, Angew. Chem. 2006, 118, 562-565; Angew. Chem. Int. Ed. 2006, 45, 548-551; b) M. C. Pirrung, Chem. Eur. J. 2006, 12, 1312-1317; S. Otto, J. B. F. N. Engberts, Org. Biomol. Chem. 2003, 1, 2809-2820; c) K. Aplander, R. Ding, U. M. Lindström, J. Wennerberg, S. Schultz, Angew. Chem. 2007, 119, 4627-4630; Angew. Chem. Int. Ed. 2007, 46, 4543-4546.
- [4] a) M. Hofmann, N. Hampel, T. Kanzian, H. Mayr, Angew. Chem.
 2004, 116, 5518-5521; Angew. Chem. Int. Ed. 2004, 43, 5402-5405; b) M. Westermaier, H. Mayr, Org. Lett. 2006, 8, 4791-4794.
- [5] a) G. C. Gullickson, D. E. Lewis, *Aust. J. Chem.* 2003, *56*, 385–388; b) F. Bisaro, G. Prestat, M. Vitale, G. Poli, *Synlett* 2002, 1823–1826; S. J. Coote, S. G. Davies, D. Middlemiss, A. Naylor, *Tetrahedron Lett.* 1989, *30*, 3581–3584.
- [6] S. Shirakawa, S. Kobayashi, Org. Lett. 2007, 9, 311-314.
- [7] For recent reports of catalyzed C--C, C--N, and C-O bond formation through direct substitution of allylic or propargylic alcohols with nucleophiles, see: a) V. Terrasson, S. Marque, M. Georgy, J.-M. Campagne, D. Prim, Adv. Synth. Catal. 2006, 348, 2063–2067; b) Z. Zhan, W. Wang, R. Yang, J. Yu, J. Li, H. Liu,

Chem. Commun. **2006**, 3352–3353; c) Y. Nishibayashi, A. Shinoda, Y. Miyake, H. Matsuzawa, M. Sato, *Angew. Chem.* **2006**, *118*, 4953–4957; *Angew. Chem. Int. Ed.* **2006**, *45*, 4835–4839; d) K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *Angew. Chem.* **2006**, *118*, 2667–2671; *Angew. Chem. Int. Ed.* **2006**, *45*, 2605–2609; e) H. Qin, N. Yamaginawa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2007**, *119*, 413–417; *Angew. Chem. Int. Ed.* **2006**, *45*, 793–766; g) R. Sanz, D. Miguel, A. Martínez, J. M. Álvarez-Gutiérrez, F. Rodrìguez, *Org. Lett.* **2007**, *9*, 2027–2030.

- [8] For a discussion of reactions performed in water, see: Ref. [2]. See also: a) A. P. Brogan, T. J. Dickerson, K. D. Janda, Angew. Chem. 2006, 118, 8278-8280; Angew. Chem. Int. Ed. 2006, 45, 8100-8102; b) Y. Hayashi, Angew. Chem. 2006, 118, 8281; Angew. Chem. Int. Ed. 2006, 45, 8103; c) J. E. Klijn, J. B. F. N. Engberts, Nature 2005, 435, 746-747.
- [9] P. G. Cozzi, L. Zoli, Green Chem. 2007, 9, 1292-1295.
- [10] For the reaction of a ferrocenyl alcohol promoted by an indium salt, see: P. Vicennati, P. G. Cozzi, *Eur. J. Org. Chem.* 2007, 2248– 2253.
- [11] Mayr et al. introduced the following equation: log k = s(N+E) The parameter E in the equation represents the electrophilicity parameter, defined by comparison to a reference compound. See: a) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* 2005, 77, 1807– 1821; b) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* 2003, 36, 66–77. For recent work, see: c) S. T. A. Berger, F. H. Seeliger, F. Hofbauer, H. Mayr, *Org. Biomol. Chem.* 2007, 5, 3020–3026; d) F. Seeliger, S. T. A. Berger, G. Y. Remennikov, K. Polborn, H. Mayr, *J. Org. Chem.* 2007, 72, 9170–9180.
- [12] J. P. Richard, T. L. Amyes, M. M. Toteva, Acc. Chem. Res. 2001, 34, 981–988.
- [13] The 4,4'-bis(dimethylamino)diphenylmethane carbocation has a half-life of 10–20 s; see: R. A. McCLelland, V. M. Kanagasabapathy, N. S. Banait, S. J. Steenken, J. Am. Chem. Soc. 1989, 111, 3966–3972.
- [14] Other nucleophiles—2,5-dimethylthiophene, 1,3-(MeO)C₆H₄, *t*BuOCONH₂, allyltin, allylsilane, 4-MeOC₆H₄NH₂, Bu₃SnCN, 4-butyn-1-ol, 3-acetylbutanol, 2,4-di*tert*butylphenol, *p*-toluensufonamide, and NaN₃—were tested in reactions with ferrocenylethanol **1** on water at 80 °C for 24 h. In these cases only starting material was recovered: see Ref. [9]. Allylsilanes are weak nucleophiles according to the nucleophilicity scale proposed by Mayr et al., see Ref. [11b]. Me₃SiCN is hydrolyzed to the weak nucleophilic HCN under the reaction conditions, and the nucleophilic reaction does not take place. In the reaction of Me₃SiCN with ferrocenenylethanol **1**, ether byproducts, derived by the attack of the alcohol **1** with ferrocenylcarbenium, were isolated; see Ref. [9] for further details.
- [15] The solubility of indole in water is 16 μmmL⁻¹, see: R. S. Peariman, S. H. Y. Yalkowski, S. Banerjee, *J. Chem. Phys. Data Rep.* 1984, *13*, 555–562. The solubility of ferrocene in water is very low. For its solubility in organic solvents, see. M. Dabrowski, B. Mazurkiewicz, A. Boguslaw; A. Starzynski, *J. Chem. Eng. Data* 2001, *46*, 1627–1631; A. Starzynski, *J. Chem. Eng. Data* 2001, *46*, 1627–1631.
- [16] a) R. Pellicciari, G. Costantino, M. Marinozzi, A. Macchiarulo, L. Amori, P. J. Flor, F. Gasparini, R. Kuhn, S. Urwyler, *Bioorg. Med. Chem. Lett.* 2001, *11*, 3179–3182; b) M. Prashad, Y. Lu, O. Repič, J. Org. Chem. 2004, 69, 584–586.
- [17] For other interesting reaction "on water", see: a) M. C. Pirrung, K. Das Sarma, J. Am. Chem. Soc. 2004, 126, 444-445; b) B. K. Price, J. Tour, J. Am. Chem. Soc. 2006, 128, 12899-12904; c) D. Gonzáles-Cruz, D. Tejedor, P. de Armas, F. Garcia-Telaldo, Chem. Eur. J. 2007, 13, 4823-4832; d) H.-B. Zhang, L.-Y.-J. C. Liu, D. Wang, C.-J. Li, Eur. J. Org. Chem. 2006, 869-873.

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- [18] Ferrocenyl alcohol **6** reacts with nucleophiles in the presence of catalytic amounts of InBr₃ or Bi(OTf)₃ in C₂H₄Cl₂ at reflux; P. G. Cozzi, L. Zoli, unpublished results. When the Lewis acid is added to the reaction mixture containing the nucleophile, a stable blue color results, indicating formation of the carbocation.
- [19] Y. Jung, R. A. Marcus, J. Am. Chem. Soc. 2007, 129, 5492-5502.
- [20] I. Vilotijevic, T. Jamison, Science 2007, 317, 1189-1192.
- [21] M. Hofmann, N. Hampel, T. Kanzian, H. Mayr, Angew. Chem. 2004, 116, 5518–5521; Angew. Chem. Int. Ed. 2004, 43, 5402– 5405.
- [22] For a recent report of 2,2,2-trifluoroethanol as a reaction solvent, see: a) I. A. Shuklov, N. V. Dubrovina, A. Börner, *Synthesis* 2007, 2925–2943; b) M. Westermaier, H. Mayr, *Chem. Eur. J.* 2008, *14*, 1638–1647.
- [23] O. Kuhn, D. Rau, H. Mayr, J. Am. Chem. Soc. 1998, 120, 900– 907.