NJC
Letter

High regio- and stereoselective Barbier reaction of carbonyl compounds mediated by $NaBF_4$/Zn (Sn) in water†

Zhenggen Zha, Zhen Xie, Cunliu Zhou, Mingxin Chang and Zhiyong Wang*

Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China. E-mail: zwang3@ustc.edu.cn; Fax: +86 551 363 1760; Tel: +86 551 360 3185

Received (in Montpellier, France) 20th March 2003, Accepted 6th June 2003
First published as an Advance Article on the web 24th July 2003

Studies with $NaBF_4$/M (M = Zn or Sn) showed that this novel mediator facilitated allylation of a variety of carbonyl compounds in water and had a great influence on the diastereoselectivity of the addition. More importantly, α- and γ-addition products of crotylations can be alternatively obtained under the control of this novel mediator. A reaction mechanism is proposed based on our quantum calculation and experimental results.

Allylation of carbonyl compounds with allyl halides is a very important reaction, and numerous reagents and methods have been developed to accomplish this transformation.[1] Particularly, over the last decade, the Barbier-type reaction in aqueous media[2] has drawn great attention. Numerous metals have been shown to mediate the addition of allyl halides to carbonyl compounds in aqueous media to give rise to the corresponding homoallylic alcohols.[3] All the reported metals are commercially available metal powders. Several studies have indicated that zinc- or tin-mediated allylation can only take place in the presence of ammonium chloride, in organic solvent or over long reaction times.[4] In some cases, the commercial metal is not active enough to mediate the allylation under benign environmental conditions.[5,6b,c] For example, commercial zinc was apparently not successful in mediating the allylation reaction in distilled water; then certain salts and reducing reagents such as fluoride salt, cupric chloride, aluminum, and $NaBH_4$ were employed to activate the metals.[6] In our studies, we focus on the development of reaction conditions in which commercial zinc or tin can be directly used in allylation reactions without requiring an acidic environment or organic solvent. In addition to nanotin,[7] we recently have found that sodium tetrafluoroborate is also effective in "activating" zinc and tin in aqueous media to facilitate addition of allyl bromide to carbonyl compounds. More interestingly, high regio- and stereoselective crotylation can be realized under these conditions while it was reported that this reaction can be carried out only in organic solvent and specifically metallorganics.[8]

In our preliminary experiments, the reaction was carried out in distilled water with the molar ratio of benzaldehyde : allyl bromide : Zn at 1 : 2 : 2 and resulted in a low amount of the corresponding homoallylic alcohol even after vigorous stirring of the reaction mixture for 24 h (entry 1, Table 1). When Zn was replaced with Sn under the same conditions, no allylation product was observed after 2 h. Only by prolonging the reaction time to more than 10 h can we get the corresponding alcohol in a modest yield. These results suggest that the metal needs to be activated in order to facilitate this reaction. We then examined a number of phase transfer catalysts[9] and salts as additives in the aqueous media. Out of a large number of conditions tested, we found that 0.12–0.50 mol L^{-1} of sodium tetrafluoroborate was quite efficient in activating zinc to give a good yield of the corresponding homoallylic alcohol (entries 2 and 3, Table 1). Moreover, it was shown that tin was more effective than zinc and the tested allylation reaction proceeded quantitatively (entries 5 and 6, Table 1). Taken together, we conclude that 0.25 mol L^{-1} of $NaBF_4$ is the optimal reaction media to activate commercial zinc and tin metal in allylation reactions.

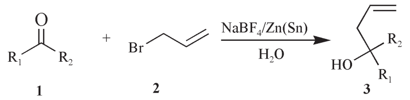
Table 1 Effects of $NaBF_4$ on the allylation of benzaldehyde

Entry	Metal	$NaBF_4$/mol L^{-1}	Time/h	% Yield[a]
1	Zn	—	24	19
2	Zn	0.25	24	76
3	Zn	0.50	24	86
4	Sn	—	2	—
5	Sn	0.25	2	88
6	Sn	0.25	16	98

[a] All yields were determined by ^1H NMR.

We examined allylations of a variety of carbonyl compounds mediated by tin or zinc in the presence of $NaBF_4$ (Scheme 1). The results are summarized in Table 2. The experimental results show that Sn-mediated carbonyl allylations gave rise to excellent yields and can be accomplished in a relatively short time (entries 1–6, entries 8–10, Table 2), whereas Zn mediated allylations exhibited only relatively good or modest yields. $NaBF_4$ appeared to facilitate the allylation reactions in both the reaction rate and the efficiency of the conversion regardless of the type of aldehyde as allylations for both aromatic and aliphatic aldehydes proceeded well (entries 1–10, Table 2).

To the best of our knowledge, ketones, either aromatic or aliphatic, hardly undergo allylation, probably due to steric hindrance. However, in the presence of $NaBF_4$, allylations of ketones proceed smoothly (entries 7 and 10, Table 2). Furthermore, allylations of aldehydes that did not occur with Zn alone in distilled water also proceeded with modest yields in the presence of Zn and $NaBF_4$ together (Table 2). As compared to zinc, tin appeared more effective and comprehensive as a mediator in various types of allylation reactions and produced the corresponding homoallylic alcohols in high yields.

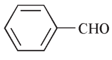
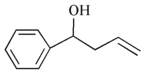
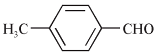
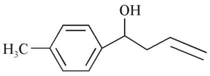
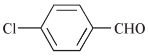
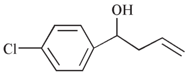
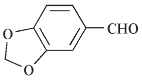
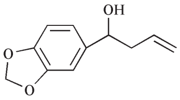
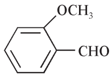
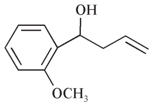
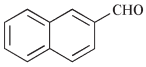
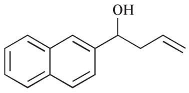
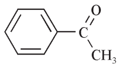
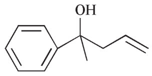
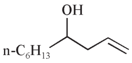
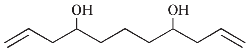
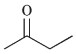
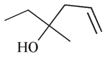


Scheme 1

---

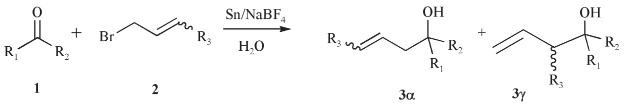
† Electronic supplementary information (ESI) available: spectral data of Barbier-type reaction products and quantum calculation results. See http://www.rsc.org/suppdata/nj/b3/b303187j/

Table 2 Allylation of carbonyl compounds mediated by $NaBF_4$/Zn (Sn) in aqueous medium

Entry	Carbonyl compound	Metal	Time/h	Product	% Yield[a]
1		Zn	18		76
		Sn	16		98
2		Zn	18		42
		Sn	2.5		100
3		Zn	20		76
		Sn	2		100
4		Zn	20		52
		Sn	2		100
5		Zn	20		50
		Sn	5		100
6		Zn	20		47
		Sn	3		100
7		Zn	18		25
		Sn	16		60
8	*n*-$C_6H_{13}CHO$	Zn	24		95
		Sn	1		100
9		Zn	24		70
		Sn	4		100
10		Zn	24		–
		Sn	4		95

[a] All yields were determined by ^1H NMR.

In an effort to determine whether $NaBF_4$ can control reaction selectivity in allylations, a property that may be important for the development of new organic synthetic methods, we studied the regioselectivity and diastereoselectivity of allylations mediated by $NaBF_4$ (Scheme 2). The investigation was focused on allylations of benzaldehyde with ethyl 4-bromobutenoate or crotyl bromide, and of 3-hydroxybutan-2-one with allyl bromide in water (entries 11–18, Table 3). First of all, $NaBF_4$ had an important influence on the distribution of products. When 1.5 mmol of tin was used without $NaBF_4$ for allylation of benzaldehyde with ethyl 4-bromobutenoate, the reaction gave rise to the corresponding γ-addition products in a yield of 58% (entry 11, Table 3), whereas the allylation afforded α-addition products in a yield of 74% in the presence of 0.25 mol L^{12} of $NaBF_4$ (entry 12, Table 3). ^1H and ^{13}C NMR spectral analysis indicated that the γ-products were diastereoisomers and the *syn* isomer was predominant because it is a chelate-controlled product, probably due to the hydrogen bond between the proton in the hydroxyl group and the oxygen in the ester group (entry 11, Table 3). Also, the reaction of benzaldehyde with crotyl bromide generated exclusively the α-addition product in the presence of $NaBF_4$ (entries 15 and 16, Table 3), whereas the same reaction gave a mixture of α- and γ-addition products without $NaBF_4$ (entry 14, Table 3). Moreover, $NaBF_4$ had an influence on the stereoselectivity of allylations. When benzaldehyde was reacted with crotyl bromide, the amount of *E* α-addition product increased from 47% to 59–62% with varying $NaBF_4$ concentration, from 0 to 0.12–0.25 mol L^{-1}, respectively (entries 14–16, Table 3). The diastereoselectivity for the allylation of 3-hydroxybutan-2-one with allyl bromide was also studied under the same conditions. This reaction gave rise to the corresponding addition products and NMR spectra (^1H and ^{13}C) indicated that the *syn* isomer was the dominant product because of the hydrogen bond between the two hydroxyl groups in the product (entry 17, Table 3).



Scheme 2

Table 3 Regio- and diastereoselectivity for the allylation and crotylation of **1** with **2** under different conditions

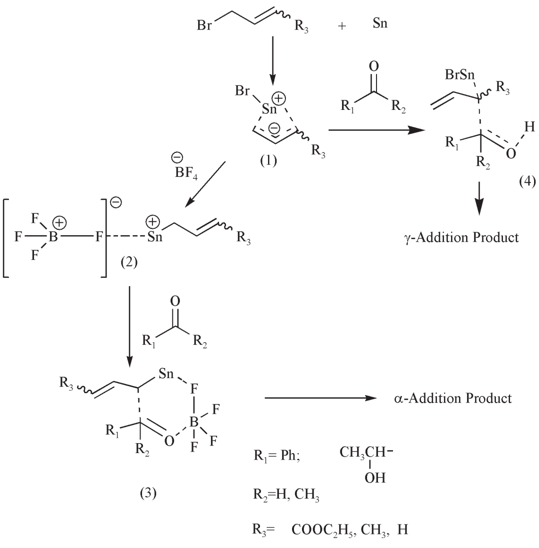
Entry	R_1	R_2	R_3	Sn/mmol	$NaBF_4$/mol L^{-1}	Time/h	% Yield[a]	
							3α (*Z*:*E*)	3γ (*syn*:*anti*)[b]
11	Ph	H	$COOC_2H_5$	1.5	0	24	—	58 (74:26)
12	Ph	H	$COOC_2H_5$	1.5	0.25	15	74 (2:98)	—
13	Ph	H	$COOC_2H_5$	1.2	0.50	10	62 (1:99)	—
14	Ph	H	CH_3	1.5	0	24	54 (53:47)	22 (37:63)
15	Ph	H	CH_3	1.5	0.12	15	75 (41:59)	—
16	Ph	H	CH_3	1.2	0.25	10	73 (38:62)	—
17	$CH_3\overset{\vert}{C}HOH$	CH_3	H	1.5	0	8	75 (63:37)[c]	
18	$CH_3\overset{\vert}{C}HOH$	CH_3	H	1.5	0.12	6	90 (66:34)[c]	

[a] Isolated yield. [b] The ratio of *syn* isomer to *anti* isomer was determined by ^1H NMR, ^{13}C NMR and quantum calculations. [c] The two products are diastereoisomers of each other.

When $NaBF_4$ was added to this reaction, the yield was enhanced from 75% to 90% but the ratio of *syn* to *anti* products was almost the same (entry 18, Table 3).

We hypothesize that $NaBF_4$ affects the stereoselectivity according to the mechanism shown in Scheme 3. Firstly, tin reacts with allyl bromide to afford a tin compound (1). In the presence of $NaBF_4$, fluoroborate can coordinate with (1) to give rise to the corresponding intermediate (2). Then this nucleophile attacks carbonyl compounds through a six-membered ring transition state (3), which results in the α-adduct. Without $NaBF_4$, quantum calculations[10] indicate that the electron density of the γ-carbon is the richest when R_3 is an ester group. When R_3 is a methyl group, the electron density of the α-carbon is slightly higher than that of the γ-carbon, leading to the mixture of α- and γ-adducts.

This proposed mechanism as shown in Scheme 3 can provide an explanation for the stereoselectivity of the allylations in Table 3. As for entry 11 in Table 3, the rich electron density of the γ-carbon (−0.875) promotes the attack on the carbonyl group of the aldehyde. In addition, the $COOC_2H_5$ group can facilitate the formation of a hydrogen bond between the hydroxyl group and the ester group in transition state (4) and promote the formation of the γ-addition product. Also, quantum calculations show that the total energy of *syn* isomers is the lowest among the isomers (see Electronic supplementary information). Thus, the formation of the *syn* product is favored. After addition of sodium fluoroborate, intermediate (2)[11] is formed as shown in Scheme 3. Quantum calculations show that the electron density of the α-carbon atom that bonds to tin in intermediate (2) is the richest ($R_3 = COOC_2H_5$: $\rho = -1.013$; $R_3 = CH_3$: $\rho = -0.959$) and thus it becomes more nucleophilic. Then intermediate (2) coordinates with the carbonyl group of the carbonyl compound to give rise to the corresponding six-membered ring transition structure. As a result, the α-addition product is the product of the allylation after addition of sodium fluoroborate (entries 12 and 13, Table 3). In entry 14 of Table 3, quantum calculations[10] show that the α-carbon has a higher electron density (−0.695) than the γ-carbon (−0.421) in transition state (1). This result reveals that the α-carbon adduct is formed preferentially, accompanied by the γ-addition product. When $NaBF_4$ is added to the reaction, intermediate (2) (the electron density of the α-carbon is −0.959 compared with an electron density of −0.118 on the γ-carbon) is generated and coordinates with the carbonyl compound to afford transition state (3) as shown in Scheme 3, resulting in the generation of the α-addition product (entries 15 and 16, Table 3). As for entries 17 and 18, two diastereoisomers are obtained. Quantum calculations indicate that the *syn* isomer is more stable (the energy difference between *syn* and *anti* is 9.32 kJ mol^{-1} under B3LYP/6-31G).[10]



Scheme 3 Proposed mechanism for allylations in the presence of $NaBF_4$.

In conclusion, $NaBF_4$ in distilled water can facilitate tin- or zinc-mediated allylations to give excellent yields as well as to shorten the reaction time. More importantly for crotylation, α- and γ-addition products can be alternatively obtained whether $NaBF_4$ in water is used or not. Quantum calculations further demonstrated that the dispersion and stereochemistry of the corresponding products are consistent with the calculated results and the proposed mechanism in which $NaBF_4$ promotes the reaction. Further studies of the effects of $NaBF_4$ on the Barbier-type reaction of carbonyl compounds in water are currently in progress.

Experimental

Spectral data—IR (Perkin–Elmer, 2000 FTIR), ^1H NMR (CD_3Cl, 500 MHz or 400 MHz), ^{13}C NMR ($CDCl_3$, 125.7 MHz or 100 MHz) and MS-GC (HP5890 (II)/HP5972, EI)—were acquired on the indicated instrumentation. All reagents were of commercial quality from Aldrich Chemical Company and J&K Chemical Ltd. All organic solvents were purchased from the First Factory of Chemical Reagents in Shanghai (China).

General experimental procedure

To a mixture of aldehyde (1 mmol) in 0.25 mol L^{-1} aqueous sodium tetrafluoroborate solution (4 mL) and allyl bromide (2.0 mmol), metal powder (2 mmol) was added in one portion and the mixture was vigorously stirred until the metal powder had reacted. Ethyl acetate was added to the reaction mixture and the organic layer was separated. The aqueous phase was extracted with ethyl acetate. The organic extracts were combined and dried over anhydrous $MgSO_4$, then was filtered and evaporated. The residue, for most of the aldehydes, afforded the corresponding alcohols with high purity. If necessary, purification was performed by flash chromatography over silica gel using ethyl acetate–petroleum ether as eluent ($R_f = 0.2$).

Spectral data are given for one product below as an example and full spectral data for all products in Tables 2 and 3 are given in the ESI.

***syn*-2-(Hydroxyphenylmethyl)-but-3-enoic acid ethyl ester.** (entry 1, Table 3) IR (NaCl, cm^{-1}): 3483, 1728, 1638, 1318, 1177, 765, 701; ^1H NMR ($CDCl_3$, ppm): 7.26–7.23 (m, 5H), 5.88 (m, 1H), 5.18 (m, 1H), 5.09 (m, 1H), 4.91 (d, $J = 6.4$ Hz, 1H), 3.95 (q, $J = 7.2$ Hz, 2H), 3.25 (q, $J = 6.4$ Hz, $\mathrm{J} = 8.8$ Hz, 1H), 1.02 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, ppm): 172.5, 140.7, 132.0, 128.2, 127.9, 126.5, 120.5, 74.0, 60.9, 58.4, 14.0; MS: m/z 220 (M^+).

Acknowledgements

This research was supported by NSFC (No. 50073021), Nature Science Foundation of Anhui Province (No. 01046301) and Education Department of Anhui Province (No. 2002kj330ZD).

References

1 Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207.

2 (*a*) P. Sinha and S. Roy, *Chem. Commun.*, 2001, 1798; (*b*) C. J. Li and T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, 1997; (*c*) C. J. Li, *Tetrahedron*, 1996, **52**, 5643; (*d*) A. Lubineau, J. Augé and Y. Queneau, *Synthesis*, 1994, 741; (*e*) C. J. Li, *Chem. Rev.*, 1993, **93**, 2023.

3 (*a*) Z. Y. Wang, S. Z. Yuan and C. J. Li, *Tetrahedron Lett.*, 2002, **43**, 5097; (*b*) W. C. Zhang and C. J. Li, *J. Org. Chem.*, 1999, **64**, 3230; (*c*) C. J. Li and T. H. Chan, *Tetrahedron*, 1999, **55**, 11 149; (*d*) C. J. Li and W. C. Zhang, *J. Am. Chem. Soc.*, 1998, **120**, 9102; (*e*) C. J. Li, Y. Meng, X. H. Yi, J. H. Ma and T. H. Chan, *J. Org. Chem.*, 1998, **63**, 7498; (*f*) C. J. Li, Y. Meng, X. H. Yi, J. H. Ma and T. H. Chan, *J. Org. Chem.*, 1997, **62**, 8632; (*g*) M. Wada, H. Ohki and K. Y. Akiba, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2751; (*h*) M. Wada, H. Ohki and K. Y. Akiba, *J. Chem. Soc., Chem. Commun.*, 1987, 708; (*i*) K. Uneyama, N. Kamaki, A. Moriya and S. Torii, *J. Org. Chem.*, 1985, **50**, 5396; (*j*) J. Nokami, S. Wakabayashi and R. Okawara, *Chem. Lett.*, 1984, 869; (*k*) C. Petrier and J. L. Luche, *J. Org. Chem.*, 1983, **50**, 910; (*l*) J. Nokami, J. Otera, T. Sudo and R. Okawara, *Organometallics*, 1983, **2**, 191.

4 (*a*) C. L. Zhou, Z. G. Zha and Z. Y. Wang, *Chin. J. Chem.*, 2002, **20**, 718; (*b*) D. Marton, D. Stivanello and G. Tagliavini, *J. Org. Chem.*, 1996, **61**, 2731; (*c*) S. R. Wilson and M. E. Guazzaroni, *J. Org. Chem.*, 1989, **54**, 3087; (*d*) C. Einhorn and J. L. Luche, *J. Organomet. Chem.*, 1987, **322**, 177.

5 (*a*) B. Alcaide, P. Almendros, C. Aragoncillo and R. Rodrìguez-Acebes, *J. Org. Chem.*, 2001, **66**, 5208; (*b*) T. H. Chen, Y. Yang and C. J. Li, *J. Org. Chem.*, 1999, **64**, 4452.

6 (*a*) X. H. Tan, B. Shen, L. Liu and Q. X. Guo, *Tetrahedron Lett.*, 2002, **43**, 9373; (*b*) L. H. Li and T. H. Chen, *Tetrahedron Lett.*, 2000, **41**, 5009; (*c*) L. H. Li and T. H. Chan, *Org. Lett.*, 2000, **2**, 1129; (*d*) P. D. Ren, Q. H. Jin and Z. P. Yao, *Synth. Commun.*, 1997, **27**, 2761; (*e*) A. Kundu, S. Prabhakar, M. Vairamani and S. Roy, *Organometallics*, 1997, **16**, 4796; (*f*) W. Wang, L. Shi and Y. Huang, *Tetrahedron*, 1990, **46**, 3315.

7 Z. Y. Wang, Z. G. Zha and C. L. Zhou, *Org. Lett.*, 2002, **4**, 1683.

8 (*a*) T. P. Loh, K. T. Tan, J. Y. Yang and C. L. Xiang, *Tetrahedron Lett.*, 2001, **42**, 8701; (*b*) R. Gewald, M. Kira and H. Sakurai, *Synthesis*, 1996, 111; (*c*) K. Mikami, Y. Kimura, N. Kishi and T. Nakai, *J. Org. Chem.*, 1983, **48**, 281.

9 (*a*) Z. G. Zha, Z. Xie, C. L. Zhou, Z. Y. Wang and Y. S. Wang, *Chin. J. Chem.*, 2002, **20**, 1477; (*b*) Z. G. Zha, Y. S. Wang, G. Yang, L. Zhang and Z. Y. Wang, *Green Chem.*, 2002, **4**, 578.

10 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, 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. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian 98, Revision A.11, Gaussian Inc., Pittsburgh, PA, 1998.

11 J. M. Blackwell, W. E. Piers and R. McDonald, *J. Am. Chem. Soc.*, 2002, **124**, 1295.