Formation and Reactions of Alkylzinc Reagents in Room-Temperature Ionic Liquids

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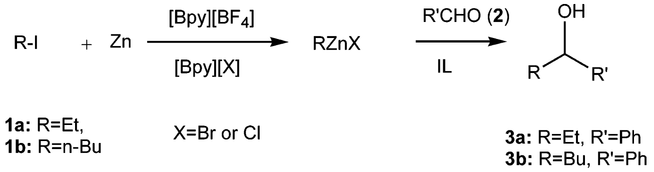

The presence of a suitable amount of bromide or chloride ions was found to be critical in forming the alkylzinc reagents from alkyl iodides and zinc metal in the room-temperature ionic liquid, *N*-butylpyridinium tetrafluoroborate. β-Hydride transfer in the reactions of butylzinc reagents with aldehydes can also be reduced by a bromide ion.

Introduction

Organozinc reagents have been studied extensively since they were first prepared by Frankland[1] in 1848. Organozinc reagents of the type RZnX are usually prepared in conventional organic solvents such as tetrahydrofuran, hexane, toluene, and ether. The choice of solvent plays an important role in the reactivity and stability of these compounds.[2] Because of concern for the environment, there has been considerable recent research into replacing the use of volatile organic solvents as the reaction media.[3] Water,[4] supercritical carbon dioxide,[5] and room-temperature ionic liquids[6] are the most commonly explored media to replace organic solvents. Reactive organometallic reagents such as alkylzinc, Grignard, or alkyllithium are well-known to react vigorously with water or carbon dioxide. Those two “clean” media therefore cannot be used for the preparation or reactions of such reactive organometallic reagents.[7] The study of organometallic reactions in room-temperature ionic liquids (RTILs) has thus far been limited to the less-reactive allyl metal reagents or their variations.[8] This is because the commonly used imidazolium-based RTILs react with reactive organometallic reagents to give imidazol-2-ylidenes (*N*-heterocyclic carbenes, NHCs).[9] Recently, we found that the RTIL *N*-butylpyridinium tetrafluoroborate, [bpy][BF_4], was stable toward diethylzinc and *preformed* diethylzinc could be used to react with aldehydes in [bpy][BF_4] to give the adducts in high yields.[9,10] Furthermore, the ionic liquid could be easily recovered and reused.[9] Because the preformed organozinc reagents have to be prepared in volatile organic solvents, we are therefore interested in the possibility of generating organozinc reagents directly from zinc metal and alkyl halides in RTILs. In a recent report,[10] *preformed* phenylmagnesium bromide in THF was also found to be stable in phosphonium ionic liquids and could undergo the normal reactions expected of Grignard reagents; however,

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[1] Frankland, E. *Liebigs Ann. Chem.* **1849**, *71*, 171.

[2] (a) For the preparation of organozinc reagents, see: *Synthetic Methods of Organometallic and Inorganic Chemistry*; Hermann, W. A., Ed.; Thieme: Stuttgart, Germany, 1999; Vol. 5. (b) Huo, S. *Org. Lett.* **2003**, *5*, 423.

[3] (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford Science Publications: Oxford, NY, 1998. (b) Abraham, M.; Moens, L. *Clean Solvents: Alternative Media for Chemical Reactions and Processing*; ACS Symposium Series No. 819; American Chemical Society: Washington, DC, 2001.

[4] Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.

[5] Jessop, P. *Chemical Synthesis Using Supercritical Fluids*; Wiley-VCH: Weinheim, Germany, 1999.

[6] Rogers, R. D.; Seddon, K. R. *Ionic Liquids: Industrial Applications to Green Chemistry*; Oxford University Press: Washington, 2002.

[7] For the rather extensive study of less-reactive organometallic reactions in aqueous media, see, for examples: (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (b) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. (c) Keh, C. C. K.; Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 4062 and references therein.

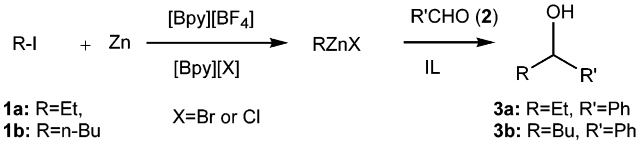
[8] (a) Law, M. C.; Wong, K. Y.; Chan, T. H. *Green Chem.* **2002**, *4*, 161. (b) Gordon, C. M.; Ritchie, C. *Green Chem.* **2002**, *4*, 124. (c) Kitazume, T.; Kasai, K. *Green Chem.* **2001**, *3*, 30. (d) Gordon, C. M.; Mccluskey, A. *Chem. Commun.* **1999**, 1431.

[9] Law, M. C.; Wong, K. Y.; Chan, T. H. *Green Chem.* **2004**, *6*, 241.

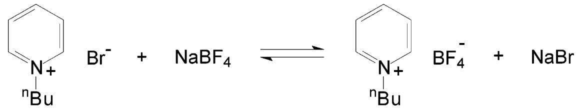
[10] Gorodetsky, B.; Ramnial, T.; Branda, N. R.; Clyburne, J. A. C. *Chem. Commun.* **2004**, 1972.

10.1021/jo051772m CCC: $30.25

SCHEME 1



SCHEME 2



the Grignard reagent could not be formed from magnesium and the halide in the ionic liquid.[10] The issues that are of interest to us are: (1) Can alkylzinc compounds be formed directly from alkyl halides and zinc metal in RTIL? (2) What is the structure of the alkylzinc reagent formed? (3) Do they show a reactivity pattern in RTIL different from that in traditional organic solvents?

Results and Discussion

A. Formation of the Alkylzinc Intermediate in [bpy][BF$_4$]. Initially, we examined the reaction of zinc metal with ethyl iodide (**1a**) in [bpy][BF$_4$] to give the presumed ethylzinc intermediate which was then quenched with benzaldehyde (**2a**) to give the adduct alcohol **3a** (Scheme 1). The reaction was found to be highly irreproducible, giving at times little or no formation of the ethylzinc intermediate (see below) and poor yield of the alcohol **3a**. After consideration of various parameters such as the mesh size, the origin of the zinc metal used, the ambient temperature, or the humidity, we came to realize that the reaction depended critically on the batch and purity of [bpy][BF$_4$] used. The [bpy][BF$_4$] used was usually prepared from [bpy][Br][11] followed by a metathesis reaction with NaBF$_4$. Because the metathetic reaction is an equilibrium process (Scheme 2), the [bpy][BF$_4$] generated inevitably contained a certain amount of the bromide ion. When [bpy][BF$_4$] had been meticulously purified using the chromatography method,[12] we were able to obtain pure [bpy][BF$_4$] with less than 0.2% of bromide ion, determined by an electrochemical method (see Supporting Information). The impure [bpy][BF$_4$] obtained before chromatographic purification, on the other hand, contained about 5.1% of bromide ion (in the form of [bpy][Br]). *The reaction of zinc metal with ethyl iodide could only occur in the impure [bpy][BF$_4$]*!

When zinc metal powder was stirred in pure [bpy][BF$_4$], nothing happened even for an extended period. On the other hand, a deep blue color developed when zinc metal powder (1 mmol) was stirred in impure [bpy][BF$_4$] (1 mL, 5.1% bromide) and the zinc metal slowly dissolved. In the presence of ethyl iodide, the blue color slowly changed to a green color which indicated the formation of the ethylzinc intermediate. It is important to note that the blue color appeared not to be due to the reduction of the pyridinium ionic liquid by metallic zinc,[13] as the NMR spectra of the recovered ionic liquid did not show any reduction product.

TABLE 1. Chemical Shifts of Methylene Protons of Various Ethylzinc Compounds in Different Solvents

compound	toluene[a]	Et$_2$O[b]	CD$_3$CN[c]
ethylzinc species prepared in RTIL			0.28
EtZnCl	0.65	0.22	
EtZnBr	0.69	0.28	
EtZnI	0.34	0.35	
Et$_2$Zn	0.13	0.21	

[a] 10% solution in toluene. [b] 10% solution in Et$_2$O. [c] 2 M solution of EtZn species in [bpy][BF$_4$] with 3 mmol of pyridine dissolved in CD$_3$CN.

TABLE 2. Ethylation of Benzaldehyde in RTIL[a]

entry	ratio of Zn/EtI (mmol)	[bpy][Br] added (% Br)	temp (°C)	yield of **3a** (%)[b]
1	1:1	(5.1)	50/rt	0
2	1:2	(5.1)	50/rt	0
3	2:1	(5.1)	50/rt	65
4	1.5:1.5	(5.1)	50/rt	84
5	2:2	(5.1)	40/40	5
6	2:2	(5.1)	rt/rt	8
7	2:2	(5.1)	50/rt	(92)
8[c]	2:2	(0)	50/rt	0
9[c]	2:2	0.05 g (4.3)	50/rt	0[d]
10[c]	2:2	0.06 g (5.1)	50/rt	89[d]
11[c]	2:2	0.075 g (6.4)	50/rt	83[d]
12[c]	2:2	0.1 g (8.5)	50/rt	(94)[d]
13[c]	2:2	0.15 g (12.8)	50/rt	89[d]
14[c]	2:2	0.2 g (17.1)	50/rt	10[d]

[a] Reaction conditions: Zn and EtI in the indicated mmol ratios were stirred in RTIL (1 mL) for 1 h at 50 °C. Benzaldehyde (1 mmol) was then added, and the stirred mixture was brought to the indicated temperature for 12 h. Impure [bpy][BF$_4$] (5.1% Br$^-$) was used except for with entries 8−14. [b] Product yield was either determined by ^{1}H NMR or by isolation (isolated yields in parentheses). [c] Entries 8−14: pure [bpy][BF$_4$] was used. [d] Entries 9−14: indicated amount of [bpy][Br] was added to pure [bpy][BF$_4$].

To deduce the nature of the ethylzinc intermediate, we examined the ^{1}H NMR of the solution in CD$_3$CN or THF-d_8 but could not observe any meaningful signals. However, by adding a small amount of pyridine to the reaction mixture to stabilize the ethylzinc intermediate followed by dissolution in CD$_3$CN, we were able to detect the ethylzinc species clearly. By comparing the chemical shift of the methylene protons of the ethylzinc species with those in organic solvents[14] (Table 1), we concluded that ethylzinc halide species were likely formed in the ionic liquid.

The ethylzinc reagent thus generated reacted with benzaldehyde to give the adduct **3a** after the normal aqueous workup and extraction. The reaction was relatively inefficient at room temperature; however, at 50 °C, the yield was quite satisfactory (Table 2). The optimal ratio of Zn and EtI to benzaldehyde was found to be 2:2:1 to give a high yield (90%) of the adduct. This high reactivity of the ethylzinc intermediate in RTIL is rather surprising, as alkylzinc halides are generally unreactive toward aldehydes in organic solvents.[15] Some kinds of activation are usually required.[16] Previously, it had been

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(11) Law, M. C.; Wong, K. Y.; Chan, T. H. *Green Chem.* **2002**, *4*, 328.

(12) Park, S.; Kazlauskas, R. J. *J. Org. Chem.* **2001**, *66*, 8395.

(13) It is well-known that substituted pyridinium ions can undergo reductive coupling to give highly colored species. See: Gale, R. J.; Osteryoung, R. A. *J. Electrochem. Soc.* **1980**, *127*, 2167.

(14) (a) Robert, C.; Tang, J. C. *J. Am. Chem. Soc.* **1954**, *76*, 2262. (b) Boersma, J.; Noltes, J. G. *Tetrahedron Lett.* **1966**, 1521. (c) Hota, N. K.; Willis, J. *J. Organomet. Chem.* **1967**, *9*, 169. (d) Boersma, J.; Noltes, J. G. *J. Organomet. Chem.* **1967**, *9*, 551.

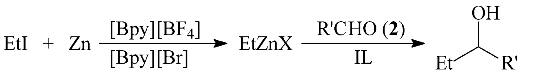
reported that addition of Bu_4NI accelerated the nickel/palladium-catalyzed cross-coupling between benzylic zinc bromides and alkyl iodide/alkenyl trifates.[17] However, in the present case, addition of Bu_4NI to the RTIL either prior to or after the formation of the ethylzinc intermediate did not have any appreciable effect in our reaction. The possibility that pyridine, which may be present as an impurity from the ionic liquid, may play a role in the activation can also be ruled out. Addition of pyridine to the organozinc intermediate prior to the addition of benzaldehyde in fact reduced the yield of **3a**.

B. Effect of Adding Bromide or Chloride Ions. To demonstrate the importance of the bromide ion in affecting the reaction, we used pure [bpy][BF_4] mixed with various amounts of [bpy][Br] as the reaction media for the same ethylation of benzaldehyde (entries 9–14). It could be seen that there was a critical window of Br^- concentration for the optimal results. With the amount of Br^- below 4.3% (entries 8 and 9), there was no formation of adduct **3a**. The optimal amount of Br^- was found to be 8.5% (entry 10) which gave **3a** in 94% isolated yield. However, as the amount of Br^- was increased to 17.1%, the yield of **3a** was only 10% with a significant amount of benzaldehyde unreacted. One consequence of having a larger amount of [bpy][Br] was that the reaction media became more viscous, eventually making the reaction difficult.

Because purification of [bpy][BF_4] by chromatography was relatively tedious and led to substantial loss of materials, we used the impure [bpy][BF_4] (5.1% Br^-) to examine the ethylation of various aldehydes (Table 3). It was clear that all aryl aldehydes could be converted to the corresponding ethylated alcohols **3** in relatively good yields. Cinnamaldehyde reacted in a 1,2-fashion to give the ethylated alcohols (entry 6). The replacement of aryl with a heteroaryl 2-pyridyl moiety presented no particular difficulty (entry 7). On the other hand, aliphatic aldehydes reacted to give a complex mixture with complete consumption of the aldehydes (entries 8 and 9). It was possible that, in addition to ethylation, aldol condensation, elimination, addition, and reduction reactions all occurred.[18]

Addition of [bpy][Cl] was also able to initiate the formation of an organozinc halide intermediate. A deep blue color developed when zinc metal powder (1 mmol) was stirred in [bpy][BF_4] with added [bpy][Cl] to give 8.5% chloride, and the zinc metal slowly dissolved (Table 4, entry 2). With the amount of Cl^- below 8.5% (entry 1), there was no formation of adduct **3a**. Ethylations of various aldehydes with activation of [bpy][Cl] (Table 4, entries 3–6) were also examined, and they showed results similar to those with [bpy][Br]. Addition of [bpy][I], however, failed to show the blue color when stirred with zinc metal powder in [bpy][BF_4] and did not give adduct **3a** under similar conditions.

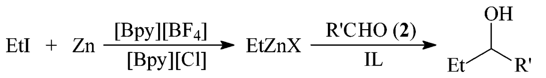
TABLE 3. Zinc-Mediated Cross-Coupling of Ethyl Iodide with Aldehydes with Added [bpy][Br][a]



entry	R′ of R′CHO	mole ratio Zn/EtI	reaction time (h)	isolated yield of **3** (%)
1	*p*-ClPh	2:2	12	**3c**, 85
2	*p*-CNPh	3:3	48	**3d**, 99
3	*p*-MeOPh	2:2	12	**3e**, 63
4	*p*-BrPh	3:3	48	**3f**, 99
5	2,6-dichloroPh	2:2	12	**3g**, 92
6	*trans*-PhCH=CH–	2:2	12	**3h**, 63
7	2-pyridyl	2:2	12	**3i**, 95
8	$(CH_3)_3C$–	1:1	12	0[b]
9	*n*-C_7H_{15}–	1:1	12	0[b]

[a] Reaction conditions: [bpy][BF_4] (1 mL) was used without purification as the reaction media. Zinc and ethyl iodide (in mmol specified) were added and stirred at 50 °C for 1 h. The carbonyl compound (1 mmol) was added to the reaction mixture and stirred for the specified time at 50 °C. The mixture was worked up to isolate **3**. [b] The starting carbonyl compound was completely consumed. The product was isolated as a mixture of complex products.

TABLE 4. Zinc-Mediated Cross-Coupling of Ethyl Iodide with Aldehydes with Added [bpy][Cl][a]



entry	R′ of R′CHO	mole ratio Zn/EtI	[bpy][Cl] added (% Cl^-)	yield of **3** (%)
1	Ph	2:2	0.047 g (5.1)	**3a**, 0
2	Ph	2:2	0.08 g (8.5)	**3a**, 87
3	*p*-CNPh	2:2	0.08 g (8.5)	**3d**, 86
4	*p*-MeOPh	2:2	0.08 g (8.5)	**3e**, 53
5	*p*-BrPh	2:2	0.08 g (8.5)	**3f**, 83
6	*trans*-PhCH=CH	2:2	0.08 g (8.5)	**3h**, 68

[a] Reaction conditions: pure [bpy][BF_4] (1 mL) was used as the reaction media. Zinc and ethyl iodide (in mmol specified) were added and stirred at 50 °C for 1 h. The carbonyl compound (1 mmol) was added to the reaction mixture and stirred for 12 h at 50 °C. The mixture was worked up to isolate **3**.

C. Other Organozinc Reagents. We have also examined the formation of the *n*-butylzinc reagent in the reaction of *n*-butyl iodide with zinc in [bpy][BF_4] (Table 5). As in the case of ethyl iodide, no formation of the blue color or the green alkylzinc reagent was observed in pure [bpy][BF_4] and unreacted benzaldehyde was recovered on quenching the reaction mixture (entry 1). When impure [bpy][BF_4] (5.1% Br^-) was used, the blue color appeared, but no green color intermediate formed upon addition of *n*-BuI. Under these conditions, the added benzaldehyde was converted to give the pinacol coupling product $(PhCHOH)_2$ (**4**) in low yield among other unidentified products (entry 2). With a still higher amount of [bpy][Br] added to the pure [bpy][BF_4] (to give 8.5% Br^-), the blue color appeared followed by the formation of the green *n*-butylzinc intermediate. Addition of benzaldehyde to the solution gave a mixture of the butylated alcohol **3b** together with benzyl alcohol **5** in a ratio of 49:51 (entry

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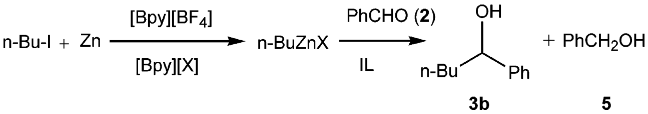
(15) See, for examples: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Knochel, P. *Synlett* **1995**, 393. (c) Tamaru, Y.; Nakamura, T.; Sakaguchi, M.; Ochiai, H.; Yoshida, Z. *Chem. Commun.* **1988**, 610.

(16) See: (a) Inoue, S.; Yokoo, Y. *J. Organomet. Chem.* **1972**, 39, 11. (b) Somsák, L.; Németh, I. *J. Carbohydr. Chem.* **1993**, *12*, 679. (c) Somsák, L.; Madaj, J.; Wiœniewski, A. *J. Carbohydr. Chem.* **1997**, *16*, 1075. (d) Ishino, Y.; Mizuno, T.; Ishikawa, A.; Kobayashi, J. I. *Synlett* **2002**, 2116. (e) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (f) Somsák, L.; Czifrák, K.; Veres, E. *Tetrahedron Lett.* **2004**, *45*, 9095.

(17) Addition of Bu_4NI had been found to accelerate the nickel/palladium-catalyzed cross-coupling between benzylic zinc bromides and alkyl iodide/alkenyl trifates, respectively. See: Piber, M.; Jensen, A. E.; Rottlaender, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323.

(18) The possibility of aldol condensation under the ionic liquid/zinc halide conditions was evident in the attempted reaction of $(MeO)_2CH$-COMe. Only the aldol adduct was isolated in good yield.

TABLE 5. Zinc-Mediated Cross-Coupling of *n*-Butyl Iodide with Benzaldehyde in RTIL[a]



entry	[bpy][X] added (% X)	X	mole ratio Zn/*n*-BuI	ratio **3b/5**
1	(0)	Br	2:2	[b]
2	impure (5.1)	Br	2:2	[c]
3	0.1 g (8.5)	Br	2:2	49:51
4	0.13 g (11.1)	Br	2:2	47:53
5	0.15 g (12.8)	Br	2:2	54:46
6	0.17 g (14.5)	Br	2:2	75 (70):25
7	0.2 g (17.1)	Br	2:2	47:53
8	0.17 g (14.5)	Br	2:2	[d]
9	0.08 g (8.5)	Cl	2:2	12 (**5** only)
10	0.17 g (18.4)	Cl	2:2	0

[a] Reaction conditions: pure [bpy][BF_4] (1 mL) with the indicated amount of [bpy][Br] added was used, except in entry 2, as the reaction media. Zinc and *n*-butyl iodide (in mmol specified) were added and stirred at 50 °C for 1 h. Benzaldehyde (1 mmol) was added to the reaction mixture and stirred for 12 h at room temperature. The mixture was worked up, and the ratio of **3b/5** was determined by ^{1}H NMR. [b] Benzaldehyde was recovered. [c] Pinacol product **4** was obtained with undetermined yield. [d] Tricyclohexylphosphine (3 mmol) was added after the formation of *n*-BuZnX.

3). The formation of **5** was attributed to the well-known propensity of β-hydride reduction of aldehydes by alkylzinc. However, when we increased the amount of the bromide ion even further by adding more [bpy][Br] to the pure [bpy][BF_4] as the reaction media, the alkylation product **3b** increased substantially with **5** suppressed (entries 4−7). The optimal amount of Br^- concentration appeared to be 14.5%, at which point the ratio of **3b** to **5** was found to be 75:25 and the alcohol **3b** could be isolated in 70% yield after chromatography. Recently, Fu et al. have found that some hindered phosphines are quite useful in suppressing β-hydride elimination for alkylmetallic reagents that possess β-hydrogen.[19] We thus attempted the addition of tricyclohexylphosphine to the ionic liquid reaction using the optimal Br^- concentration. The result was disappointing, and all the starting benzaldehyde was recovered (entry 8). Addition of [bpy][Cl] instead gave little of **3b** with a poor yield of **5** as the product (entry 9). Unlike [bpy][Br], further increasing [bpy][Cl] did not improve the yield of **3b**.

We have also examined the reaction of phenyl iodide with zinc in [bpy][BF_4] under various reaction conditions. An organometallic species appeared to have been formed. However, on quenching the reaction mixture with benzaldehyde, a complex mixture was invariably obtained as the reaction product. Further studies will be required to clarify the reactions involved in this case.

D. Recovery and Reuse of IL. One problem anticipated in the use of ionic liquids as solvents for organometallic reactions is the issue of recycling and reusing the ionic liquids after removal of the organic product. After the formation of the alkylzinc intermediate and its subsequent reaction with aldehyde, the reaction mixture was usually quenched with water and the organic product was extracted with organic solvents (usually ether). There was usually little loss of the ionic liquid in the extraction process because the extract in each workup was free of ionic liquid according to its NMR. However, the recovered ionic liquid may contain inorganic products insoluble in the organic solvent extract. In the present reaction, it was the presumed formation of ZnXOH as the inorganic product which may remain in the recovered ionic liquid and interfere with subsequent alkylation reactions. Indeed, when the ionic liquid [bpy][BF_4], recovered after extraction of the organic product and diluted with a small amount of methylene chloride to precipitate the inorganic zinc salt, was reused for the alkylzinc formation, the reaction failed. Apparently, the inorganic zinc salt was not completely removed by this recovery process. On the other hand, when the reaction mixture was quenched with anhydrous sodium oxalate instead of water and the resultant inorganic salts (presumably zinc oxalate and sodium halide) were precipitated from the ionic liquid by the addition of a small amount of acetone, the IL [bpy][BF_4] thus recovered could then be reused for the reaction to give the ethylated product **3a** in similar yields. The results are summarized in Table 6. The ionic liquid, added with either [bpy][Br] (entry 3) or [bpy][Cl] (entries 1 and 2) could be recycled and reused readily to give the alkylation product with similar yields for at least five cycles (Table 6). In the case of entry 2, where a greater excess of Zn and EtI were used, there was no noticeable change in yields throughout the five cycles and only a slight reduction in the yield of **3a**, by a few percent in each cycle, was observed in the other cases (entries 1 and 3).

TABLE 6. Recycling of [bpy][BF$_4$] in the Ethylation of Benzaldehyde[a]

entry	mole ratio Zn/EtI	[bpy][X] added (% X)	yield of **3a** in each cycle (%)[c] 1	2	3	4	5
1[b]	2:2	Cl (8.5)	87	80	90	85	81
2[b]	3:3	Cl (8.5)	94	95	97	93	94
3[b]	2:2	Br (8.5)	94	67	89	75	80

[a] Reaction conditions: Zn and EtI in the indicated mmol ratios were stirred in RTIL (1 mL) for 1 h at 50 °C. The carbonyl compound (1 mmol) was added to the reaction mixture and stirred for 12 h at 50 °C. Sodium oxalate was used to quench the reaction mixture, followed by precipitation of inorganic salt with acetone. [b] Entries 1−3: pure [bpy][BF_4] was used with the indicated amount of [bpy][X] added at each cycle. [c] Isolated yields.

E. Mechanistic Discussions. We have shown that alkylzinc reagents can be formed from alkyl iodide and zinc metal in the ionic liquid [bpy][BF_4]. The bromide or chloride ion was found to be essential for the reaction to occur. The function of the bromide ion (or chloride ion) was not due to the possible conversion of the alkyl iodide to the alkyl bromide under the reaction conditions. The use of ethyl bromide in place of ethyl iodide in pure [bpy][BF_4] failed to lead to the formation of the ethylzinc intermediate. The bromide (or chloride) ion appeared to have a role in assisting the zinc metal to dissolve in the ionic liquid, forming a blue colored solution. This facilitates the formation of the alkylzinc intermediate subsequently. Scheme 3 presents a plausible mechanism to

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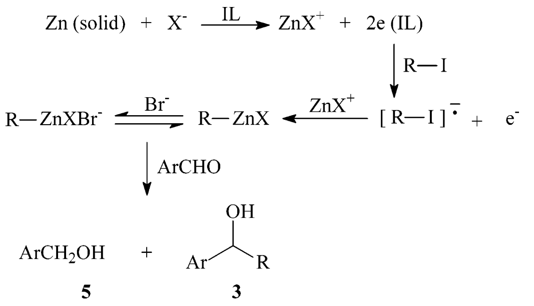
(19) Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.

SCHEME 3



account for the observations. The bromide (or chloride) ion reacts with the zinc metal to generate ZnX^+ (X = Br or Cl) and the solvated electron in ionic liquid, giving the blue color typical of solvated electrons. The solvated electron then reacts with alkyl iodide to generate a radical anion intermediate, which can react with ZnX^+ to give RZnX (X = Br or Cl). The RZnX then reacts with aldehyde to give both the alkylation product **3** and/or the hydride reduction product **5**. In the *n*-BuZnX case, where β-hydride transfer to aldehydes normally predominates, the presence of more bromide ion may lead to the formation of complex $RZnXBr^-$ which may facilitate the alkyl transfer more than the β-hydride transfer, thus accounting for the greater amount of **3**.

Conclusion

We have shown that alkylzinc intermediates can be formed directly from alkyl iodide and zinc metal in the ionic liquid [bpy][BF_4]. However, the presence of [bpy][X] either as an impurity or as an additive was required for the reaction to occur. The role of the X ion is believed to be to facilitate the dissolution of zinc metal in the IL to give the solvated electron to assist in the subsequent reaction with the alkyl iodide. The structure of the alkylzinc intermediate is likely to be RZnX according to ^{1}H NMR. The alkylzinc intermediate thus formed reacts efficiently with aryl aldehydes to give the corresponding ethylated products. The IL can be recovered and reused for at least five cycles.

Experimental Section

Preparation of Ionic Liquids. The crude *N*-butylpyridinium tetrafluoroborate [bpy][BF_4] was prepared by a metathesis reaction in acetonitrile (300 mL) from sodium tetrafluoroborate (121 g, 1.1 mol) (purchased commercially with 98% purity in fine powder form) and its bromide precursor [bpy][Br] (216 g, 1.0 mol) which was in turn prepared from the microwave-assisted method.[11] The mixture was stirred for 3 days at room temperature and then filtered. The filtrate was evaporated, and the residue crude [bpy][BF_4] was vacuum-dried overnight at 70 °C (0.1 mmHg) and stored under nitrogen. Pure [bpy][BF_4] could be obtained by column chromatography of the crude [bpy][BF_4] on silica gel with dichloromethane as eluent.[12] The recovery of [bpy][BF_4] after chromatography was about 60%.

Electrochemical Determination of Bromide Ion Concentration in [bpy][BF_4]. A conventional three-electrode setup was utilized with all Pt electrodes acting as working, counter-, and pseudoreference electrodes. The platinum working electrode was polished with a slurry of alumina suspension in water on a clean cloth before use. Cyclic voltammetry was carried out on a BAS 100B/W electrochemical workstation with 3 mL of purified and predried [bpy][BF_4] in a glass electrochemical cell and performed by scanning from −0.2 to +1.4 V. The background of pure [bpy][BF_4] did not show any signal corresponding to the bromide anion. A stock solution of the bromide ion was prepared by dissolving a weighed amount of pure *N*-butylpyridinium bromide into pure [bpy][BF_4] (3 mL). Calibration was done by addition of the prepared stock solution (0.1 mL) to a solution of purified [bpy][BF_4] (3 mL) and by repetition a few times between consecutive CV runs. Figure 1 (in Supporting Information) shows the cyclic voltammograms for the oxidation of bromide (0.01−0.03 M) in [bpy][BF_4] at a Pt electrode. A wave was observed at $E = 700$ mV vs platinum. An anodic wave observed on the forward potential sweep is attributable to the oxidation of bromide to bromine, and the cathodic wave is due to the reverse process.[20] A calibration curve was obtained by the linear plot of current against bromide ion concentration (Figure 2 in Supporting Information). The unknown bromide concentration of the crude [bpy][BF_4] was then determined using the calibration curve.

General Procedure for the Preparation of Alkylzinc Reagents in Ionic Liquid. To a 50 mL reaction vessel containing the colorless ionic liquid [bpy][BF_4] (1 mL) (Figure 3 in Supporting Information) was added metallic zinc (2 mmol). Commercially available zinc dust (purity 99.9, −325 mesh), zinc powder (purity 99.999, −40 mesh or purity 99.999, −100 +200 mesh), and zinc granules (purity 99.8+, −10 +50 mesh) could all be used without any pretreatment. Zinc metal powder, which had been stored for a long time, could be washed with dilute acid before use.[21] For ionic liquid, which contained between 5% and 12.8% bromide ion, the solution slowly turned blue (Figure 4 in Supporting Information) after stirring at room temperature for 1/2 h. Alkyl iodide (2 mmol) was then added, and the solution was stirred at 50 °C overnight and then turned green (Figure 5 in Supporting Information), indicating the formation of the alkylzinc intermediate. ^{1}H NMR was then examined by adding pyridine (3 mmol) to the reaction mixture followed by dissolving a drop of the ionic liquid in d_3-acetonitrile in an NMR tube. One set of ethyl group absorption (one triplet at $^{\delta}CH_3 = 1.18$ ppm and one quartet at $^{\delta}CH_2 = 0.28$ ppm) was observed with J_{AB} (Hz) = 8.

General Procedure for the Alkylation of Aldehydes with Organozinc Reagents in Ionic Liquid. A 50 mL reaction vessel was charged with the ionic liquid (1 mL, bromide containing [bpy][BF_4]), powdered metallic zinc (2 mmol), and alkyl iodide (2 mmol) under an inert nitrogen atmosphere. The reaction mixture was stirred at 50 °C for 1 h followed by the addition of the carbonyl compound (1 mmol). The mixture was stirred at the indicated temperature for the time period (see Tables 2 and 3) under an inert nitrogen atmosphere (Figure 6 in Supporting Information). The resulting mixture was quenched with a few drops of water followed by extraction with Et_2O (3 × 10 mL).[22] After removal of the ether solvent in vacuo, the residue was purified by flash chromatography on silica gel to yield the pure adduct alcohol **3**. Specific conditions and yields of the alkylation of aldehydes are given in Tables 2−4. Compounds **3a**, **3b**, and all the isolated products in Table 3 are known compounds. Their structures and purities were confirmed by their ^{1}H NMR spectra (Figures 7−13 in Supporting Information) and comparison with known samples previously synthesized.[9]

Recycling and Reusing Ionic Liquids. After complete reaction, an equivalent amount of sodium oxalate to zinc metal

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[20] Allen, G. D.; Buzzeo, M. C.; Villagran, C.; Hardacre, C.; Compton, R. G. *J. Electroanal. Chem.* **2005**, *575* (2), 311.

[21] Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; Oxford: Boston; Butterworth: Heinemann, 1996.

[22] It is assumed generally that, if necessary, extraction of organic substrates from ionic liquids can be carried out with supercritical carbon dioxide in place of nonpolar organic solvents. See: (a) Blanchard, L. A.; Hancu, D.; Beckman, E. J.; Brennecke, J. F. *Nature* **1999**, *399*, 28. (b) Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254.

powder was added to the reaction mixture. The zinc residue could be removed by dissolution of the ionic liquid in acetone (5 mL) or methylene chloride, and the solid precipitates of $Zn(C_2O_4)$ and NaX were filtered. The ionic liquid was recovered on removal of acetone/methylene chloride followed by extraction with Et_2O (2 × 5 mL) and dried by further heating overnight at 70 °C (0.1 mmHg). The experimental procedure for ethylation in recycled ionic liquid was the same as that described above.

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Supporting Information Available: Cyclic voltammograms and ^{1}H NMR spectra of **3a**, **3b**, and other isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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