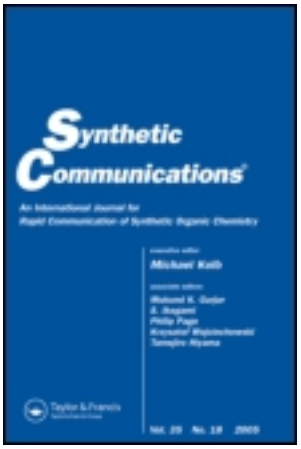


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# Improved Preparation of 1,3-Bis(2,6-di-iso-propylphenyl)imidazolium Tetrafluoroborate

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# IMPROVED PREPARATION OF 1,3-BIS(2,6-DI-*ISO*-PROPYLPHENYL)IMIDAZOLIUM TETRAFLUOROBORATE

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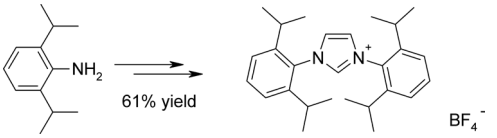
## GRAPHICAL ABSTRACT




**Abstract** *A convenient, high-yielding, multi-hundred-gram preparation of 1,3-bis(2,6-di-*iso*-propylphenyl)imidazolium tetrafluoroborate is described. The preparation of this salt has significant advantages over the chloride as it eliminates potential bis(chloromethyl) ether formation. The improved conditions provided the tetrafluoroborate salt in 61% overall yield in two steps from 2,6-di-*iso*-propylaniline.*

**Keywords** *N*-Heterocycle carbene; IPr-$HBF_4$; ligand preparation

## INTRODUCTION

*N*-Heterocycle carbenes are commonly used as highly active ligands in a variety of different metal-catalyzed coupling reactions.[1] Published syntheses of 1,3-bis(2,6-di-*iso*-propylphenyl)imidazolium chloride (IPr-HCl, **1**, Scheme 1) often suffered from poor yields, particularly in the ring-formation step,[2] until the publication of Nolan's improved procedure.[3] In the patent he reports a 70% yield for this step, using hydrogen chloride gas and paraformaldehyde in ethyl acetate to convert the glyoxaldiimine **4** to the imidazolium salt. The combination of hydrogen chloride gas and paraformaldehyde has been reported to form bis(chloromethyl) ether,[4] a known potent human carcinogen,[5] which was considered undesirable for large-scale preparation. The tetrafluoroborate salt **2** has been prepared not only from chloride **1**[6] but also directly from **4** using tetrafluoroboric acid.[7] In the latter preparation glyoxaldiimine **4** and paraformaldehyde were heated in tetrahydrofuran (THF) and then treated with tetrafluoroboric acid diethyl ether complex to give **2** in 38% isolated yield.

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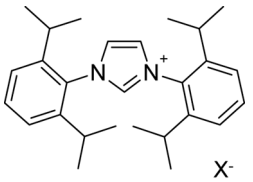



**1**, X = Cl
**2**, X = $BF_4$

**Scheme 1.** IPr salts.



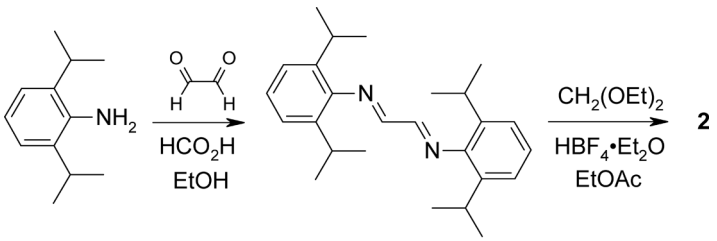
## RESULTS AND DISCUSSION

The need to prepare multi-hundred-gram quantities of the IPr ligand for use in a pilot plant-scale Buchwald–Hartwig coupling reaction resulted in development of an optimized procedure (Scheme 2).

The preparation of glyoxaldiimine **4** has been reported in the literature using **3** and 40% aqueous glyoxal in ethanol in 78% yield.[2a,3] The yield of these previously described procedures was increased to 90% by using a slight excess of glyoxal (0.52 equiv.), an extended reaction time, and increased concentration. A similar yield was recently reported using methanol as the solvent.[6] *n*-Propanol was also investigated and gave a lower yield, consistent with this trend in solvent polarity.

Conversion of **4** to **2** with tetrafluoroboric acid diethyl ether complex was screened in a range of solvents including toluene, THF, dibutyl ether, $CH_2Cl_2$, dimethoxyethane, cyclohexane, and ethyl acetate. Diethoxymethane, *s*-trioxane, and paraformaldehyde were investigated for the one carbon unit. Of the solvents, the best results were obtained in ethyl acetate. For the one carbon unit, diethoxymethane gave a salt of superior color and in greater yield than either *s*-trioxane or paraformaldehyde. In the final procedure a solution of diethoxymethane in ethyl acetate was first treated with tetrafluoroboric acid diethyl ether complex at 0 °C, followed by addition of an ethyl acetate solution of **4**. After warming to room temperature, isolation provided analytically pure **2** in 68% yield.

Even though significant counterion effects have been observed in other systems,[6,8] **2** performed equally well as **1** in the downstream amination chemistry. The Buchwald–Hartwig chemistry, after scale-up in 22-L glass, was ultimately carried out on a 7-kg scale in the pilot plant.




**Scheme 2.** Preparation of **2**.

## CONCLUSION

An improved two-step process for the preparation of IPr-$HBF_4$ was developed with an overall yield of 61% from commercially available 2,6-di-*iso*-propylaniline. The simple and efficient procedures were demonstrated at a multi-hundred-gram scale.

## EXPERIMENTAL

### *N,N′*-Bis(2,6-di-*iso*-propylphenyl)glyoxaldiimine (4)[9]

Glyoxal (199 g of a 40% aqueous solution, 1.37 mol) was added to a solution of 2,6-di-*iso*-propylaniline (470 g, 2.65 mol) in ethanol (1.25 L) followed by 4 drops of formic acid. The mixture was stirred at 18–23 °C for 65 h. The product was collected by filtration, washed with ca. −10 °C methanol (2 × 250 mL), and dried under vacuum at ~65 °C to give **2** (447.1 g, 90%) as a yellow solid. Mp 107–108 °C; $^1$H NMR ($CDCl_3$): δ 8.10 (s, 2H), 7.12–7.23 (m, 6H), 2.94 (septet, $J = 6.8$ Hz, 4H), 1.21 (d, $J = 6.8$ Hz, 24H).

### 1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolium tetrafluoroborate (2)[10]

Tetrafluoroboric acid diethyl ether complex (198 mL, 234 g, 1.44 mol) was added to a solution of diethoxymethane (157 mL, 1.25 mol) in ethyl acetate (950 mL) at 0–2 °C. A solution of glyoxaldiimine **4** (359 g, 0.95 mol) in ethyl acetate (1.9 L) was added over 1 h, keeping the temperature at 0–2 °C. The mixture was allowed to slowly warm to room temperature overnight. The product was collected by filtration, washed with ethyl acetate (450 mL, in portions), and dried under vacuum at ~65 °C to give **2** (306.9 g, 68%) as a white solid. Mp > 300 °C; $^1$H NMR (DMSO-$d_6$): δ 10.15 (t, $J = 1.5$ Hz, 1H), 8.54 (d, $J = 1.5$ Hz, 2H), 7.69 (t, $J = 7.4$ Hz, 2H), 7.53 (d, $J = 7.4$ Hz, 4H), 2.36 (septet, $J = 6.8$ Hz, 4H), 1.27 (d, $J = 6.8$ Hz, 12H), 1.17 (d, $J = 6.8$ Hz, 12H); $^{13}$C NMR (DMSO-$d_6$): δ 145.2, 139.6, 132.2, 130.4, 126.6, 125.0, 29.0, 24.4, 23.5. Anal. calcd. for $C_{27}H_{37}N_2BF_4$: C, 68.07; H, 7.83; N, 5.88. Found: C, 68.32; H, 7.67; N, 6.07.

## ACKNOWLEDGMENT

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## REFERENCES

1. For a recent review, see Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151–5169.
2. (a) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49–54; (b) McCarroll, A. J.; Sandham, D. A.; Titcomb, L. R.; de K. Lewis, A. K.; Cloke, F. G. N.; Davies, B. P.; de Santana, A. P.; Hiller, W.; Caddick, S. *Mol. Divers.* **2003**, *7*, 115–123.
3. Nolan, S. P. Synthesis of 1,3-disubstituted imidazolium salts. U.S. Patent 7,109,348, Sep. 19, 2006; *Chem. Abstr. 145*, 356776.
4. Stephen, H.; Short, W. F.; Gladding, G. *J. Chem. Soc.* **1920**, *117*, 510–527.

5. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service, and U.S. Environmental Protection Agency. *Toxicological Profile for Bis(chloromethyl) Ether*; U.S. Government Printing Office: Washington, DC, 1989. Available at http://www.atsdr.cdc.gov/ToxProfiles/tp128.pdf.
6. Bantreil, X.; Nolan, S. P. *Nat. Protocols* **2011**, *6*, 69–77.
7. Böhm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 1602–1604.
8. Blanc, R.; Commeiras, L.; Parrain, J.-L. *Adv. Synth. Catal.* **2010**, *352*, 661–666.
9. Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889–9890.
10. Wei, S.; Wei, X.-G.; Su, X.; You, J.; Ren, Y. *Chem.—Eur. J.* **2011**, *17*, 5965–5971.