SYNTHETIC COMMUNICATIONS, 27(24), 4265-4274 (1997)

REDUCTIVE AMINATION WITH ZINC BOROHYDRIDE. EFFICIENT, SAFE ROUTE TO FLUORINATED BENZYLAMINES

Sukanta Bhattacharyya

Arindam Chatterjee and John S. Williamson

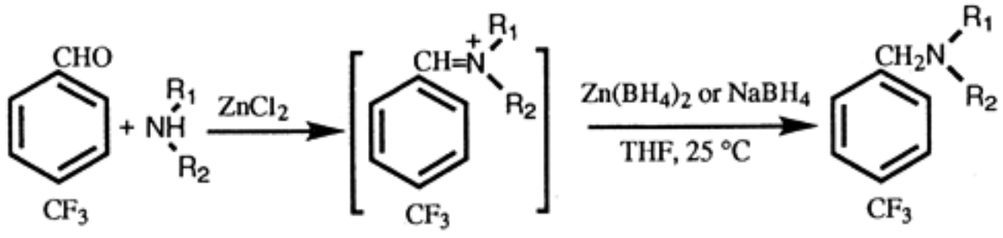
Abstract: Fluorinated benzylamines are synthesized in high yields by reductive alkylation of secondary amines with appropriate fluoroaldehydes using a combination of zinc chloride and zinc borohydride. The present method offers an alternative to toxic sodium cyanoborohydride and is adaptable to multigram-scale preparations.

The design and synthesis of fluorinated organic molecules have gained interest[1] in recent years because of the unique physical and chemical behaviour imparted by fluorine. This heightened interest is particularly focused in the area of new chemotherapeutic drug design[2] involving fluorinated analogs of bioactive molecules. Fluorine's ability to form hydrogen bonds, to mimic hydroxy groups, its very high electronegativity, and the increased lipophilicity of perfluorinated compounds are all contributing factors[1,3] for the enhanced activity of fluorinated analogs of pharmaceutical agents. Since a large number of target molecules of

medicinal and agrochemical interest contain[4] one or more amino groups, the development of safe and efficient methods for the synthesis of fluorinated amines[5] is a current theme in chemical research.

Reductive amination[6] of an appropriate carbonyl compound is the most direct approach for the preparation of amines. Accordingly, we envisaged that application of this strategy to commercially available fluoro carbonyl compounds would provide an easy access to fluorinated amines in one-step. Among the hydride reagents, sodium cyanoborohydride[7] (Borch reduction) has been widely used to effect this transformation in recent years. However, the toxicity[8] and disposal problems associated with sodium cyanoborohydride makes this procedure less attractive to industry. Other hydride-based reagents for carrying out this reaction include sodium triacetoxyborohydride (Gribble reduction)[9] in neutral or acidic media, sodium borohydride in aqueous sulphuric acid,[10] and pyridine-borane.[11]

In the context of developing borohydride-based reagent systems[12] for selective transformations, we have recently utilized[13] a combination of zinc chloride and zinc borohydride for the reductive methylation of amines. As a sequel to this work, we now present the details of the application of this reagent system in the reductive alkylations of a number of secondary amines with a variety of commercially available fluorobenzaldehydes. The reactions that proceed at room temperature provide an effective, mild alternative method for the preparation of fluorinated benzylamines of high purity in good to excellent yields. The use of zinc borohydride, prepared from sodium borohydride and zinc chloride, as a uniquely mild reducing agent has been amply demonstrated in the literature.[14]



SCHEME

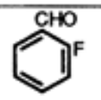
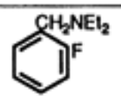
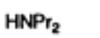
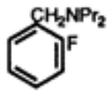
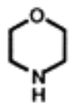
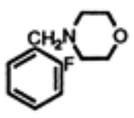
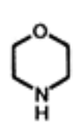
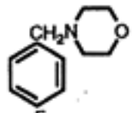
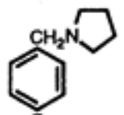
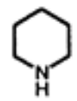
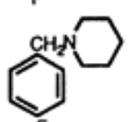
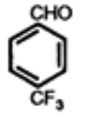
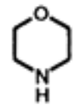
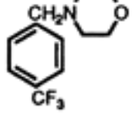
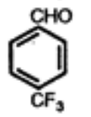
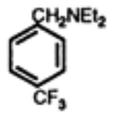
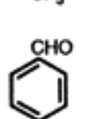
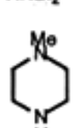
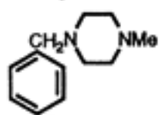
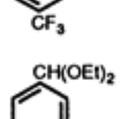
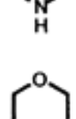
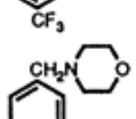
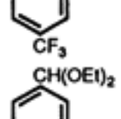
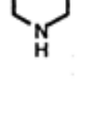
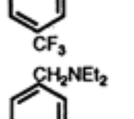
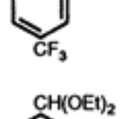
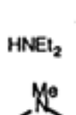
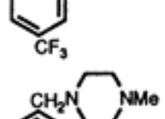
We have further advanced this concept to a more convenient, short and straightforward procedure. We have reasoned that a one-pot reagent system comprising of zinc chloride and sodium borohydride which would generate zinc

borohydride *in situ* may be used as an effective alternative to zinc chloride and zinc borohydride. Indeed this has been the case. We repeated all the transformations using zinc chloride and sodium borohydride and established that this combination was equally efficient for reductive amination reactions. This is an interesting development of our previous findings in that the preparation of zinc borohydride is avoided, thereby allowing for further improvements in the conditions of the reductive amination reactions.

The experimental procedures are simple and straightforward. Typically, zinc chloride (1 mol equiv.) was added to a mixture of a secondary amine (1 mol equiv.) and a fluorobenzaldehyde (1 mol equiv.) in anhydrous THF. The reaction mixture was stirred for 30 min. at room temperature and then treated with 1.5 mol equiv. of zinc borohydride in anhydrous THF which was prepared from sodium borohydride and zinc chloride according to the reported procedure.[15] The resulting solution was further stirred at room temperature for 7 h, poured into aqueous ammonia and extracted with diethyl ether. Separation of the organic layer, drying of this layer over K_2CO_3, and removal of the solvent provided the crude fluoroamines in high yields and fair purity. For reactions with zinc chloride/sodium borohydride system, the same general procedure was used except that a mixture of zinc chloride (25 mmol), fluoroaldehyde (10 mmol) and amine (10 mmol) was stirred at 25 °C for 30 min. Sodium borohydride (30 mmol) was next added and the resulting mixture was then stirred for a period of 10 h. The isolation of the products is same as described above. In both cases, most of the preparations needed no chromatographic separation; the product fluoroamines were isolated in their pure forms by simple extraction with hydrochloric acid (1 N). Attempts to effect this transformation with both sodium borohydride and zinc borohydride were unsuccessful in the absence of zinc chloride. Evidently, zinc chloride is functioning as a Lewis-acid to produce intermediate iminium ions which are reduced by zinc borohydride.

The results obtained for a representative group of fluorobenzaldehydes and secondary amines are presented in Table 1. The procedure also works well with acetals; p-trifluorobenzaldehyde diethyl acetal (entries 10-12) underwent clean reductive amination in these reaction conditions. These reaction conditions, however, failed to induce reductive aminations in fluorophenyl ketones. The neutral non-aqueous reaction conditions, simple work-up, isolation of pure products without chromatographic separations, high yields and the use of safe and

Table 1. Reductive Amination of Fluoroaldehydes using $Zn(BH_4)_2/ZnCl_2$.

Entry	Starting Aldehyde	Starting Amine	Product	Yield[a] (%)
1				80
2				78
3				85
4				82
5				77
6				75
7				78
8				82
9				75
10				75
11				80
12				75

(a) Yields are of isolated and purified products.

inexpensive reagents requiring no special handling techniques are the notable advantages of this method. Furthermore, due to the compatibility of this reagent system with a variety of otherwise reducible functional groups, this method can provide an easy access to analogous fluoroamines bearing functionalized pendant chains.

In conclusion, a general, preparatively efficient, simple method for the preparation of fluorinated benzylamines is identified, *via* reductive amination reactions of commercially available fluorobenzaldehydes, using zinc chloride/zinc borohydride and zinc chloride/sodium borohydride reagent systems. Because of the safe and inexpensive reagents requiring no special handling techniques, simple work-up, high yields of pure products and compatibility of this one-pot procedure with a number of otherwise reducible and acid-sensitive functional groups, this method should find wide application.

Experimental Section

Proton NMR spectra were recorded at 60 MHz on an EM 360 spectrometer of Varian Associates and at 300 MHz on a Bruker AM 300 spectrometer in $CDCl_3$ solutions with $SiMe_4$ as an internal standard (J values in Hz). Thin layer chromatography was performed on pre-coated silica gel plates with fluorescent indicators. All commercial amines were distilled over KOH prior to use. The commercially available fluorobenzaldehydes and other reagents were used as received from their respective suppliers. Tetrahydrofuran was distilled from $LiAlH_4$ before use. All reactions were magnetically stirred and performed in a dry nitrogen atmosphere.

General Procedure for the Reductive Alkylations of Fluorinated Benzaldehydes with $ZnCl_2$ and $Zn(BH_4)_2$:

To a solution of the starting fluorobenzaldehyde (10 mmol) and secondary amine (10 mmol) in anhydrous THF (25 mL) was added zinc chloride (1.36 g, 10 mmol) in one portion. The reaction mixture was stirred at 25 °C for 30 min., after which a solution of zinc borohydride (15 mmol) in anhydrous THF (30 mL) was

added dropwise. The resulting mixture was further stirred for a period of 7 h at 25 °C. The reaction was then quenched by pouring into aqueous ammonia (30 mL, 2N), the contents were stirred for 10 min., and the organic materials were extracted with diethyl ether (50 mL x 2). The combined organic solutions were next extracted with hydrochloric acid (1N, 2 x 10 mL) to separate the neutral materials. The acidic aqueous solution was then made alkaline (pH 10 by Hydrion pH test paper) by slow addition of aqueous NaOH (10%, w/v) and extracted with diethyl ether (50 mL x 2). The combined diethyl ether extracts were dried (K_2CO_3) and concentrated *in vacuo* to furnish pure fluorobenzylamines. Analytically pure samples were obtained by flash chromatography over silica gel and by bulb to bulb distillation.

For the reductive aminations involving acetals, the same general procedure was used except that a mixture of zinc chloride (2.70 g, 20 mmol), acetal (10 mmol) and amine (10 mmol) was stirred at 25 °C for 1 h. A solution of zinc borohydride (15 mmol) in anhydrous THF (30 mL) was added to the mixture which was then further stirred for 8 h with isolation of products as described above.

General Procedure for the Reductive Alkylations of Fluorinated Benzaldehydes with $ZnCl_2$ and $NaBH_4$:

A mixture of the starting secondary amine (10 mmol), fluorobenzaldehyde (10 mmol) and zinc chloride (3.4 g, 25 mmol) in anhydrous THF (50 mL) was stirred at 25 °C for 30 min. To this reaction mixture, sodium borohydride (1.14 g, 30 mmol) was then added in four portions and the resulting mixture was allowed to stir for 10 h. The reaction mixture was then poured into aqueous ammonia (40 mL, 2N) and the product fluorobenzylamines were isolated following the same procedure as described above.

For the reductive aminations involving acetals, a mixture of zinc chloride (4.76 g, 35 mmol), acetal (10 mmol) and amine (10 mmol) was stirred at 25 °C for 1 h., after which sodium borohydride (1.14 g, 30 mmol) was added portionwise. The resulting mixture was further stirred for a period of 10 h at 25 °C. The reaction was quenched by pouring into aqueous ammonia (30 mL, 2N) and the product amines were isolated following the same procedure as described above.

Data below correspond to the entries in Table 1.

1. N,N-Diethyl(*o*-fluorobenzyl)amine: ^{1}H NMR: δ 1.07 (t, 6 H, J 7.0), 2.56 (q, 4 H, J 7.0), 3.65 (s, 2 H), 7.0 (t, 1 H, J 8.0), 7.11 (t, 1 H, J 8.0), 7.17-7.28 (m, 1 H), 7.45 (t, 1 H, J 8.0). Anal Calcd. for $C_{11}H_{16}NF$: C 72.89, H 8.89, N 7.72; Found: C 72.61, H 8.95, N 7.52.

2. N,N-Dipropyl(*o*-fluorobenzyl)amine: ^{1}H NMR: δ 0.86 (t, 6 H, J 7.2), 1.49 (sextet, 4 H, J 7.2), 2.38 (t, 4 H, J 7.2), 3.61 (s, 2 H), 6.99 (t, 1 H, J 9.0), 7.11 (t, 1 H, J 9.0), 7.17-7.27 (m, 1 H), 7.45 (t, 1 H, J 9.0). Anal Calcd. for $C_{13}H_{20}NF$: C 74.59, H 9.63, N 6.69; Found: C 74.71, H 9.72, N 6.90.

3. N-(*o*-Fluorobenzyl)morpholine: ^{1}H NMR: δ 2.48 (t, 4 H, J 4.8), 3.57 (s, 2 H), 3.71 (t, 4 H, J 4.8), 7.03 (t, 1 H, J 7.0), 7.12 (t, 1 H, J 7.0), 7.20-7.28 (m, 1 H), 7.37 (dt, 1 H, J 6.0, 1.8). Anal Calcd. for $C_{11}H_{14}NOF$: C 67.67, H 7.23, N 7.17; Found: C 67.89, H 7.15, N 7.34.

4. N-(*p*-Fluorobenzyl)morpholine: ^{1}H NMR: δ 2.41 (t, 4 H, J 4.5), 3.44 (s, 2 H), 3.69 (t, 4 H, J 4.5), 6.98 (t, 2 H, J 8.7), 7.27 (t, 2 H, J 8.7). Anal Calcd. for $C_{11}H_{14}NOF$: C 67.67, H 7.23, N 7.17; Found: C 67.51, H 7.45, N 7.00.

5. N-(*p*-Fluorobenzyl)pyrrolidine: ^{1}H NMR: δ1.76-1.84 (m, 4 H), 2.51 (t, 4 H, J 3.0), 3.58 (s, 2 H), 6.99 (t, 2 H, J 9.0), 7.29 (t, 2 H, J 8.7). Anal Calcd. for $C_{11}H_{14}NF$: C 73.71, H 7.87, N 7.81; Found: C 73.51, H 7.99, N 7.60.

6. N-(*p*-Fluorobenzyl)piperidine: ^{1}H NMR: δ 1.37-1.50 (m, 2 H), 1.52-1.62 (m, 4 H), 2.35 (br. s, 4 H), 3.45 (s, 2 H), 6.98 (t, 2 H, J 8.0), 7.25 (t, 2 H, J 8.0).Anal Calcd. for $C_{12}H_{16}NF$: C 74.57, H 8.34, N 7.24; Found: C 74.73, H 8.55, N 7.43.

7. N-(*p*-Trifluoromethylbenzyl)morpholine: ^{1}H NMR: δ 2.45 (t, 4 H, J 6.0), 3.54 (s, 2 H), 3.71 (t, 4 H, J 6.0), 7.46 (d, 2 H, J 8.0), 7.57 (d, 2 H, J 8.1). Anal Calcd. for $C_{12}H_{14}NOF_3$: C 58.77, H 5.75, N 5.71; Found: C 58.68, H 5.96, N 5.94.

8. N,N-Diethyl(*p*-trifluoromethylbenzyl)amine: ^{1}H NMR: δ 1.04 (t, 6 H, J 9.0), 2.51 (q, 4 H, J 9.0), 3.60 (s, 2 H), 7.46 (d, 2 H, J 8.0), 7.55 (d, 2 H, J 8.0). Anal Calcd. for $C_{12}H_{16}NF_3$: C 62.32, H 6.97, N 6.05; Found: C 62.23, H 7.18, N 6.20.

9. 1-Methyl,4-(*p*-trifluoromethylbenzyl)piperazine: ^{1}H NMR: δ 2.29 (s, 3H), 2.30-2.62 (m, 8 H), 3.55 (s, 2 H), 7.44 (d, 2 H, J 8.1), 7.56 (d, 2 H, J 8.1). Anal Calcd. for $C_{13}H_{17}N_2F_3$: C 60.45, H 6.63, N 10.84; Found: C 60.35, H 6.90, N 10.56.

References

1 (a) Sheppard, W. A.; Sharts, C. M. *Organic Fluorine Chemistry*, Benjamin, New York, **1969**; (b) Schlosser, M. *Tetrahedron*, **1978**, *34*, 3; (c) Purrington, S. T.; Kagan, B. S.; Patrick, T. B. *Chem. Rev.* **1986**, *86*, 997; (d) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307; (e) Walba, D. M.; Razavi, H. A.; Clark, N. A.; Parmar, D. S. *J. Am. Chem. Soc.* **1988**, *110*, 8686; (f) Kitazume, T.; Ohnogi, T.; Ito, K. *ibid*, **1990**, *112*, 6608; (g) *Selective Fluorination in Organic and Bioorganic Chemistry;* Welch, J. T.; Ed.; American Chemical Society, Washington, **1991**; (h) Welch, J. T.; Eswarakrischnan, S. *Fluorine in Bioorganic Chemistry*, Wiley, New York, **1991**; (i) Yoneda, N. *Tetrahedron* **1991**, *47*, 5329; (j) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505; (k) Robins, M. J.; Wnuk, S. F. *J. Org. Chem.* **1993**, *58*, 3800; (l) Xiao-Qing, T.; Chang-Ming, H. *J. Chem. Soc. Chem. Commun.* **1994**, 631.

2 (a) Scherer, O. *Fortschr., Chem. Forschnung,* Vol. 14/2, Springer Verlag, Heidelberg, **1970**; (b) Wettstein, A. in *Carbon-Fluorine Compounds: Chemistry, Biochemistry and Biological Activities*, Ciba Foundation Symposium, Associated Scientific Publishers, Amsterdam, **1972**, p. 281; (c) *Biomedical Aspects of Fluorine Chemistry*, Filler, R.; Kobayashi, Y.; Ed. Elsevier, Amsterdam, **1982**; (d) Sieler, M.; Jung, M. J.; Koch-Waser, *Enzyme-Activated Irreversible Inhibitors*, Elsevier, Amsterdam, **1988**; (e) Bravo, P.; Resnati, G. *Tetrahedron Asymmetry*, **1990**, *1*, 661; (f) Resnati, G. *Tetrahedron*, **1993**, *49*, 9385: (g) Haddad, M.; Molines, H.; Wakselman, C. *Synthesis*, **1994**, 167; (h) Schloser, M.; Michel, D.; Guo, Z.; Shi, C. J. *Tetrahedron*, **1996**, *52*, 8257; (i) Goj, O.; Kotila, S.; Haufe, G. *ibid* **1996**, *52*, 12761.

3 (a) Ishikawa, N. *Synthesis and Utilization of Organofluorine Compounds*, CMC, Tokyo, **1987**; (b) Uneyama, K. *J. Synth. Org. Chem. Jpn.* **1991**, *49*, 612;

(c) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C.; Ed. Plenum Press, New York, **1994**.

4 For some leading references see : (a) Kirschbaum, J. in *Analytical Profiles of Drug Substances*, Florey, K.; Ed. Academic Press, NY, **1983**, *12*, p.1; (b) Shaw, K. T.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515; (c) Roush, W. R.; Staub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127; (d) Ojima, I.; Kato, K.; Nakahashi, K.; Fuchikami, T.; Fujita, M. *J. Org. Chem.* **1989**, *54*, 4511 and references cited therein; (e) Manchand, P. S.; Cerruti, R. L.; Martin, J. A.; Hill, C. H.; Merrett, J. H.; Keech, E.; Belshe, R. B.; Connell, E. V.; Sim, I. S. *J. Med. Chem.* **1990**, *33*, 1992; (f) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771; (g) Main, B. G.; Tucker, H. *in Medicinal Chemistry*, 2nd Ed., Genellin, C. R.; Roberts, S. M.; Ed. Academic Press, NY, **1993**, p 187.

5 (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123; (b) Barney, C. L.; Huber, E. W.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *39*, 5547; (c) Kukhar, V. P.; Svistunova, N. Y.; Soloshonok, V. A.; Solodenko, V. A. *Russ. Chem. Rev. Engl.* **1993**, *62*, 284; (d) Soloshonok, V. A.; Kirilenko, A. G.; Kukhar, V. P.; Resnati, G. *Tetrahedron Lett.* **1993**, *34*, 3621; (e) *Fluorine Containing Amino Acids: Synthesis and Properties*; Kukhar, V. P.; Soloshonok, V. A.; Ed. Wiley, NY **1994**; (f) Soloshonok, V. A.; Kirilenko, A. G.; Kukhar, V. P.; Resnati, G. *Tetrahedron Lett.* **1994**, *35*, 3119; (g) Soloshonok, V. A.; Kukhar, V. P. *Tetrahedron* **1996**, *52*, 6953; (h) Soloshonok, V. A.; Ono, T. *ibid*, **1996**, *52*, 14701; (i) Ono, T.; Kukhar, V. P.; Soloshonok, V. A. *J. Org. Chem.* **1996**, *61*, 6563.

6 For reviews on reductive aminations see: (a) Emerson, W. S. *Organic Reactions*, Wiley, New York **1948**, *4*, 174; (b) Lane, C. F. *Synthesis* **1975**, 135; (c) Hutchins, R. O.; Natale, N. *Org. Prep. Proced. Int.* **1979**, *11*, 201; (d) Whitesell, J. K. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. Ed. Pergamon Press, Oxford, **1991**, Vol. 6, p. 724 and Vol. 8 p. 25; (e) Gribble, G. W. in *Reductions in Organic Synthesis, ACS Symposium Series 641*, Abdel-Majid, A. F. Ed. American Chemical Society, Washington, DC, **1996**, p. 167; (f) Abdel-Majid, A. F. *ibid*, p. 201.

7 (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897; (b) Borch, R. F. *Org. Synth. Coll. Vol. 6*, **1988**, 499.

8 (a)*The Sigma-Aldrich Library of Chemical Safety Data*, Ist Edition, Lenga, R. E.; Ed. Sigma-Aldrich Corp. **1985**, p. 1609; (b) Moorman, A. E. *Synth. Commun* **1993**, *23*, 789.

9 (a) Gribble, G. W; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812; (b) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766; (c) Abdel-Majid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595; (d) Abdel-Magid, A. F.; Maryanoff, C. A. *Synlett* **1990**, 537; (e) Abdel-Majid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

10 Verado, G.; Giumanini, A. G.; Strazzolini, P.; Poina, M. *Synthesis* **1993**, 121.

11 (a) Pelter, A.; Rosser, R. M.; Mills, S. *Ventron Alembic* **1983,** 30; (b) Bomann, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995.

12 (a) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401; (b) Bhattacharyya, S. *Synlett* **1994**, 1029; (c) Bhattacharyya, S. *J. Org. Chem.* **1995**, *60*, 4928; (d) Bhattacharyya, S. *Synlett* **1995**, 971; (e) Bhattacharyya, S.; Chatterjee, A.; Williamson, J. S. *Synlett* **1995**, 1079; (f) Bhattacharyya, S. *Organometallics,* **1996**, *15*, 1065; (g) Bhattacharyya, S. *J. Chem. Soc. Perkin Trans 1* **1996**, 1381.

13 Bhattacharyya, S.; Chatterjee, A.; Duttachoudhury, S. K. *J. Chem. Soc. Perkin Trans 1* **1994**, 1.

14 Ranu, B. C. *Synlett.* **1993**, 885 and references cited therein.

15 Grabbe, P.; Garcia, G. A.; Rius, C. *J. Chem. Soc. Perkin Trans 1* **1973**, 810.