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Safe Handling of Boranes at Scale

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Abstract:

The safe handling of borane complexes and alkylboranes (trialkylboranes, dialkylboranes, and trialkylborohydride reagents) and related workup issues are addressed. Oxidation of alkylboranes and quenching of reaction mixtures to safely decompose the reagent or products are discussed. Several case studies demonstrate large-scale applications of borane reagents for carboxylic acid reduction, reductive amination, and hydroboration followed by oxidation.

Introduction

Borane and trialkylborohydride reagents have become an important part of today's chemical industry. Many industries have adopted and exploited the properties and synthetic utility of various borane complexes in numerous applications. Commercially available boron compounds have found their way into pharmaceutical and polymer synthesis, paints and pigment applications, electronics, and printed circuit board manufacturing. The successful use of boranes on large scale requires effective implementation of safety and handling procedures. The focus of this article is to elaborate on the safe handling of these reagents and related workup considerations.

General Considerations

1. Alkyl Boranes. Dialkylborane,[2] trialkylborane, and trialkylborohydride derivatives are pyrophoric (spontaneously combustible) in pure form and when dissolved in solvents at higher concentrations. In general, concentrations less than 15 wt % are not pyrophoric. Compounds with a higher molecular weight than triethylborane are nonpyrophoric at somewhat higher concentrations, depending on the nature of the substituents. A quick test of pyrophoricity can be performed by syringing small amounts of solution onto dry Whatman #3 filter paper in a hood.[3] Burning or charring of the filter paper without flames is considered a positive indication of pyrophoricity. However, testing of dialkylboron triflates for pyrophoricity can give false positives due to discoloration of the filter paper by triflic acid.

The greatest safety concern when dealing with reaction solutions containing alkylboranes (dialkylborane, trialkylborane, or alkali metal trialkylborohydride complexes) is the pyrophoric nature of the reagents and reaction products. The following section addresses safe oxidation methods for reaction workup of mixtures containing alkylboranes.

Hydroboration processes generate trialkylboranes, which are often oxidized to obtain alcohols. In addition, reductions using alkali metal trialkylborohydride reagents leave trialkylborane or "ate" complexes in the reaction solution. Trialkylboranes are not hydrolyzed by water or aqueous base and will remain in the organic layer. Upon acidic (mineral acid) workup, the trialkylborane remains intact and, in some cases, exists at pyrophoric levels in the organic layer. For example, this can occur when tetrahydrofuran (THF) or methanol is partitioned into the aqueous layer, thereby concentrating the trialkylborane in the organic layer. Acetic acid will rapidly react with a trialkylborane to give the corresponding dialkylacetoxyborane. Dialkylacetoxyborane and dialkylalkoxyborane compounds may still be pyrophoric in concentrated solutions. For example, methoxydiethylborane is pyrophoric at concentrations greater than 75 wt %. Therefore, diluted trialkylborane or other alkylboranes in a reaction mixture must be chemically oxidized prior to air exposure to avoid rapid exothermic air oxidation[4] and possible spontaneous combustion.[5]

Assessment of the thermal stability of oxidizing agents and feasibility to scale up the reaction are critical to safely handle the organoborane oxidation. During the basic hydrogen peroxide oxidation[6] of organoboranes on a large scale to deliver the corresponding alcohol, oxygen released from the hydrogen peroxide at high pH could enrich the reactor atmosphere to an unsafe level of oxygen. Recently, Astbury reported the scale-up of an oxidation by hydrogen peroxide.[7] He demonstrated that safe oxidation of dialkylboranes required the determination of maximum oxygen release rate of the oxidant. The oxygen evolution rate was used to calculate the inert gas flow needed to reduce oxygen levels to less than 5% v/v and minimize loss of solvent during the oxidation. At a nitrogen flow of 8.55 $m^3\ h^{-1}$, Astbury carried out a 150-kg dialkylborane oxidation with an acceptable solvent loss of only 1.4 kg h^{-1}.

Reaction temperature is another parameter to consider when using hydrogen peroxide as the oxidizing agent. At higher temperatures, hydrogen peroxide releases oxygen

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[2] Dialkylborane is used generically to represent R_2BH as well as R_2BOR, and R_2BX, such as methoxydiethylborane, dibutylboron triflate, and dicyclohexylchloroborane.

[3] *Recommendations on the Transport of Dangerous Goods - Manual of Tests and Criteria*, 11th rev.; United Nations: NY, 2003; p 361.

[4] Mirviss, S. B. *J. Org. Chem.* **1967**, *32*, 1713.

[5] ^{11}B NMR spectroscopy can be used to indicate reaction completeness: singlet at 1 ppm for boric acid in aq 3 M NaOH, singlet at 4 ppm for methylboronic acid in aq 3 M NaOH. The chemical shifts can vary with concentration and pH.

[6] (a) Zweifel, G.; Brown, H. C. *Org. React.* **1963**, *13*, 1. (b) Snyder, C.; Rao, B. C. S.; Zweifel, G. *Tetrahedron* **1986**, *42*, 5505. Oxidation of tri-*sec*-butylborane requires a large excess of base (4-9 equiv) along with the hydrogen peroxide oxidant to completely oxidize the boron−carbon bonds.

[7] Astbury, G.R. *Org. Process Res. Dev.* **2002**, *6*, 895.

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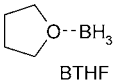
faster.[8] The best practice is to slowly add the hydrogen peroxide solution to a mixture of the organoborane and base at temperatures between 20 and 30 °C while maintaining a nitrogen gas flow. This protocol minimizes oxygen formation in the reactor head space by ensuring fast hydrogen peroxide deprotonation and oxidation of the organoborane.[9] Alternatively, the use of acidic hydrogen peroxide oxidation allows the oxidation of organoboranes at ambient temperatures.[10] The oxidation by addition of hydrogen peroxide in the presence of 10% $CaCl_2$ in 2.0 N HCl solution provides the desired alcohol from an alkylborane intermediate without requiring extended reaction times at elevated temperatures.

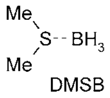
The oxidation of organoboranes has also been evaluated with 2−3 equiv of Oxone,[11] sodium peroxide,[12] sodium percarbonate,[13] and trimethylamine-*N*-oxide.[14]

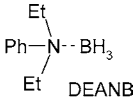
Another method for removal of alkylboranes uses an azeotropic distillation of the alkylborane with methanol.[15] However, one must take care to ensure that the distillation system, especially the column and condenser, are airtight and have a sufficient positive nitrogen sweep to prevent oxygen/air from entering the system. The distillate must still be subjected to oxidation for safe handling or alternatively diluted to below pyrophoric levels with a suitable solvent. Even diluted solutions of pyrophoric boranes should be protected from air exposure because exothermic oxidation of the boron−carbon bond will occur upon contact with oxygen in air.

2. Borane Complexes. The most useful borane complexes for organic synthesis on a large scale are borane tetrahydrofuran complex (**BTHF**), dimethyl sulfide borane (**DMSB**), and *N*,*N*-diethylaniline borane (**DEANB**). The safety and handling requirements are different, depending on the borane complex selected to carry out the application.

Borane complexes must be stored under dry nitrogen or argon at all times. BTHF requires refrigeration (0−5 °C) to maintain product quality for long storage periods. DMSB and DEANB can be stored at ambient temperatures.


BTHF


DMSB


DEANB

Transfer of boranes from a cylinder to a reactor system requires the use of positive, dry, inert gas pressure. Precautions must be taken to eliminate all sources of oxygen during loading because air exposure can create a potentially hazardous situation. An inert environment preserves reagent purity and minimizes the possibility of a flammable mixture in the vessel.

Boranes are compatible with carbon steel, stainless steel, and glass. Aluminum components in the transfer connections and piping should be avoided since boric acid formed from borane's reaction with water, even atmospheric moisture, will corrode aluminum components. Some aprotic solvents such as acetone, *N*,*N*-dimethylacetamide, and acetonitrile should be avoided because of their reduction by borane to the corresponding alcohol and amine products, respectively.

These borane complexes exothermically react with atmospheric moisture, water, alcohols, and acids to produce hydrogen. Hydrogen generated as a result of quenching a reaction mixture must be adequately vented from the system. A methanol scrubbing system is recommended when scaling up borane reactions. Methanol will convert any escaping diborane to hydrogen and methyl borate rapidly and completely. Although aqueous scrubbing solutions will react with diborane, the solid boric acid generated could cause plugging of lines. Caustic media can leave alkali metal borohydride products capable of hydrogen release if neutralized or made acidic.

Borane tetrahydrofuran complex (**BTHF**) is the most versatile of the borane complexes and is available at 1 M concentration. BTHF undergoes thermal decomposition via cleavage of the THF ring at temperatures ranging from 10 to 50 °C, ultimately producing butyl borate, Scheme 1.

In this reaction, the alkoxyborane **4** readily disproportionates, but dialkoxyborane **5** remains in solution for extended periods. Ether cleavage may be enhanced by trace Lewis acid (BF_3) coordinated to the THF.

At temperatures above 50 °C, it is possible to liberate diborane (**7**) from the solution.This pathway is dominant at higher temperatures, especially without backpressure on the reaction vessel. Because of these decomposition reactions, it is recommended to perform reaction chemistry involving BTHF at temperatures below 35 °C. Addition of BTHF to the substrate, instead of vice versa, decreases the thermal exposure of BTHF and often eliminates over-reduction byproducts. To ensure that the substrate does not influence BTHF decomposition at the selected reaction temperatures, the thermal profile of any chemistry involving the addition of substrate to BTHF should be carefully evaluated.[16]

Dimethyl sulfide borane (**DMSB**) is another extremely useful borane reagent. Although the reactivity of this complex falls slightly behind BTHF, it offers higher concentration (∼10 M) and thermal stability. The purity of DMSB dropped

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(8) FMC reports in a technical bulletin the decomposition rate of hydrogen peroxide (neutral) increases at 2.2 times for each 10 °C rise in temperature from 10 to 100 °C, but at low pH the rate of decomposition is higher.

(9) Oxidation methods have been compared: H_2O_2, $NaBO_3$, O_3, and dimethyldioxirane. Majewski, M.; Nowak, P. *J. Org. Chem.* **2000**, *65*, 5152.

(10) Ripin, D. H. B.; Abele, S.; Cai, W.; Blumenkopf, T. Casavant, J. M.; Doty, J. L.; Flanagan, M.; Koecher, C.; Laue, K. W.; McCarthy, K.; Meltz, C.; Munchhoff, M.; Pouwer, K.; Shah, B.; Sun, J.; Teixeira, J.; Vries, T.; Whipple, D. A.; Wilcox, G. *Org. Process Res. Dev.* **2003**, *7*, 115.

(11) (a) Oxone is a registered trademark of DuPont for potassium monopersulfate in a mixture with potassium hydrogen sulfate and potassium sulfate. It is 25 wt % soluble in water (b) Ripin, D. H. B. *et al. Tetrahedron Lett.* **2000**, *41*, 5817. (c) Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.

(12) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

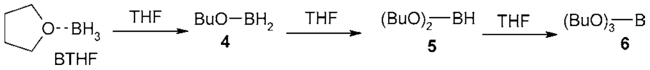
(13) Kabalka, G. W.; Wadgaonkar, P. P.; Shoup, T. M. *Organometallics* **1990**, *9*, 1316.

(14) (a) Kabalka, G. W.; Hedgecock, H. C. *J. Org. Chem.* **1975**, *40*, 1776. (b) Soderquist, J. A.; Najafi, M. R. *J. Org. Chem.* **1986**, *51*, 1330.

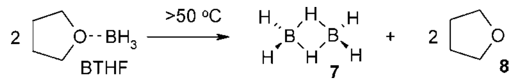
(15) (a) Horsley, L. H., Ed. *Advances in Chemistry Series*; American Chemical Society: Washington, D.C., 1973; Vol. 116, p 211 for methyl borate with various solvents and p 357 for ethyl borate with several solvents. (b) Horsley, L. H., Ed. *Advances in Chemistry Series*; American Chemical Society: Washington, D.C., 1952; Vol. 6, p 29. Methanol/methylborate azeotrope, bp 54.6 °C, 32% methanol. (c) *Inorg. Synth.* **1983**, *22*, 190 for a constant boiling azeotrope with equal amounts of methanol and methoxydiethylborane (bp = 54 °C/760 torr).

(16) (a) Hoppe, T. *Chem. Eng. Prog.* **1992**, *88*, 70. (b) Schwanebeck, W. *Thermochim. Acta* **1991**, *187*, 201.

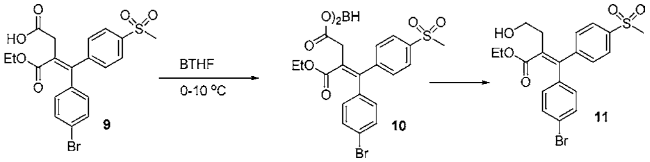
Scheme 1



Scheme 2



Scheme 3



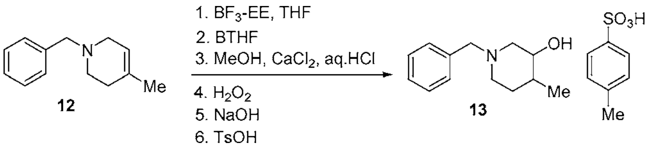
less than 1% (from 97.3[17] to 96.6%) after 6 years at ambient temperature, demonstrating its long shelf life. An isothermal differential scanning calorimetry[18] (DSC) scan at 133.5 °C for 3000 min on the material showed no detectable decomposition. On the basis of this thermal information, DMSB reductions may be run at temperatures of up to 70 °C.[19] However, it is recommended that individual reactions be evaluated using accelerating rate calorimetry (ARC) since specific reaction conditions may influence DMSB or reaction intermediate decomposition.

One consideration when working with DMSB at scale is the odor of dimethyl sulfide (DMS) byproduct. Safe and simple ways to mitigate DMS odor are available. The most straightforward method for scrubbing DMS from a vent stream is the use of activated carbon in a drum. If this method is chosen, any diborane in the vent stream must be destroyed before venting through the carbon. Due to the high surface area and significant water content of activated carbon, any vented diborane will react, generating localized hot spots and potentially igniting the evolving hydrogen.

Alternative methods to achieve destruction of DMS are via oxidation. Sodium hypochlorite can be used to oxidize the DMS.[20] This method works well in a recirculation scrubber, but one must be sure that the scrubber system is compatible with a dilute bleach solution and the small amount of DMSO and/or dimethyl sulfone that is produced. Finally, dimethylsulfone can be produced via the reaction with a potassium persulfate slurry (Oxone). As the persulfate is consumed, the slurry becomes a solution. The only drawback of this method is that the scrubber system must be capable of recirculating a slurry.

Another important factor to consider when working with DMSB is deactivation of small samples. DMSB, or preferably samples diluted with a solvent (e.g., THF), should always be slowly added to the material (e.g., methanol) being used to deactivate the product. Addition of methanol to a flask containing DMSB is not recommended because it could cause a runaway reaction. Following these common practices will enable the safe handling of DMSB on laboratory- and large scale.

Scheme 4



N,*N*-Diethylaniline borane (**DEANB**) derived from a less basic amine, performs the same types of reaction chemistry as BTHF and DMSB and is hydrolyzed by water or methanol. This compound offers excellent long-term stability at ambient temperatures. A 3-year stability study in a cylinder with a nitrogen atmosphere showed no detectable change in concentration or impurities by ^{11}B NMR spectroscopy. Thermal studies indicate exothermic decomposition at 200 °C, which allows reaction chemistry to be performed at temperatures up to 100 °C.

An important consideration when working with DEANB on large scale is removal of diethylaniline from the desired reduced product. High temperatures are needed to remove diethylaniline (bp 217 °C) via distillation, and sensitive molecules could be damaged. Crystallization of the intermediate product, a tertiary amine−borane complex, from diethylaniline and solvent has been quite effective following an amide reduction.[22b] A third method involves washing the reaction mixture two to three times with dilute, aqueous HCl (2−3 M).[21]

Other amine boranes are very useful reducing agents for large-scale reductions and reductive aminations. In addition, amine boranes are generated as an intermediate in borane reductions of amides. Due to the higher Lewis basicity of aromatic and alkylamines, compared to ethers or sulfides, the strong interaction between the borane and amine leads to remarkable stability of amine boranes toward hydrolysis. In fact, some amine boranes are even stable toward aqueous mineral acids; therefore, quenching of amine boranes in reaction mixtures requires rigorous conditions.

The main safety consideration when quenching an amine borane is the concomitant hydrogen evolution. Trialkylamine borane complexes are not readily hydrolyzed by mineral acids in nonprotic solvents. For example, hydrochloric acid (1 M) in a 50:50 mixture of water and ethylene glycol is more effective for the hydrolysis of amine boranes than 1 M HCl in 50% aqueous diglyme.[22] An effective method to quench amine boranes is via palladium catalysis. Courtier[23] used Pearlman's catalyst, $Pd(OH)_2/C$, along with allyl alcohol to act as a proton source and to scavenge the hydrogen released during the destruction of the amine borane.

3. Case Studies. The following examples demonstrate the safe scale-up of several borane reactions.

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(17) Dimethyl sulfide borane typically contains 2−7 % dimethyl sulfide.

(18) Differential scanning calorimetry (DSC) is a rapid screening test useful for detecting potentially hazardous reactions and estimating thermal decomposition temperatures.

(19) The boiling point of dimethyl sulfide is 38 °C; dimethyl sulfide will distill from the reaction mixture.

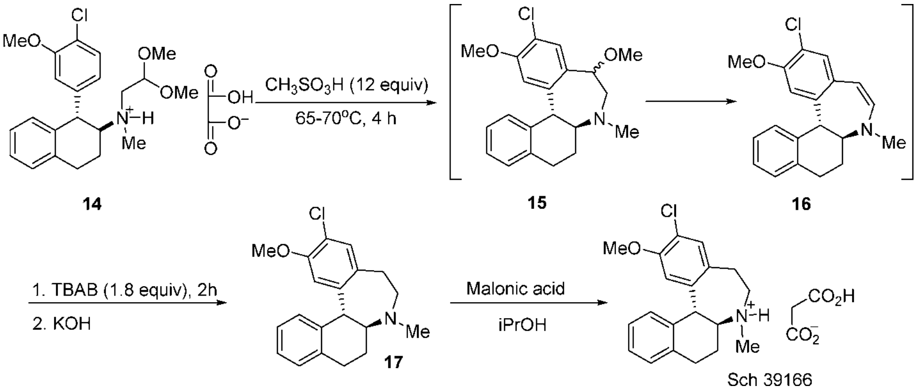
(20) Schank, K. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C., Eds.; Wiley: New York, 1988; pp 165 and 205.

(21) Wilkinson, H. S.; Tanoury, G. J.; Wald, S. A.; Senanayake, C. H. *Org. Process Res. Dev.* **2002**, *6*, 146.

(22) Brown, H. C.; Murray, L. T. *Inorg. Chem.* **1984**, *23*, 2746.

(23) (a) Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dubé, P.; Negri, J. T. *Org. Lett.* **2001**, *3*, 465. (b) Couturier, M.; Andresen, B. M.; Jorgensen, J. B.; Tucker, J. L.; Busch, F. R.; Brenek, S. J.; Dubé, P.; Am Ende, D. J.; Negri, J. T. *Org. Process Res. Dev.* **2002**, *6*, 42.

Scheme 5



Carboxylic Acid Reduction. Lobben and co-workers[24] successfully carried out a reduction of **9** with BTHF (Scheme 3) by optimizing the addition rate and reaction temperature. During scale-up, a delayed exotherm was seen. The carbonyl reduction was approximately 3.5 times more exothermic than the initial reaction of BTHF and the acidic proton on the carboxylic acid to give the diacyloxyborane intermediate **10**. From thermal measurements and the kinetic model, a slow addition rate of the BTHF was proposed on the basis of the cooling capacity of the reaction vessel. Thus, a safe, controlled scale-up of this reduction was achieved.

Hydroboration Followed by Oxidation. The use of additives to decrease borane equivalents is another way to increase safety during scale-up of BTHF reactions. For example, Ripin and co-workers[25] used 1.2 of equiv of boron trifloride diethyl etherate (BF_3-EE) to complex the amino group in molecule **12**, allowing the hydroboration to be carried out with 1.4 equiv of borane rather than the 2.2 equiv required to achieve consistent results (Scheme 4). Another benefit of BF_3-EE was less hydrogen evolution during the quench. Both processes gave >85% yield, showing the effectiveness of the reaction. After the hydroboration, the slight excess of borane was quenched with methanol, followed by addition of aqueous acidic calcium chloride solution to quench the amine borane and trap the boron trifluoride. The oxidation to the amino alcohol product with hydrogen peroxide was conducted in the acidic solution and then neutralized with sodium hydroxide.

Reductive Amination. In the process development of a dopamine D1 antagonist (Sch 39166, Scheme 5) Gala and co-workers refined an earlier route to shorten the synthesis and provide large quantities of Sch 39166 in higher yields.[26] *tert*-Butylamine borane (TBAB) was used, rather than other hydride reagents, to eliminate potentially hazardous hydrogen evolution when the reducing agent was added to the acidic solution. TBAB gave a faster and more complete reduction of **16** than other reagents. Furthermore, a neutralization step was not required because the acidity of the media was moderated by the liberated *tert*-butylamine. The processing time was decreased from 7 days to 2 days, the throughput was improved 4-fold, and the reaction yield was 20% higher than previous routes. This is an excellent example that demonstrates the usefulness of borane complexes such as TBAB to develop environmentally friendly commercial processes.

Many other literature examples[27] demonstrate the effective implementation of safe handling procedures to carry out borane chemistry on a large scale.

Conclusions

Safe handling of borane and borohydride reagents in the synthesis of critical drug intermediates is crucial to successfully implement borane chemistry on a large scale. This article provides some general guidelines to handle borane compounds. However, thorough evaluation of reaction parameters such as reagent equivalents, order of addition, and temperature, as well as thorough hazard review of equipment, are recommended when scaling up borane and borohydride reactions. The exothermic nature of many borane reductions and hydroborations requires evaluation by DSC, ARC,[28] and/or reaction calorimetry to understand the specific heat effects associated with the reaction of interest.

The future of borane and borohydride reagents for use in large-scale synthesis is very promising due to the excellent selectivity, mild reaction conditions, high yields, and commercial availability. A large number of compounds, reactions, and applications using borane chemistry have been developed at the industrial level in recent years. This is only the beginning of organoborane chemistry at the industrial scale as many new uses of boranes are expected in years to come.

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(26) Gala, D.; Dahanukar, V. H.; Eckert, J. M.; Lucas, B. S.; Schumacher, D. P.; Zavialov, I. A. *Org. Process Res. Dev.* **2004**, *8*, 754.

(27) (a) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Grimler, D.; Koch, G.; Daeffler, R.; Osmani, A.; Hirni, A.; Schaer, K.; Gamboni, R.; Bach, A.; Chaudhary, A.; Chen, S.; Chen, W.; Hu, B.; Jagoe, C. T.; Kim, H-Y.; Kinder, F. R.; Liu, Y.; Lu, Y.; McKenna, J.; Prashad, M.; Ramsey, T. M.; Repi, O.; Rogers, L.; Shieh, W-C.; Wang, R-M.; Waykole, L. *Org. Process Res. Dev.* **2004**, *8*, 101. (b) Repic, O.; Prasad, K.; Lee, G. T. *Org. Process Res. Dev.* **2001**, *5*, 519. (c) Chung, J. Y. L.; Cvetovich, R.; Amato, J.; McWilliams, J. C.; Reamer, R.; DeMichele, L. *J. Org. Chem.* **2005**, *70*, 3592. (d) Zanka, A.; Nishiwaki, M.; Morinaga, Y.; Inoue, T. *Org. Process Res. Dev.* **1998**, *27*, 230. (e) Larsen, R.; Cai, D.; Journet, M.; Campos, K. WO 02/32892, 2002. (f) Hirokawa, Y.; Hirokawa, T.; Noguchi, H.; Yamamoto, K.; Kato, S. *Org. Process Res. Dev.* **2002**, *6*, 28.

(28) Accelerated Rate Calorimetry (ARC) Fenlon, W. J. *Plant/Oper., Prog.* **1984**, *3*, 197.