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A Scalable Zinc Activation Procedure Using DIBAL-H in a Reformatsky Reaction

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Abstract:

The highly exothermic nature of Reformatsky reagent formation and the reported unpredictability of the induction time for its formation pose challenging problems for scaling up Reformatsky reactions. A zinc-activation procedure using DIBAL-H was developed and investigated using reaction calorimetry along with subsequent parts of the process. This procedure was shown to have important advantages for scale-up relative to previous zinc activation methods, including an immediate start of Reformatsky reagent formation with addition-controlled reaction. Calorimetric analysis was especially useful in specifying quickly a suitable temperature for Reformatsky reagent formation. The process was scaled up successfully.

Introduction

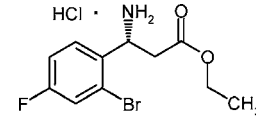
The classic Reformatsky reaction comprises the zinc-mediated formation of a β-hydroxyester from an α-haloester and an aldehyde or ketone. Its scope has been broadened to other electrophiles such as imines.[1] The reaction is typically carried out by first activating zinc using a chemical treatment to remove the zinc oxide layer from the metal surface and/or to obtain a high specific surface area of zinc metal. Various zinc activation methods have been reported,[1−3] including treatment with ultrasound, iodine, chlorotrimethylsilane, sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al), 1,2-dibromoethane, and cuprous chloride, with the latter two reagents having been used in large-scale reactions.[4,5] Reaction between the activated zinc and the α-haloester to form a zinc enolate (*i.e.*, the Reformatsky reagent) then occurs. The latter reacts with the electrophile, with subsequent hydrolysis affording the product. The electrophile may also be present during Reformatsky reagent formation.[5]

The formation of the Reformatsky reagent is highly exothermic with unpredictable induction times reported in some cases.[5] The unpredictable start of a highly exothermic reaction poses severe problems on large scale, as a sudden heat release will lead to a large batch-temperature excursion if cooling cannot be applied quickly. If the temperature rise is sufficiently large, pressure buildup (due to rapid solvent vaporization) and/or highly exothermic decomposition reactions can occur. A temperature runaway, possibly accompanied by an explosion, can ultimately result.

In the synthesis of multikilogram quantities of an intermediate for a developmental drug,[6] it was necessary to introduce a chiral center by reaction of imine **1**, substituted with chiral auxiliary *tert*-butylsulfinamide, with ethyl bromoacetate **2** to make amine intermediate **3** (Scheme 1).

A suitable process for scale-up of the zinc activation as well as for formation of the Reformatsky reagent was thus essential. For such exothermic reactions, a well-defined, detectable start of reaction on large scale is ideal, since it is then possible to continue the process safely. Preferably, the reaction should start when a reagent is added to a vessel and terminate when reagent addition stops. Such reactions are termed "addition-controlled". Processes involving induction periods during addition should be especially avoided, as reactions that initiate suddenly after significant amounts of reagent have been added will lead to large and sudden heat releases (*i.e.*, heat accumulation) and hazardous conditions.

Because the reaction between the Reformatsky reagent and **1** required a temperature below −5 °C to obtain **3** with high optical purity, the zinc activation, typically carried at or above room temperature, had to be performed separately from the coupling. Thus, procedures similar to the one devised by Schekenbeek and Siegel,[5] involving the addition of a haloester to a mixture containing the electrophile and activated zinc above 40 °C, though giving an addition-controlled reaction, could not be applied here. Compound **3** was not isolated, but was converted to the corresponding amino ester hydrochloride (**4**) for characterization purposes (see Experimental Section).



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In this paper, we report on an effective and scalable zinc activation procedure utilizing diisobutylaluminum hydride (DIBAL-H). This reagent has been used previously for activation of magnesium in Grignard reactions.[7] All reactions in the process, especially zinc activation and Reformatsky reagent

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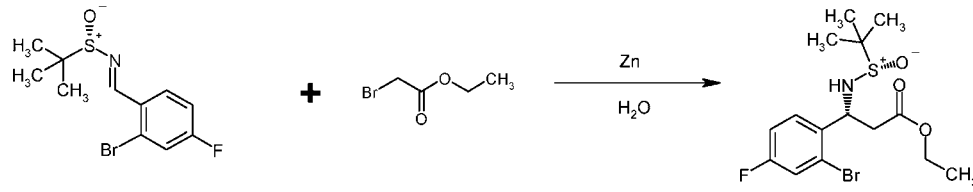
Scheme 1. **Introduction of chiral center by Reformatsky reaction between imine 1 and α-bromoester 2**



1 **2** **3**

formation, were investigated by reaction calorimetry, allowing rapid determination of conditions suitable for scale-up.

Results and Discussion

Background. In the original Research procedure, the Reformatsky reagent was prepared in THF by activation of zinc dust at reflux with 1,2-dibromoethane, followed by the addition of the ethyl bromoacetate (**2**) while maintaining reflux conditions. The mixture was then cooled to −8 °C prior to the addition of **1**.

On scale-up, these conditions did not work well. The yields were 50−60%, and several impurities were present according to HPLC analysis. The use of very dry conditions and activated zinc did not improve the reaction. However, it was found that one major factor affecting the reaction was the temperature used for the formation of the Reformatsky reagent. Lowering the temperature from 65 °C (reflux) to 45−50 °C afforded excellent conversion with little or no side-product formation. Carrying out the addition of **1** at −8 °C gave **3** in 98% yield and 99% optical purity.

Further study revealed that different batches of zinc gave different results with regard to yield and purity of **3**. The reaction was not reproducible when 1,2-dibromoethane was used to activate the newer batches of zinc. Since different lots and types of zinc did not give reliable results, a more reproducible method for the zinc activation was investigated. It was found that a catalytic amount of chlorotrimethylsilane was a viable activator for any grade of zinc. One drawback to this method of zinc activation was the fact that a minimum of 12 h was needed to completely activate the zinc. In order to render the process more efficient for the pilot plant, several other methods of zinc activation were investigated. DIBAL-H was found to give the best results in that the activation was instantaneous, or nearly so, as discussed below.

Zinc Activation with DIBAL-H. The activation procedure comprises addition of a 20 wt % DIBAL-H solution in toluene to a slurry of zinc granules (−30 to 100 mesh particle size) suspended in THF solvent and 5% of the total charge of bromoester **2**. In preliminary experiments performed in ordinary laboratory glassware, the presence of at least some bromoester before DIBAL-H addition was necessary to obtain good zinc activation (*i.e.*, evidenced by detection of an immediate exotherm upon adding the majority of bromoester); when DIBAL-H addition was carried out in the absence of bromoester, a delayed exotherm was seen when the latter was added subsequently. The value of 5% of bromoester present before DIBAL-H addition was selected because it gave good zinc activation, as described above.

The −30 to 100 mesh zinc particles were not suspended completely in the RC1 experiments. Even at a 600 rpm agitation rate with a pitched-blade impeller, it was not possible to suspend all the zinc granules, consistent with calculation of the just-suspended agitation speed N_{js} value of >8000 rpm from a literature correlation.[8] Calculation of N_{js} for the pilot-plant reactor to be used for the scale-up showed that an agitation rate >1500 rpm would be needed to suspend all the zinc particles. As such an agitation rate is greater than achievable values, complete zinc particle suspension would also not occur on large scale. As will be seen below, good reactivity was still obtained despite incomplete suspension of zinc particles.

The first task for scale-up was the selection of suitable temperatures for both zinc activation and Reformatsky reagent formation. Suitable temperatures should give immediate and detectable start-of-reaction (indicated by exothermic behavior), preferably with minimal heat accumulation. In a first experiment, 5.6 g of a 20 wt % solution of DIBAL-H in toluene (0.008 mol of DIBAL-H) was added at 30 °C to a slurry containing zinc (53.4 g, 0.82 mol), 5% of the total charge of bromoester **2** (*viz.*, 0.02 mol), and 350 mL of THF solvent. A sharp but short-lived heat evolution profile resulted (Figure 1), giving an adiabatic temperature rise of 10 °C, which would be easily detectable on large scale.

When addition of the remaining solution of bromoester **2** in THF was started at a reaction time of 0.18 h and a 30 °C batch temperature (Figure 1), heat evolution did not occur immediately. Instead, heat evolution started at about 0.27 h, and reached a constant value of about 9 W/kg. Upon heating the reaction mixture at 1 °C/min to 40 °C, the heat evolution attained a constant value during the temperature ramp, giving the profile of an addition-controlled reaction. Thus, a single calorimetric experiment indicated that Reformatsky reagent formation did not immediately start when the remaining bromoester **2** was added at 30 °C (*i.e.*, a ∼5-min delayed exotherm occurred), suggesting that this temperature was too low for immediate reagent formation. This result motivated examining a higher temperature to see if an immediate reaction start could be obtained.

Addition of the second portion of bromoester **2** at 40 °C (Figure 2) gave immediate heat evolution upon addition, thus avoiding heat accumulation. In this experiment, DIBAL-H was added with the RC1 in jacket temperature control mode, causing the batch temperature to increase by about 2 °C. DIBAL-H addition at 30 °C in a large-scale vessel, where the heat transfer

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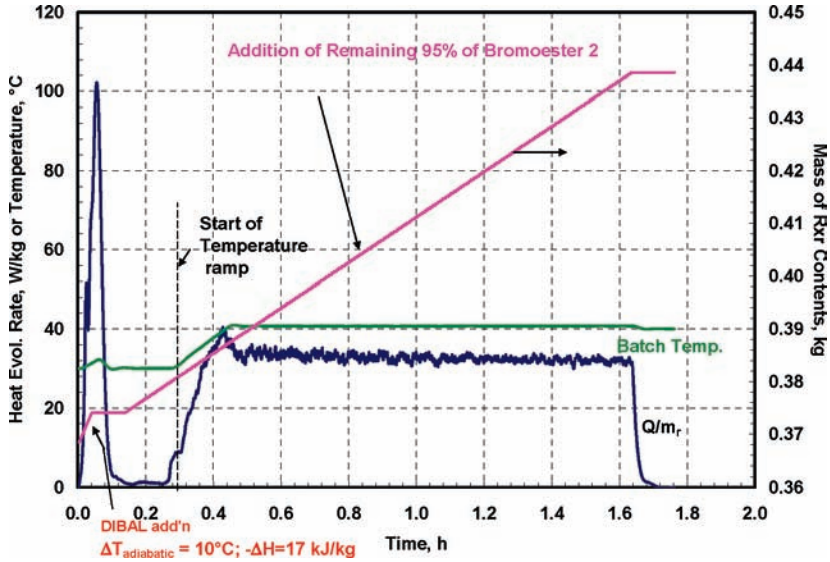

Figure 1. **First experiment calorimetric results, with DIBAL-H addition at 30 °C followed by addition of bromoester initially at 30 °C. (The horizontal arrow pointing rightward signifies that the data at the arrow's origin are to be read on the right-hand axis.)**

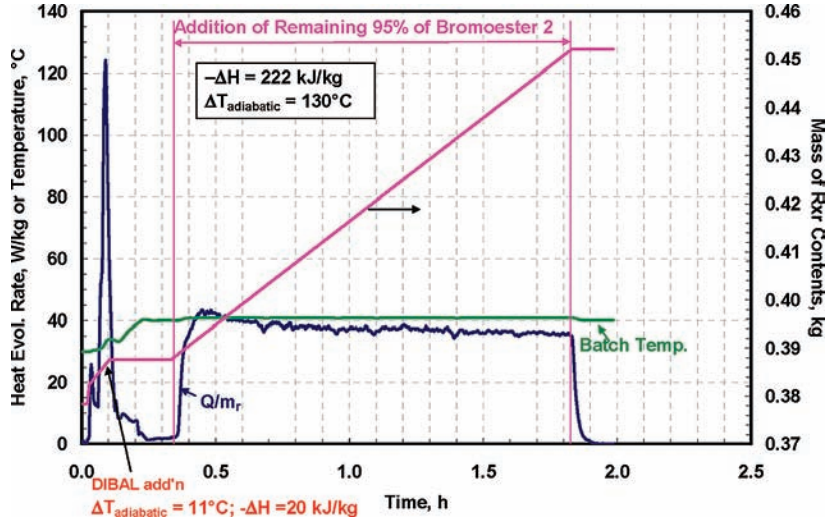

Figure 2. **Calorimetric profile when adding remaining amount of bromoester 2 at 40 °C. In this experiment, the initial bromoester portion was added immediately before DIBAL-H (*i.e.*, between 0.02 and 0.04 h).**

area per unit volume is smaller relative to the RC1 and where adiabatic behavior would be approached, would give a temperature rise close to the adiabatic temperature rise of ∼11 °C, thus allowing facile detection on large scale and giving a temperature near the target temperature for subsequent bromoester **2** addition. The addition of the second bromoester portion was carried out over a 1.5 h period, giving the desired addition-control calorimetric profile with a maximum heat evolution rate under 45 W/kg (Figure 2). The latter figure is well below the estimated 60 W/kg value for maximum heat removal capability of large-scale (*viz.*, 10 m^3) vessels having an overall heat transfer coefficient of 300 W/m^2·K, a heat transfer area of 20 m^2, and a maximum temperature difference between jacket and batch of 80 °C.[9] The heat evolution during bromoester **2** addition would also be detected easily at large scale and would thus give a quick indicator of reaction initiation and progress. The large 130 °C adiabatic temperature rise further indicates the importance of having an addition-controlled reaction.

Comparison of these results with those reported earlier for zinc activation and Reformatsky reagent formation reveals several advantages of the current process. First, the zinc activation occurs at or near room temperature, avoiding the need for heating to reflux, as was reported for activation with 1,2-dibromoethane[2] or cuprous chloride.[5] The process time is thus shortened by at least 2 h, without exposing any reactant to higher temperatures. Second, no induction period was observed. Thus, when the reaction was scaled-up to ∼800 L, a single addition of bromoester was performed, as shown in Figure 2. This allowed immediate detection of the start of the reaction, avoiding the need to add the haloester in portions and waiting between

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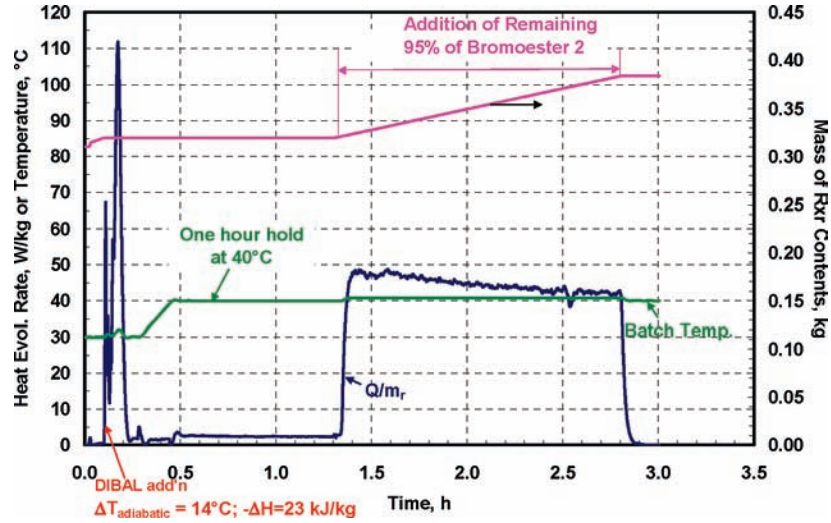

Figure 3. **Reformatsky reagent formation after a 1-h delay between zinc activation and the start of addition of second bromoester portion.**

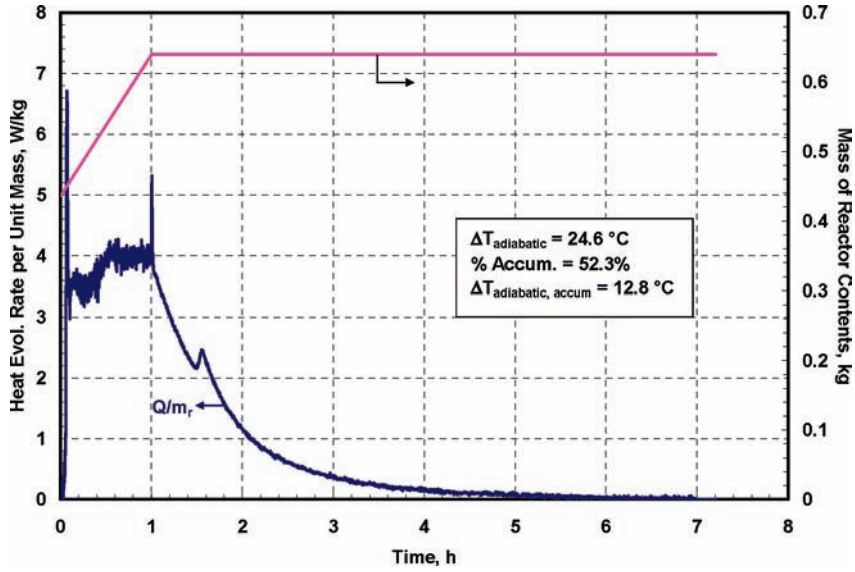

Figure 4. **Calorimetric profile during imine addition to Reformatsky reagent.**

each addition to verify that reaction occurred or diluting the reaction mixture, as was done earlier.[4,5]

The addition-controlled reaction indicated in Figure 2 also provided processing flexibility. Thus, if the reaction is carried out in smaller pilot-plant vessels which have heat removal capabilities greater than 60 W/kg,[9] a faster addition is possible without compromising process safety. Indeed, when the process was scaled up to ~800 L (see the Experimental Section), the addition could be carried out in 1 h. On the other hand, because mixing times typically increase with increasing vessel size, further scale-up may require either slower addition or addition in portions to give more time for the bromoester to mix and to thus avoid high local concentrations of the latter. This can lead to localized high-temperature regions (*i.e.*, hot spots) that could impact selectivity adversely.

An experiment was also conducted in which the second bromoester portion was added 1 h after zinc activation to simulate the impact of an interruption on large scale. As shown in Figure 3, reagent formation was not impacted adversely by the 1-h delay, as heat evolution began immediately after the start of bromoester addition and the addition-controlled reaction profile was maintained, further demonstrating process flexibility. We caution that, while some delay after zinc activation still leads to a well-defined start of reaction, the impact of longer interruptions is unknown.

Calorimetric Analysis: Imine Addition and Quench. Calorimetric analysis was also useful in obtaining process insight for subsequent steps of the process. After Reformatsky reagent formation, the reaction mixture was cooled to −8 °C, and imine **1** was added over 1 h. Heat evolution results indicated that the reaction was complete in ~7 h (confirmed by HPLC analysis), but was not addition-controlled, giving heat accumulation greater than 50% (Figure 4). Such heat accumulation would give an adiabatic temperature rise of 13 °C, which would adversely impact product selectivity, but not pose a safety concern. A longer addition time could be explored to decrease heat accumulation and decrease the risk of selectivity loss if temperature control problems occur.

The calorimetric analysis was also useful in optimizing the quench procedure performed by adding brine solution over a

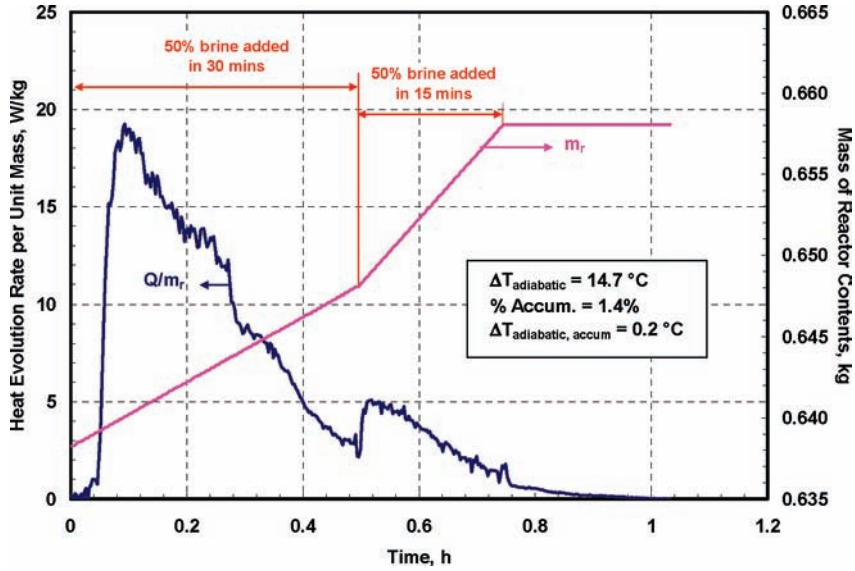

Figure 5. **Calorimetric profile during quench with brine.**

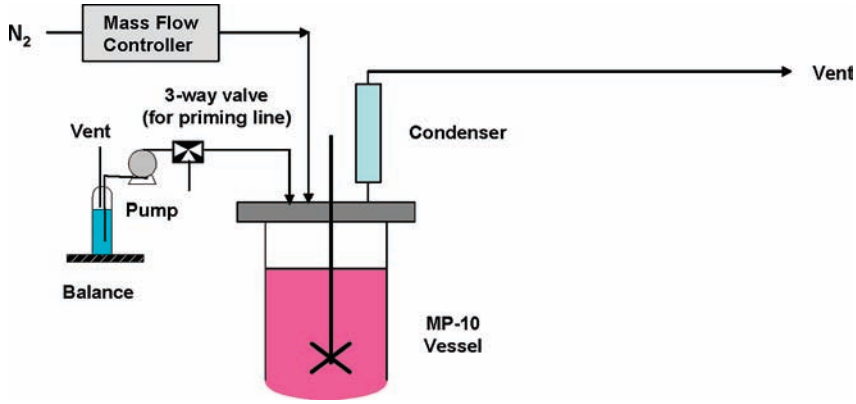

Figure 6. **Schematic diagram of reaction apparatus.**

0.75-h period. It was found that the first portions of brine addition were much more exothermic than subsequent amounts. To select suitable rates that would give good control on scale-up, a procedure was developed in which the first half of the brine solution was added over 30 min, and the remaining amount added over 15 min. As shown in Figure 5, this procedure gave an acceptable heat evolution rate with a process time of 1 h.

A total of six batches of **3** were completed in the pilot plant. The reactions were carried out at −8 °C overnight to afford **3** with high diastereoselectivity (>99% de). The combined product was obtained as a 22% MTBE solution in >99% yield and >95% purity by HPLC (area normalization). The Plant Procedure is given in Experimental Section below.

Experimental Section

Calorimetry. Reaction experiments were performed using a Mettler-Toledo RC1 reaction calorimeter equipped with a jacketed 1-L MP-10 glass vessel, a Hastelloy pitched-blade impeller, Hastelloy temperature and calibration probes, and a dosing station (comprising a ProMinent model G4 diaphragm pump and an electronic balance). A nitrogen purge (28 cm^3/min) was maintained using a Brooks 5880i mass flow controller. A schematic diagram of the reaction apparatus is shown in Figure 6.

Reaction calorimetry, discussed in more detail previously,[10] is used to measure the instantaneous heat evolved due to chemical reaction. When a single chemical reaction takes place, the calorimeter indicates the instantaneous reaction rate and is thus very useful for determining the start and end of a reaction as well as the degree of addition control.

General. NMR spectra were recorded on a Bruker AVANCE DPX-500 spectrometer (^{1}H NMR at 500 MHz). Analytical high performance liquid chromatography (HPLC) was carried using a Waters Alliance 2695 separations module, a Waters 996 photodiode array detector (MaxPlot), and a 3.0 × 15 cm Agilent Zorbax SB C-18 column (3.5 μm particle size). Acetonitrile was used as mobile phase A and 0.1% trifluoroacetic acid in water as mobile phase B. A gradient method (10% A to 90% A over 15 min) was used, at a 1 mL/min mobile phase flow rate and 40 °C column temperature; The retention times of **1** and **3** were 9.57 and 9.5 min, respectively. Samples for HPLC analysis were prepared by diluting 1−2 mg of reaction mixture in 6 mL of methanol; a 2-μL sample size was used. Reactions were carried out under an atmosphere of nitrogen. Unless reported otherwise, all reaction temperatures refer to the

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measured temperature of reaction mixtures not to the cooling- or heating-bath temperatures.

Laboratory Procedure. *(β-R)-Ethyl 2-Bromo-β-[[(S)-(1,1-dimethylethyl)sulfinyl]amino]-4-fluorobenzene-propanoate (**3**).* The RC1 calorimeter was charged with Zn (granular, −30−100 mesh, 53.4 g, 0.82 mol) and dry THF (311.2 g). The agitator speed was set to 600 rpm and the internal temperature to 30 °C. Ethyl bromoacetate (**2**) (3.4 g) and 5.81 g of a 20 wt % solution of DIBAL-H in toluene were added. The suspension was warmed to 40 °C, and ethyl bromoacetate (**2**) (64.55 g, 0.39 mol) was added over 1.5 h. The reaction mixture was maintained at 40 °C for 50 min. The reaction mixture was cooled to −8 °C, and a solution of (*S*)-,*N*-[(2-bromo-4-fluorophenyl)methylene]-*tert*-butylsulfinamide (**1**) (70 g, 0.23 mol) in THF (133.4 g) was added over 1 h. The reaction mixture was stirred at −8 °C for 14 h. At −8 °C saturated sodium chloride solution (20 g) was added over 1 h followed by ethyl acetate (225 g). The mixture was transferred by vacuum to a flask, and the reactor was rinsed with ethyl acetate (225 g). A solution of citric acid (60 g) in water (300 g) was added to the combined solution, and the mixture was stirred at room temperature for 20 min. The clear solution was filtered through Celite, and the filter cake was washed with ethyl acetate (100 g). The combined layers were separated, and the upper organic layer was washed with saturated sodium chloride (300 g). The organic layer was diluted with *tert*-butyl methyl ether (MTBE) (450 g), and the solvent was removed by distillation at 40 °C/400 mbar to give ∼500 mL of concentrate. The concentrate was diluted with MTBE (450 g), and the distillation was continued to give a solution containing 22% by weight of (*β-R*)-ethyl 2-bromo-*β*-[[(*S*)-(1,1-dimethylethyl)sulfinyl]amino]-4-fluorobenzenepropanoate (**3**) (113 g of **3** in 408 g of MTBE, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.23 (m, 1H), 6.97 (m, 1H), 5.09 (m, 1H), 4.92 (s, 1H), 4.04 (m, 2H), 2.82 (m, 2H), 1.17 (m, 9H), 1.14 (t, 3H); MS (positive-ion DCI) 394 (MH^+).

*(β-R)-Ethyl β-Amino-2-bromo-4-fluorobenzene-propanoate Hydrochloride (1:1) (**4**).* A solution of (*β-R*)-ethyl 2-bromo-*β*-[[(*S*)-(1,1-dimethylethyl)sulfinyl]amino]-4-fluorobenzene-propanoate (**3**) (260 g of solution containing 45 g of **3**) was added to a solution of 5−6 N HCl/isopropanol solution (61.5 g, ∼0.34 mol) over a 30-min period. The reaction mixture was stirred at 20−23 °C for 18 h. The resulting yellow suspension was filtered, and the filter cake was washed with MTBE (3 × 150 g) and dried at 35 °C/20 mm to give (*β-R*)-ethyl *β*-amino-2-bromo-4-fluorobenzene-propanoate hydrochloride (1:1) (**4**, 23.2 g, 62%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (bs, 2H), 7.95 (m, 1H), 7.65 (m, 1H), 7.40 (m, 1H), 4.96 (m, 1H), 4,02 (q, 2H), 3.24 (m, 1H), 3.07 (m, 1H), 1.10 (t, 3H); MS (positive-ion DCI) 291 (MH^+).

Plant Procedure. *(β-R)-Ethyl 2-Bromo-β-[[(S)-(1,1-dimethylethyl)sulfinyl]amino]-4-fluorobenzene-propanoate (**3**).* A slurry of granular Zn (11.4 kg, 174.9 mol) and THF (67.6 kg) was warmed to 32 °C and ethyl bromoacetate (0.73 kg, 4.4 mol) was added followed by a THF rinse (2 kg). Diisobutylaluminum hydride (25% solution in toluene, 1.0 kg, 1.7 mol) was added from a cylinder over 5 min using nitrogen pressure. The addition was slightly exothermic. The contents were heated to 41 °C over 5 min. Ethyl bromoacetate (13.9 kg, 83.2 mol) was added over 1 h via diaphragm pump while maintaining the batch temperature below 45 °C. The lines were rinsed with THF (3 kg) which was added to the batch. The contents were stirred at 40 °C for 1 h and then cooled to −10 °C. A solution of (*S*)-*N*-[(2-bromo-4-fluorophenyl)methylene]-*tert*-butylsulfinamide in THF (15 kg, 49 mol in 42.9 kg of solution) was added over 1 h via diaphragm pump while maintaining the temperature ≤−5 °C. The lines were rinsed with THF (1 kg) which was added to the batch. The reaction mixture was stirred at −8 °C for 15 h. Sodium chloride solution (25%, 4.3 kg) was charged to the batch over 1 h while maintaining the temperature ≤−5 °C. After all of the sodium chloride solution had been added, the mixture was stirred for 15 min at −5 °C. The batch was warmed to 20 °C over 30 min. A slurry of Celite Hyflo (5 kg) in ethyl acetate (30 kg) was added, and the heterogeneous mixture was stirred at 20 °C for 15 min. The contents were filtered using a Nutsche filter, and the filter cake was washed with ethyl acetate (83 kg). The filtrate and wash were combined and washed with 17% citric acid solution (78 kg) and 25% sodium chloride solution (65 kg). The organic solution was concentrated to 100 L by vacuum distillation (25−30 °C/400−600 mbar). The concentrate was diluted with methyl *tert*-butyl ether (97 kg), and the distillation was continued under the same conditions to a final volume of 40 L. This step was repeated until the water content by Karl Fisher was <0.3%. The solution of (*β-R*)-ethyl 2-bromo-*β*-[[(*S*)-(1,1-dimethylethyl)sulfinyl]amino]-4-fluorobenzene-propanoate (**3**) was used as is in the next step.

Conclusions

A zinc-activation procedure using DIBAL-H was developed for a Reformatsky reaction. The zinc activation and subsequent Reformatsky reagent formation were investigated by reaction calorimetry, which was especially useful in selecting a reaction temperature giving immediate reaction start. The process was shown to have key advantages for large-scale production over previously reported processes, including: (a) room-temperature and easily detectable zinc activation, (b) the absence of an induction period for Reformatsky reaction formation, and (c) processing flexibility in conducting Reformatsky reagent formation. Calorimetric analyses were also useful for optimizing the quench procedure.

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