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Modified Chelation-Controlled Reduction of an *N*-Acryloyloxazolidin-2-one†

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Abstract:

A key step in the synthesis of an optically active aminoalcohol-containing active pharmaceutical ingredient (API) involved the diasteroselective reduction of a chiral 3-acryloyl-4-benzyloxazolidin-2-one. Preliminary work identified that excellent facial selectivity could be achieved by performing the hydrogenation in tetrahydrofuran in the presence of magnesium bromide. During an intermediate scale-up to support a 500-g batch of API, a side reaction between the product and magnesium bromide was observed that led to a significant deterioration in the isolated yield of product. An examination of alternative chelators and processing solvents identified that magnesium chloride in 2-methyltetrahydrofuran offered comparable facial selectivity with significantly diminished liabilities for scale-up. This revised process was incorporated into campaigns to produce larger lots of API and afforded the product in 85% yield, averaged over 18 batches.

Introduction

Recently, we disclosed details on the route selection and early scale-up efforts that resulted in the successful synthesis of **5** from **1**[1] (Scheme 1). Conversion of **2** to **3** used a newly discovered diastereoselective hydrogenation protocol, followed by an enolization−azidation sequence at −40 °C[2,3] based on Evans methodology.[4] The details surrounding the development of conditions for conversion of **2** to **3** and the robust process that resulted are the subjects of this communication.

Results and Discussion

As reported previously, direct hydrogenation of **2** over dry palladium on carbon[5] at 450 psig hydrogen produced a mixture of diastereomers, shown as **3** and **dist-3** in Figure 1, with the latter being favored by a ratio of 75:25 (entry 1, Table 1). Addition of 1.2 equiv of magnesium bromide led to a reversed sense of stereoinduction, and **3** was formed over **dist-3** in a ratio of 95:5.

These results were explained on the basis of the preferred conformation of **2**. In the absence of Lewis acid, compound **2** existed predominantly as the ***anti*-2** conformer. Literature precedent based on other oxazolidin-2-one derivatives supports the major conformation as ***anti*-2** based on dipole−dipole interactions between the two carbonyl groups.[6,7] Addition of magnesium bromide appeared to change the preferred conformation to the ***syn*-2** form, and the major product from hydrogenation became **3**. Others have reported similar magnesium salt-mediated reversals in the facial selectivity of α,β-unsaturated imides during conjugate additions and oxidations and have invoked similar mechanistic explanations.[8,9]

The effects of reaction temperature and applied pressure of hydrogen were evaluated briefly (entries 2−6, Table 1). This limited data set indicated that the working pressure of hydrogen could be reduced to 40 psig if the temperature was maintained at 50 °C. At lower temperatures, conversion slowed significantly, and the reduction was not complete after 4 h (entries 4−6, Table 1).[10]

To support the preparation of a 500-g batch of active pharmaceutical ingredient (API) **5**, the reduction was scaled up 15-fold and performed in a kilo-lab reactor at 50 °C and 55 psig hydrogen. Laboratory experiments had shown that the solubility of magnesium bromide was sufficient enough in a mixture of IPA and water that it would not interfere with the isolation of **3**. Therefore, following removal of the catalyst, the solvent was exchanged to IPA and water added to effect crystallization of the product. Although laboratory yields had been 80%, the first scale-up to the kilolab resulted in 33% yield. An impurity was found in the filtrate that had *m*/*z* of 369, and a stress test done *after* the kilolab run showed that **3** reacted with $MgBr_2$ at elevated temperature in a mixture of THF and IPA to generate a peak with *m*/*z* 369, presumably formed via **6**[11,12] (Figure 2). Preparative LC was eventually used to obtain

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(2) Safety screening performed in-house generated results in line with those reported previously by Merck workers for triisopropylbenzene sulfonyl azide. See: Tuma, L. D. *Thermochim. Acta* **1994**, *243*, 161–167.

(3) Details on the work that enabled the conversion of **3** to **4** to be performed at −40 to −50 °C have been communicated recently. See: Connolly, T. J.; Hansen, E. C.; MacEwan, M. F. *Org. Process Res. Dev.* **2010**, *14*, 466–469.

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(5) The process does require that dry catalyst be used since water has a significant detrimental impact on the process. Palladium on alumina can be used in cases where handling pyrophoric, dry palladium on carbon is not acceptable.

(6) Prashad, M.; Liu, Y.; Kim, H.-Y.; Repic, O.; Blacklock, T. J. *Tetrahedron: Asymmetry* **1999**, *10*, 3479–3482.

(7) Davies has published single-crystal data for valine-derived products related to **3** that also support the anti-relationship between the carbonyl groups of the oxazolidinone and *N*-acyl groups. See: Bull, S. D.; Davies, S. G.; Garner, A. C.; Kruchinin, D.; Key, M.-S.; Roberts, P. M.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2006**, *294*, 5–2964.

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(10) This screening was performed using an Endeavor Catalyst Screening System from Biotage/Argonaut. Longer reaction times at lower temperatures were not evaluated.

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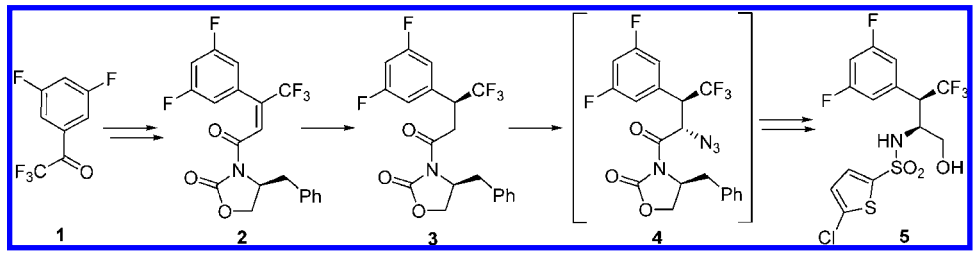
Scheme 1. **Condensed synthetic scheme for the conversion of 1 to 5**



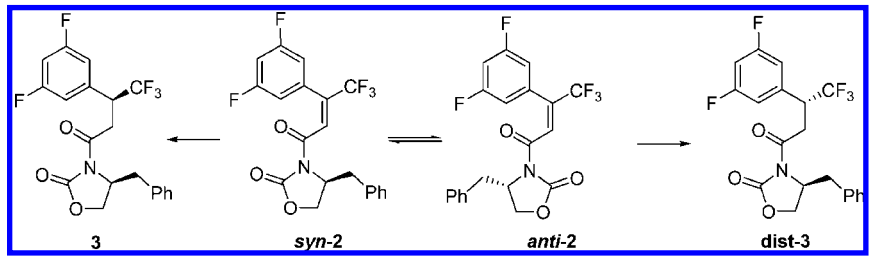


Figure 1. **Conformer equilibrium and facial selectivity observed during hydrogenation.**

Table 1. **Screening results for reduction of 2 with $MgBr_2$**

entry	additive	temperature (°C)	hydrogen pressure (psig)	conversion (%)	ratio[a] **3**:**dist-3**
1	none	50	450	100	25:75
2	$MgBr_2$	50	450−80	100	95:5
3	$MgBr_2$	50	40	99	95:5
4	$MgBr_2$	25	450	89	94:6
5	$MgBr_2$	25	80	56	96:4
6	$MgBr_2$	25	40	57	97:3

[a] Determined by HPLC.

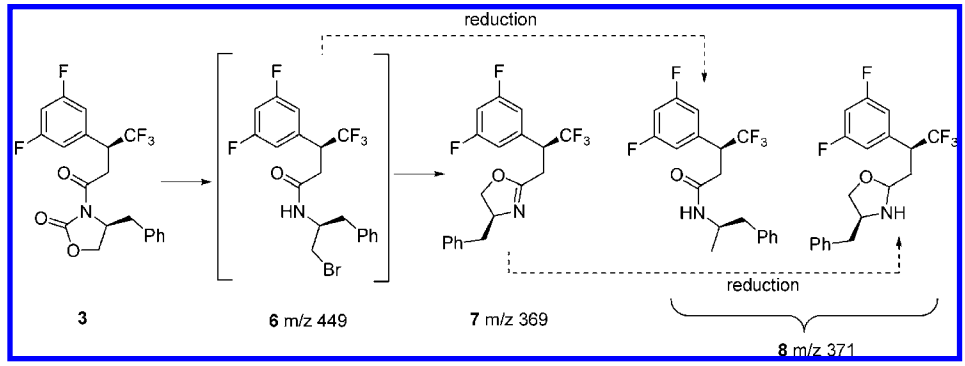


Figure 2. **Degradation products and impurities generated during $MgBr_2$-mediated reduction.**

a fraction that contained both *m*/*z* 449 and *m*/*z* 369 impurities, and the structures were assigned as **6** and **7**, respectively, on the basis of 1D- and 2D-NMR techniques.[13] A re-examination of the $MgBr_2$-mediated reduction showed that **6** and **7** were also formed during the reaction and not just during the workup and isolation process. Additionally, another degradation product having *m*/*z* 371 was identified and assumed to be one of two structures and shown as **8** since **6** and **7** could be reduced under the hydrogenation conditions.[14]

The process was stabilized to provide the required amount of **3** to enable timely delivery of **5** by further dilution of the reduction conditions, incorporation of an aqueous work up to remove $MgBr_2$,[15] and the use of vacuum during the solvent exchange (T_j < 50 °C). Incorporation of these process changes afforded a 76% yield of **3** when the process was scaled up to

(11) A mass of 369 corresponds to loss of HBr from **6** (*m*/*z* 449).
(12) Compound **6** could be detected in stress tests performed using **3**, $MgBr_2$, and THF only. After 18 h at 65 °C in THF, the relative amount of **3**:**7**:**6** formed was 2:1:2. Performing the same stress test in 1:1 THF/IPA provided relative amounts for **3**:**7**:**6** of 1:2:0.
(13) Details are provided in the Supporting Information. It should be noted that both **6** and **7** were hydrolyzed in the NMR sample tube when DMSO was used as the solvent. The fraction isolated by prep-LC initially contained three components; **6**, **7**, and a product consistent with hydrolysis of **7**. After three days, the sample contained 4 components: the three components mentioned above and the product that was the result of hydrolysis of **6**. We assume that the hydrolysis product originally identified was an artifact of the prep-LC conditions since the reduction is performed under anhydrous conditions.
(14) This byproduct was not isolated to determine the structure since it was a secondary byproduct resulting from hydrogenation of the primary byproducts. Limiting the amount of **6** and **7** formed during the reaction would reduce the amount of **8**, regardless of structure.
(15) Following removal of the catalyst and addition of MTBE, the reaction mixture was washed three times with an aqueous brine solution to remove $MgBr_2$.

Table 2. **Expanded chelator screen in THF**

entry	additive	conversion (%)	ratio **3**:**dist-3**
1	$MgBr_2$	100	98:2
2	$MgCl_2$	100	80:20
3	$MgSO_4$	100	36:64
4	$Mg(OTf)_2$	100	41:59
5	$Ca(OTf)_2$	100	49:51
6	$Cu(OTf)_2$	100	24:76
7	$CuCl_2$	0	−
8	$FeCl_2$	100	43:57
9	$ZnCl_2$	25	22:88
10	$ZnBr_2$[a]	42	28:72

[a] A significant unidentified impurity was observed with $ZnBr_2$.

1 kg of **2**; however, the process was viewed as having significant liabilities for further scale-up. Even with the measures taken, approximately 5% byproducts were formed during the 4 h reduction.[16] The total amount of the two primary impurities (**6** and **7**) increased at a rate of approximately 2%/h once the reaction had progressed to ~97% completion. Further, $MgBr_2$ still remained in the organic layer even after three brine washes[17] and continued to cause formation of **6** and **7** during the solvent exchange required for isolation.

Re-examination of Alternative Chelators

In light of the identified issues and the knowledge that processing time would be extended significantly upon further scale-up,[18] the reduction was screened with other potential chelators, and the results are shown in Table 2.[19]

Of the potential chelators examined, only the previously identified $MgBr_2$ and $MgCl_2$ showed any promise as additives for the hydrogenation that would maintain the desired facial selectivity. Another round of screening was performed that focused on these two additives and $MgBr_2-OEt_2$[20] in various solvents with the goal of identifying a solvent that would either provide increased selectivity with $MgCl_2$ or attenuate the decomposition observed with $MgBr_2$. Results from the screening are shown in Table 3 and are sorted in terms of conversion. Generally, ethers performed better than other solvents in terms of conversion. The notable exception was 1,2-dimethoxyethane, which performed quite poorly, potentially due to a poisoning effect caused by its ability to act as a chelator for metals. Although the highest selectivity was achieved with $MgBr_2$ and $MgBr_2-OEt_2$, significant decomposition was also observed (entries 8 and 9). The additive that offered the best balance of selectivity with minimal decomposition and therefore lowest liability for scale-up was $MgCl_2$ in 2-methyltetrahydrofuran (entry 1). It is worth noting that running the reaction at elevated temperatures in 2-methyltetrahydrofuran with magnesium chloride offered better facial selectivity than the original $MgBr_2$/THF conditions.

The magnesium chloride-2-methyltetrahydrofuran conditions were selected for further evaluation. Experiments demonstrated that the solvent volume could be reduced from 20 volumes to 15 volumes without adversely impacting the diastereoselectivity of the reduction. Decreasing solvent use further to 10 volumes caused a slight drop in selectivity, but in all cases the isolated yield was >80%, and decomposition of the product was minimal (<1%), even when the reaction mixture was left under hydrogen at 70−75 °C for 18 h.

One final improvement was made when the reaction mixture was adjusted to the reaction temperature prior to charging hydrogen which led to consistently better ratios of **3**:**dist-3**. The isolated yield using these conditions was 87−90% in the lab and averaged 85% over 18 hydrogenations in the kilogram laboratory at a 2.1-kg scale.[21] The improved selectivity observed when the reaction mixture was heated prior to charging hydrogen was presumably related to the solubility of $MgCl_2$. If hydrogen was applied to the system before all of the $MgCl_2$

Table 3. **Expanded solvent screen focused on $MgBr_2$, $MgCl_2$, and $MgBr_2 \cdot OEt_2$ as chelators**

entry	additive	solvent	temp (°C)	conv (%)	ratio **3**:**dist-3**	decomp (%)
1	$MgCl_2$	2-MeTHF[a]	75	100	98:2	1.4
2	$MgBr_2 \cdot OEt_2$	2,2-DMP[b]	75	100	95:5	0.5
3	$MgBr_2$	tetrahydrofuran	60	100	96:4	4.8
4	$MgCl_2$	tetrahydrofuran	60	100	90:10	0
5	$MgBr_2 \cdot OEt_2$	tetrahydrofuran	60	100	97:3	11.1
6	$MgBr_2 \cdot OEt_2$	2-methoxyethanol	80	100	84:16	0
7	$MgCl_2$	2,2-DMP[b]	75	100	77:33	0.5
8	$MgBr_2 \cdot OEt_2$	2-MeTHF[a]	75	100	100:0	26.1
9	$MgBr_2$	2-MeTHF[a]	75	100	100:0	26.5
10	$MgCl_2$	diethoxymethane	80	100	46:54	0.5
11	$MgCl_2$	2-methoxyethanol	80	100	43:57	0.6
12	$MgCl_2$	NMP[c]	80	100	27:73	2.1
13	$MgCl_2$	toluene	80	100	25:75	0.5
14	$MgBr_2$	2-methoxyethanol	80	99	83:17	0
15	$MgBr_2$	NMP[c]	80	99	59:41	1.8
16	$MgBr_2$	diethoxymethane	80	97	18:82	5.7
17	$MgBr_2 \cdot OEt_2$	NMP[c]	80	96	58:42	2.2
18	$MgBr_2 \cdot OEt_2$	diethoxymethane	80	96	27:73	10.1
19	$MgBr_2$	2,2-DMP[b]	75	79	98:2	0
20	$MgBr_2$	toluene	80	62	91:9	21
21	$MgBr_2 \cdot OEt_2$	toluene	80	53	70:30	7
22	$MgBr_2 \cdot OEt_2$	1,2-dimethoxyethane	80	<5	nd	nd
23	$MgCl_2$	1,2-dimethoxyethane	80	<5	nd	nd
24	$MgBr_2$	1,2-dimethoxyethane	80	<5	nd	nd

[a] 2-Methyltetrahydrofuran. [b] 2,2-Dimethoxypropane. [c] *N*-Methylpyrrolidinone.

was in solution, reduction of the nonchelated conformer **2a** would dominate, leading to the formation of **dist-3** and a lower ratio of **3**:**dist-3**. Residual water also adversely impacted the overall yield and observed selectivity. The isolated yield of **3** dropped from 90% to 86% when the water content of the palladium on carbon increased from 1.3% to 3.6%,[22] and use of 50% water-wet catalyst caused the ratio of **3**:**dist-3** to decrease to approximately 70:30. The decreased yield and selectivity were presumably an impact of hydrolysis of the Lewis acid that resulted in there being less available for chelation.

Conclusion

A Lewis acid-mediated hydrogenation of an *N*-acryloyloxazolidin-2-one was developed. Addition of specific Lewis acids to the reaction mixture caused the facial selectivity of the hydrogenation to be reversed. Although magnesium bromide was used successfully on a small laboratory scale, stress tests showed that the product was degraded by the magnesium bromide when processing times were extended. Magnesium chloride was identified as a suitable replacement; however, 2-methyltetrahydrofuran was required as the solvent, and the reaction temperature had to be increased to 75 °C. The process was scaled up to a kilo-lab, and over the 18 batches run to date, the isolated yield has averaged 85%.

The change in facial selectivity may be best explained on the basis of a shift in the preferred conformer of the starting material in solution caused by Lewis acid coordination of the two carbonyl groups. Attempts to further elucidate the reaction mechanism using either NMR or *in situ* FTIR were not successful. The *in situ* FTIR profile and heat-flow pattern did reveal that the reduction was slower when conducted in the presence of magnesium chloride. These data are consistent with Lewis acid coordination of the carbonyl groups that would lead to lower electron density of the carbon−carbon bond.[23] Although we have not been successful in obtaining direct evidence that supports the proposed reaction mechanism, we have reported robust reaction conditions and expect that this methodology could be useful for related substrates.

Experimental Section

General. Reaction monitoring was carried out on a Waters Alliance HPLC with PDA monitoring (215 nm) equipped with a Waters Symmetry C18 column (4.6 mm × 150 mm) at 25 °C. Elution was performed with a flow rate of 1.0 mL/min and an isocratic method using 30% mobile phase A (water/acetronitrile, 95:5) and 70% mobile phase B (water/acetonitrile, 5:95). The mobile phase was modified with 0.07% NH_4Cl as buffer. Observed retention times were as follows: $MgBr_2$ (1.4 min), **6** (5.9 min), **5** (6.2 min), **dist-3** (6.4 min), **3** (6.8 min), **2** (7.2 min).

Reaction screening was performed in an Endeavor Catalyst Screening System from Biotage/Argonaut using 10-mL cells with a fill volume of 3 mL. Each experiment was performed using 0.2 g of **2** and 1.2 molar equiv of chelator. The vessels were adjusted to the specified operating temperature at 250 rpm and held at that temperature before hydrogen was introduced. Upon introduction of hydrogen (60 psig), stirring was increased to 500 rpm, and these conditions were maintained through the course of the experiment.

Lab-Scale Demonstration. To a 2-L Parr pressure reactor, compound **2** (82 g, 200 mmol), dry palladium on carbon (10% Pd, 8.3 g, 7.8 mmol), $MgCl_2$ (23 g, 240 mmol, 1.2 equiv), and 2-methyltetrahydrofuran (1230 mL, 15 parts v/w) were added. The mixture was heated to 70 °C and held for 20 min, and the atmosphere inside the pressure vessel was converted to hydrogen (55 psig). The reaction mixture was stirred at 70 °C, maintaining hydrogen pressure at 55 psig until the conversion to **2** to **3** was greater than 95% (AN HPLC, typically 1 h). The reactor was purged of hydrogen, inerted with nitrogen, and cooled to 40 °C. The reaction mixture was filtered through Celite (82 g, 1 part w/w) at 40 °C under nitrogen (**Caution: Spent catalyst is pyrophoric!)**, and the reactor and cake were rinsed forward with MTBE (820 mL, 10 parts v/w). The combined filtrate was washed with brine (410 mL, 5 parts v/w) to remove $MgCl_2$ and was concentrated to a volume (330 mL, 4 parts v/w) at 40 °C under vacuum. To the concentrate was charged IPA (820 mL, 10 parts v/w). The mixture was concentrated to 330 mL (4 parts v/w) at 40 °C under vacuum. The concentrate was heated to 70−80 °C to give a cloudy solution, and water was added water (160 mL, 2 parts v/w) to afford a suspension. The resulting suspension was cooled to ambient temperature and filtered. The filter cake was dried at 60 °C under vacuum to give 71.8 g of **3** as a white solid in 87% yield with purity of 98% (w/w). The material was found to be identical to that prepared previously.[1]

Kilolab-Scale Experiment. To a 40-L hydrogenator were charged compound **2** (2.1 kg, 5.1 mol), dry palladium on carbon (10% Pd, 0.21 kg) (**Caution: Dry catalyst is pyrophoric!)**, anhydrous $MgCl_2$ (0.59 kg, 6.2 mol, 1.2 equiv), and 2-methyltetrahydrofuran (27.1 kg). The mixture was heated to 70−75 °C and held for 15 min, and then the atmosphere inside the pressure vessel was converted to hydrogen (60−65 psig) while the contents were stirred at 900−1100 rpm. The reaction mixture was held under these conditions until the pressure drop on the supply line slowed to <10 psig/15 min. The reactor

(16) In process analysis of a scale-up run performed on 1 kg of **2** showed 1.6% **2**, 4.8% **7**, and 5.0% **6** after 4 h of reaction.
(17) Magnesium bromide had sufficient absorption in the UV region that it could be monitored by HPLC. After three brine washes, the organic layer still contained 2 area % $MgBr_2$.
(18) McConville, F. X. *The Pilot Plant Real Book*; FXM Engineering and Design: Worcester, MA, 2002.
(19) For screening purposes, all reductions were performed in THF at 50 °C with 50 psig hydrogen using dry palladium on carbon (10 wt % Pd) and 1.2 equiv of additive.
(20) Magnesium bromide diethyletherate was examined when the Process Safety Group raised concerns regarding the high heat of dissolution of $MgBr_2$ in THF. Use of pre-solvated magnesium bromide was expected to lower the exotherm noted when $MgBr_2$ and THF were mixed.
(21) A total of 32 kg of **3** was prepared in six batches. Each batch of **3** required three hydrogenations of **2** that were then combined, providing isolated batch sizes of 5.0−5.5 kg of **3**.
(22) Palladium on alumina was also evaluated for this process. It offers the advantages of being dry and safer to handle than dry palladium on carbon. In our evaluation, the reaction took slightly longer, but the isolated yield was approximately 88%. The decision to scale up the dry palladium on carbon was based largely on the fact that the dry palladium on carbon had been ordered to support the $MgBr_2$ campaign and was in stock.
(23) Partial NMR spectra for starting material in the presence and absence of magnesium salts, and *in-situ* FTIR and heat-flow data for hydrogenations performed in the presence and absence of magnesium chloride are available as Supporting Information.

contents were cooled to 40−45 °C, and the atmosphere inside the reactor was converted from hydrogen to nitrogen. The reaction was sampled for HPLC, and 0% **2** was detected after 2.5 h. The reactor contents were filtered through a Sparkler filter (**Caution: Spent catalyst is pyrophoric!**), and then the reactor and filter were rinsed forward with MTBE (15 kg). The filtrate was collected in a common receiving vessel and held for later processing. The hydrogenations were repeated twice more on the same scale. When the third reduction was complete, the combined filtrates were washed with a solution of water (32 kg) and sodium chloride (3.1 kg). The organic layer was separated and concentrated to 20−25 L final volume under vacuum with a maximum jacket temperature of 35 °C (max. pot temperature was 21 °C). 2-Propanol (50 kg) was charged, and the reactor contents were reduced to a final volume of 20−25 L.[24] The reactor contents were adjusted to 70−80 °C, and water (12 kg) was added over 10 min while the batch temperature was maintained at 65−80 °C. The reactor contents were cooled to 20−25 °C over 1 h and then filtered and rinsed with a mixture of 2-propanol (5.0 kg) and water (6.3 kg). The product was dried on the filter for 24 h at ambient temperature under a stream of nitrogen and was discharged.[25] The filter was discharged to provide **3** as a white solid, 5.64 kg (89.5% yield) with a purity >99% (w/w).

(24) In-process GC analysis showed there to be 1.9% 2-methyltetrahydrofuran present at this point.

(25) After 24 h, the product had a water content of 0.03% (KF method) and residual IPA of 0.11%.

Acknowledgment

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Supporting Information Available

Partial NMR spectra for starting material **2** in the presence and absence of magnesium salts, *in situ* FTIR and heat-flow data for hydrogenations of **2** performed in the presence and absence of magnesium chloride, details of the preparative LC separation conditions used to isolate **5** and **6** and NMR data used to identify **5** and **6** are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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