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Oxidative Dehydrogenation of Dihydropyrimidinones and Dihydropyrimidines

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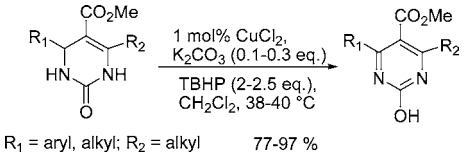
ABSTRACT



A mild, practical procedure for oxidative dehydrogenation with catalytic amounts of a Cu salt, K_2CO_3, and *tert*-butylhydroperoxide (TBHP) as a terminal oxidant has been developed. This oxidation procedure is generally applicable to dihydropyrimidinones and most dihydropyrimidines.

The production of heteroaromatics by oxidative dehydrogenation is of fundamental importance in organic synthesis. While a number of methods have been developed,[1] most procedures require stoichiometric reagents and/or harsh reaction conditions. Therefore the development of mild, catalytic oxidation systems is highly desirable.[2]

The dehydrogenation of dihydropyrimidines and dihydropyrimidinones has received much attention.[3] Because of their facile access via the Biginelli three-component coupling,[3] dihydropyrimidines and their derivatives are widely used for diversity- and target-oriented synthesis. In addition, they have shown various biological activities, and are a common motif in drug substances.[4]

In contrast to Hantzsch-type dihydropyridines, where aromatization to pyridines is typically facile, the dehydrogenation of dihydropyrimidines is known to be nontrivial.[3a,5] Previously identified oxidants for this process include HNO_3,[6] DDQ,[7] CAN,[8] and Pd/C[9] as well as electrochemical oxidation.[10] None of these oxidations are ideal, particularly for scale-up, due to their safety profile[11] and/or difficulty in product isolation. Therefore, an alternative procedure was

† Recipient of a Bristol-Myers Squibb 2004 summer internship.

(1) (a) *Comprehensive Organic Syntheses*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, UK, 1992; Vol. 7. (b) *Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W. J., De Jonge, C. R. H. I., Eds; Plenium Press: New York, 1986.

(2) For representative examples of oxidative aromatization of thiazolines and oxazolines: (a) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L., Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497−501. (b) Meyers, A. I.; Taveres, F. X. *Tetrahedron Lett.* **1994**, *35*, 2481−2484. (c) Meyers, A. I.; Tavares, F. X. *J. Org. Chem. Soc.* **1996**, *61*, 8207−8215. (d) Barrish, J. C.; Singh, J.; Spergel, S. H.; Han, W. C.; Kissik, T. P.; Kronenthal, D. R.; Mueller, R. H. *J. Org. Chem.* **1993**, *58*, 4494−4496. (e) Williams, D. R.; Lowder, P. D.; Gu, Y.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331−334. (f) North, M.; Pattenden, G. *Tetrahedron*, **1990**, *46*, 8267−8290. (g) McGarvey, G. J.; Wilson, K. J.; Shanholtz, C. E. *Tetrahedron Lett.* **1992**, *33*, 2641−2644. Dihydropyridines and pyrazolines: (h) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Synthesis* **2004**, *7*, 1015−1020. (i) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 22, 3955−3957. (j) Nakamichi, N.; Kawabata, H.; Hayashi, M. *J. Org. Chem.* **2003**, *68*, 8272−8273. A related oxidative synthesis of benzoxazoles: (k) Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.*, **2003**, *5*, 3713−3715.

(3) (a) Kappe, C. O. *Tetrahedron Lett.* **1993**, *49*, 6937−6963. (b) Kappe, C. O.; Stadler, A. *Org. React.* **2004**, *63*, 1−116.

(4) For representative drugs and pharmacologically active compounds, see The Merck Index Online. The structure search with pyrimidine gave 177 hits, including Bleomycin (glycopeptide antibiotics), Buspirone (anxiolytic), Pyrithiobac (herbicide), and Monastrol (Kinesin EG5 inhibitor).

(5) Vanden Eynde, J. J.; Audiart, N.; Canonne, V.; Michel, S.; Van Haverbeke, Y.; Kappe, C. O. *Heterocycles* **1997**, *45*, 1967−1978.

(6) (a) Puchala, A.; Belaj, F.; Bergman, J.; Kappe, C. O. *J. Heterocycl. Chem.* **2001**, *38*, 1345−1352. (b) Matsushima, A.; Oda, M.; Kawachi, Y.; Chika, J. PCT WO 03/006439 A1.

(7) Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437−444.

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(9) Kappe, C. O.; Roschger, P. *J. Heterocycl. Chem.*, **1989**, *26*, 1555−1560. This Pd/C dehydrogenation without the use of oxidant requires rigorous conditions (210 °C) in Ph_2O.

(10) Kadis, V.; Strandins, J.; Khanina, E. L.; Duburs, G. *Electrochim. Acta* **1989**, *34*, 899−904.

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sought. We report herein the finding and scope of a new, catalytic dehydrogenation for dihydropyrimidinones and dihydropyrimidines.[12]

A preliminary screening of terminal oxidants for metal-catalyzed systems revealed that the use of *tert*-butylhydroperoxide (TBHP) is crucial for this oxidative dehydrogenation.[13] Upon further survey of optimal catalysts, Cu^{I} or Cu^{II} salts were found to be the most effective (Table 1, cf. entries 16−19), while the difference between counterions was negligible (entries 11−15). Among the solvents screened, halogenated solvents such as CH_2Cl_2 or $(CH_2Cl)_2$ gave the best reaction profiles (entries 1−2). The use of other solvents retarded the reaction, presumably in part due to the low solubility of the substrate. Addition of up to ~0.3 equiv of K_2CO_3 led to significant rate acceleration.[14] These parameters were then evaluated to ensure the completion of the reaction within a reasonable time frame, while avoiding using a large excess of the reagents. The following optimal conditions were used in the subsequent investigation: $CuCl_2$ (1 mol %), TBHP (2−2.5 equiv), K_2CO_3 (0.1−0.3 equiv), CH_2Cl_2 (10 mL/g), 40 °C, 15−24 h.

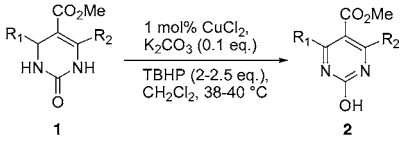
Table 1. Solvent and Catalyst Screening[a,b]

entry	solvent	catalyst	conv (area %)[c]	product (area %)[c]
1	CH_2Cl_2	$CuCl_2$	>99	97
2	$(CH_2Cl)_2$	$CuCl_2$	>99	99
3	PhMe	$CuCl_2$	59	36
4	MeOH	$CuCl_2$	70	67
5	MTBE	$CuCl_2$	57	29
6	THF	$CuCl_2$	21	17
7	DMF	$CuCl_2$	49	17
8	DMSO	$CuCl_2$	85	81
9	MeCN	$CuCl_2$	95	91
10	acetone	$CuCl_2$	90	78
11	CH_2Cl_2	CuCl	>99	96
12	CH_2Cl_2	$Cu(OAc)_2$	>99	97
13	CH_2Cl_2	$CuSO_4$	>99	97
14	CH_2Cl_2	$CuNO_3$	>99	97
15	CH_2Cl_2	CuO	>99	97
16	CH_2Cl_2	$Pd(OAc)_2$	72	70
17	CH_2Cl_2	Pd/C	81	78
18	CH_2Cl_2	$RuCl_3$	67	67
19	CH_2Cl_2	$FeCl_3$	76	74

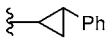
[a] Substrate **1a** was used. [b] Sampled after 17 h. [c] Determined by HPLC.

A survey of the dihydropyrimidinone system demonstrated that these conditions are applicable to alkyl and aryl substituents with a range of electronic properties (Table 2).

Table 2. Oxidative Dehydrogenation of Dihydropyrimidinones



1 2

entry	sub.	R_1	R_2	yield (%)[a]
1	**1a**	Ph	Me	80
2	**1b**	*p*-MeO-Ph	Me	83
3	**1c**	*p*-F-Ph	Me	93
4	**1d**	*p*-Cl-Ph	Me	85
5	**1e**	*p*-Me-Ph	Me	84
6	**1f**		Me	97
7[b]	**1g**		Me	–
8	**1h**	Ph	*i*-Pr	93
9	**1i**	*p*-F-Ph	*i*-Pr	97
10[c]	**1j**	*i*-Pr	Ph	77
11[d]	**1a**	Ph	Me	8
12[e,f]	**1a**	Ph	Me	–

[a] Isolated yield. [b] Mixture of diastereomers. [c] Ethyl ester. [d] In the absence of Cu catalyst. [e] In the absence of TBHP. [f] 50 mol % Cu catalyst used.

Only when the substrate possesses oxidatively sensitive functionality did the reaction fail (entry 7). Under forcing conditions,[15] only a mixture of products resulting from benzylic oxidation was obtained. Without the Cu catalyst, a small amount of product was still produced (entry 11).[16] However, without the oxidant, no products were observed even when 0.5 equiv of Cu salt was employed (entry 12).

Most 2-substituted dihydropyrimidines behaved analogously to the dihydropyrimidinones (Table 3). Notably, oxidatively labile functionalities such as thioether and amines were not affected (e.g., entries 1−4, 6, 7, 9, and 10). However, cleavage of the side chain was observed with substrates having a branched C-4[17] substituent (entries 3−6).[18,19] Interestingly, the corresponding dihydropyrimidinone (Table 2, entry 10) did not show this lability.

(11) Evaluation of the reaction stream of the HNO_3 oxidation (for substrate **1i)** with use of an ARC apparatus (Fauske, Inc) determined it to be thermally unstable within the test conditions. A runaway event occurred with an onset temperature of 40 °C, with heat evolution of 157.5 cal/g (adiabatic rise of 205 °C) and severe pressure buildup.

(12) Metal-catalyzed oxidations in related systems: Kuwabe, T.; Okuyama, S.; Hashimoto, S. Jpn. Kokai Tokkyo Koho, 1998, 9 pp; JP 10114755 A2 19980506 Heisei.

(13) In addition to TBHP, H_2O_2, H_2SO_4, bleach, and molecular oxygen were tested. Only TBHP gave >10% (by HPLC area) conversion.

(14) The effect becomes less obvious when more then 0.3 equiv is used. This may be due to saturation of K_2CO_3 in the aqueous phase, which is introduced from the aqueous TBHP solution.

(15) A total of 20 equiv of oxidant was used and the reaction was carried out over an extended period of time.

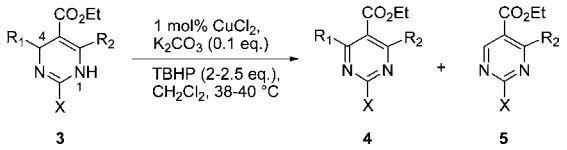
(16) To eliminate trace amounts of Cu salts introduced from the previous step, the substrate was prepared without a Lewis acid catalyst. See the Supporting Information.

(17) The carbon numbering of dihydropyrimidines and dihydropyrimidinones depends on the substituent pattern. For clarity, the numbering for compound **1a** is used for all the substrates in this letter.

(18) Branched side chains are particularly susceptible to oxidation; a similar observation was reported under other oxidation conditions.[3]

(19) An analogous side-chain cleavage was also observed with $Pd(OAc)_2$ catalyst.

Table 3. Oxidative Dehydrogenation of 2-Substituted Dihydropyrimidines



3 4 5

					yield (%)[a]	
entry	sub.	X	R_1	R_2	**4**	**5**
1[b]	**3a**[f]	SMe	*p*-F-Ph	*i*-Pr	>68[h]	
2[b]	**3b**	NHMe	*p*-F-Ph	*i*-Pr	88[i]	
3[c]	**3c**	SMe	*i*-Pr	*p*-F-Ph	21	68
4[d]	**3d**[f]	SMe	*i*-Pr	Ph	25	46
5	**3e**[f]	OMe	*i*-Pr	*p*-F-Ph	42	43
6	**3f**	NHMe	*i*-Pr	*p*-F-Ph	14	63
7	**3g**[f]	SMe	Me	Ph	72	
8	**3h**[f]	OMe	Me	Ph	84	
9	**3i**	NHMe	Me	Ph	80	
10[e]	**3j**[g]	NEt_2	*p*-F-Ph	*i*-Pr	64	

[a] Isolated yield. [b] Methyl ester. [c] 5.5% of the peroxide **15**c (Figure 3) was also isolated. [d] 9% of the peroxide **15d** (Figure 3) was also isolated. [e] Purified by silica gel chromatography. [f] Mixture of double bond isomers. [g] The regioisomer (3,4-dihydro-3) of the shown structure (1,4-dihydro-3). [h] Over two steps. [i] Corrected for the purity of substrate **3b**.

Our mechanistic proposals are drawn from those of known oxidations under analogous conditions. It is well established that Cu salts (as well as Pd, Pt, Co, Fe, etc.),[20] when combined with base, generate the *tert*-butylperoxy radical (*t*-BuOO•) or *tert*-butoxy radical (*t*-BuO•) from TBHP.[21] In one possibility (Figure 1), in the dihydropyrimidinone

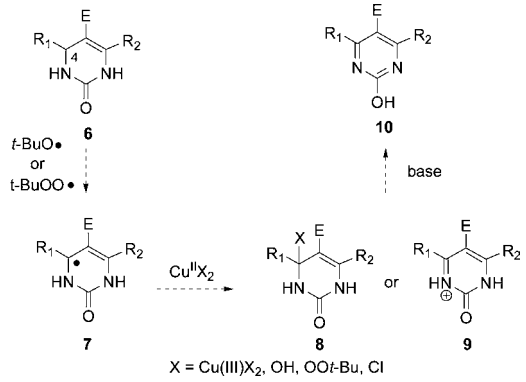


Figure 1. Proposed radical dehydrogenation.

system, the abstraction of hydrogen would most likely occur at C-4, generating intermediate **7**. This radical intermediate would then react with $Cu^{II}X_2$ to give species such as **8** or iminium ion **9**.[22,23] Subsequent base-promoted elimination or deprotonation would lead to aromatized product **10**.

Alternatively, metal-catalyzed dehydrogenations of primary or secondary amines are also well-known.[24] The presumed catalytic cycle drawn analogously to the postulated mechanism involves an initial ligand exchange with $Cu^{II}X_2$ and dihydropyrimidine **6** (Figure 2). Subsequent oxidation

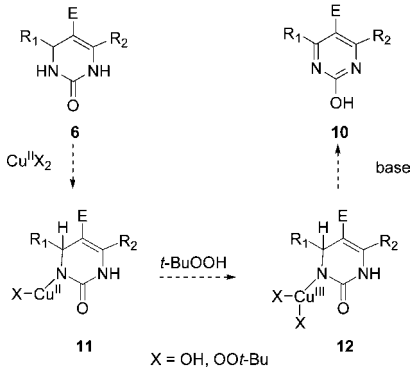


Figure 2. Alternative dehydrogenation.

would generate transient Cu^{III} complex **12**,[25,26] which would reductively eliminate to give the product **10**,[27] simultaneously regenerating the catalyst.[28,29]

We favor the latter mechanism based on several observations.[30] Most notable was the isolation and identification of the peroxide **15** (Figure 3), which possesses the *tert*-butylperoxy group at C-5 (Table 3, entries 3 and 4).[31] The

(20) (a) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727−2730. (b) Yu, J.-Q.; Corey, E. J. *J. Am. Chem.* Soc. **2003**, *125*, 3232−3233. (c) Yu, J.-Q.; Wu, H.-C.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1415−1417.

(21) (a) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1958**, *23*, 324−325. (b) Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1959**, *24*, 72−78. (c) Kochi, J. K. *Tetrahedron* **1962**, *18*, 483−497.

(22) The precise mechanism for the corresponding step in the Kharasch−Sosnovsky reaction has been controversial.[23] While recent evidence points to the presence of a Cu^{III} intermediate,[23a] the detailed mechanistic investigation was not performed in the present study.

(23) (a) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, 845−866 and references sited therein. (b) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 856−865. (c) Minisci, F.; Fontana, F.; Araneo, S.; Recupero, F.; Banfi, S.; Quici, S. *J. Am. Chem. Soc.* **1995**, *117*, 226−232.

(24) Copper: (a) Maeda, Y.; Nishimura, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399−2403. (b) Capdevielle, P.; Lavigne, A.; Sparfel, D.; Baranne-Lafont, J.; Nguyen, K. C.; Maumy, M. *Tetrahedron Lett.* **1990**, *31*, 3305−3308. (c) Capdevielle, P.; Lavigne, A.; Maumy, M. *Synthesis* **1989**, 453−454. Ruthenium: (c) Yamaguchi, K.; Mizuno, N. *Chem. Eur. J.* **2003**, *9*, 4353−4361. (d) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1480−1483. (e) Murahashi, S.-I.; Takaya, H.; Naota, T. *Pure Appl. Chem.* **2002**, *74*, 19−24. (f) Murahashi, S.-I.; Takaya, H. **2000**, *33*, 225−233. Cobalt: (g) Maruyama, K.; Kusukawa, T.; Higuchi, Y.; Nishinaga, A. *Chem. Lett.* **1991**, 1093−1096.

(25) Preliminary kinetic experiments by us suggest that both TBHP and K_2CO_3 are involved in the rate-limiting step (unpublished results).

(26) The possibility of direct conversion from Cu^{II} complex **11** to **10** seemed less likely based on the observation that stoichiometirc oxidation with $Cu^{II}Cl_2$ did not occur (Table 2, entry 12).

(27) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351−360.

(28) Alternatively, the dehydrogenation is also possible via a radical cation formed from **6** by a single electron transfer (SET) followed by deprotonation and a second SET. Since SET is generally veiwed as the Cu^{II}/Cu^{I} process,[29] we felt it is less likely the case for our system,[26] but cannot exclude the possibility. We thank one of the reviewers for drawing our attention to this pathway.

(29) Rorabacher, D. B. *Chem. Rev.* **2004**, *104*, 651−697.

(30) As part of our exploratory study, a selection of heterocycles were tested for the dehydrogenation, which further suport the mechanism dipicted in Figure 2. See the Supporting Information.

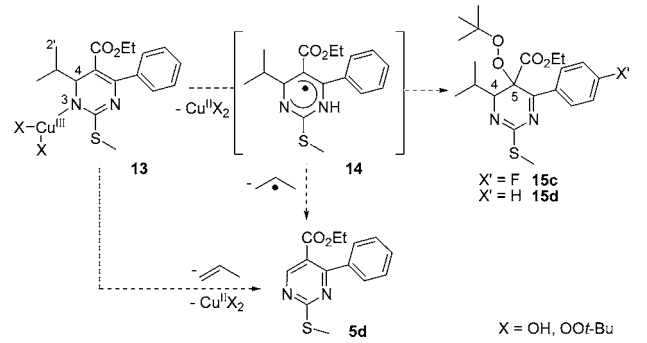


Figure 3. The formation of peroxide and isopropyl cleavage.

former mechanistic hypothesis (Figure 1) involves activation at C-4, which inherently precludes substitution at C-5.

As shown in Figure 3, formation of the peroxy substituent at C-5 can be explained when assuming the mechanism illustrated in Figure 2 (Figure 3). When the deprotonation at C-4 is slow (such as in the case with a sterically hindered branched side chain),[32] intermediate **13** could undergo alternative pathways including homolytic cleavage to radical **14**, which would then react with (presumed) Cu(OO*t*-Bu)$_x$ to peroxide **15d**.[23b,c,33]

The cleavage of the isopropyl group can also be explained by the general mechanism shown in Figure 2. Again due to steric considerations, deprotonation at C-2′ of intermediate **13** could compete with that at C-4. This would lead to side-chain cleavage upon elimination of propene, giving compound **5d**. Alternatively, loss of propyl radical from **14** would also give **5d**.

In summary, a mild, practical procedure for dehydrogenation of dihydropyrimidines and dihydropyrimidinones, has been developed, and demonstrated on a large scale.[34] A mechanistic proposal involves coordination of the metal catalyst to NH moiety, followed by oxidative elimination of the resulting metal complex. It would be of interest to explore a combination of ligands and oxidants that are known to be effective in related catalytic oxidations.[35] Efforts toward further mechanistic understanding and extension of this oxidative dehydrogenation are currently underway.[36]

Acknowledgment. We thank Drs. Rodney Parsons, David Kronenthal, Richard Mueller, and Percy Manchand for their valuable suggestions and encouragements. We also thank Dr. Kishta Katipally for helpful discussions and for providing compound **3j**. Dr. Francis Okuniewicz is acknowledged for assessment of the thermal stability of the reaction stream, Dr. Charles Pathirana for his assistance in structural determination of compound **15**, Dr. Michael Peddicord for obtaining HRMS data, as well as Ms. Louise Zelenkow and Elizabeth Khattak for obaining IR data. Profs. Donna Blackmond, Barry Carpenter, Barry Trost, and Erik Sorensen are also acknowledged for valuable consultations.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) The structure of peroxide **15d** was determined by 2D-NMR (see the Supporting Information).

(32) Preliminary results on isotope effects suggest that the cleavage of the C−H bond at C-6 is involved in the rate-limiting step.

(33) It is possible that peroxide **15** participates in the main catalytic cycle. However, although peroxide **15** converted to **10** when resubjected to the reaction conditions, we think it is less likely to be the main pathway, due to a significant rate difference ($t_{1/2} \sim 18$ h) relative to the typical reaction profile observed ($t_{1/2} \sim <30$ min).

(34) A representative procedure is as follows: A reactor was purged with nitrogen and charged with dihydropyrimidine **1i** (700 g, 2.39 mol, 1.0 equiv), $CuCl_2$ (3.25 g, 0.024 mol, 1.0 mol %), K_2CO_3 (33.1 g, 0.243 mol, 0.1 equiv), and CH_2Cl_2 (7.0 l). The suspension was heated to 35 °C and treated with *tert*-butylhydroperoxide (70% aqueous solution) (635.0 g, 677.2 mL, 2.0 equiv) over 120 min with vigorous agitation. After 24 h, HPLC indicated the consumption of the starting material (<3% by relative HPLC area). The solution was cooled to 20−25 °C, treated with a mixture of aqueous $Na_2S_2O_3$ (0.5 M solution, 7.0 l), and 25 w/w % aqueous NH_4Cl (3.5 l), and the resulting biphasic mixture was stirred vigorously for 60 min. The pH of the aqueous phase should be ∼7.5−8.0 at this point. The two phases were separated, and the absence of remaining oxidant in the aqueous phase was checked by peroxide test strip. (Additional washing with thiosulfate solution should be added when necessary.) The organic phase was concentrated to the minimum agitation volume (ca. 2.0−2.5 l) via reduced pressure distillation. During this time, the product precipitated out from the solution as a white solid. A solvent exchange to heptane was performed by repeated heptane addition (2.5 l) and distillation (1−2 times) until the amount of residual CH_2Cl_2 is below 10 v/v % CH_2Cl_2/heptane by GC area. The product was collected by filtration and washed with the filtrate (2.0 l), then heptane (1.0 l), and the wet cake was dried under vacuum (∼27−29 Torr) at 40 °C. The product **2i** (666.1 g, 2.29 mol, 96% yield) was obtained as a white powder, with requisite spectroscopic properties. This procedure has been performed on a ∼400 kg (input) scale without incident.

(35) (a) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343−3352. (b) Steinhoff, B. A.; Guzei, I. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 11268−11278. (c) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362−367.

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