Synthesis of 2,6,8,12-tetraacetyl- 2,4,6,8,10,12-hexaazaisowurtzitane (TAIW) from 2,6,8,12-tetraacetyl- 4,10-dibenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADBIW) by catalytic hydr...

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9 PUBLICATIONS **154** CITATIONS

Synthesis of 2,6,8,12-Tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (TAIW) from 2,6,8,12-Tetraacetyl-4,10-dibenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADBIW) by Catalytic Hydrogenolysis Using a Continuous Flow Process

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Ⓢ Supporting Information

ABSTRACT: Synthesis of 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (TAIW) by catalytic hydrogenolysis of 2,6,8,12-tetraacetyl-4,10-dibenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADBIW), a key step for the synthesis of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (HNIW), has been first implemented under continuous flow conditions using the commercially available H-Cube Pro reactor. Several variables (i.e., reaction temperature, flow rate, and pressure) and the stability of the system have been investigated to optimize the operating conditions. The results show that a continuous flow system provides a better yield than a batch system. For instance, the yield is 99% at the optimized conditions, while the best yield from batch reactions is 92%. Continuous flow synthesis of TAIW has potential applications in improving the production technologies of HNIW for its many advantages over batch reactions.

1. INTRODUCTION

High energy density materials (HEDMs) of the strained ring and cage family are promising materials applied to rocket, propellant, and explosive chemistry.[1−4] 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (HNIW or CL-20) has attracted great interest as powerful HEDM, which offers superior performance to current benchmark explosives cyclotetramethylenetetranitramine (HMX) and cyclotrimethylene trinitramine (RDX). Therefore HNIW has been well entrenched as not only the most powerful explosive today but also a clean, combustion-efficient oxidizer for futuristic propellants.[5−8]

A considerable amount of research on the synthesis of HNIW has been reported[9−13] since Nielsen and co-workers first prepared HNIW.[14] All of the known methods of preparing HNIW are based on the same starting material, 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (HBIW, Scheme 1), the condensation product of benzylamine and glyoxal.[14] Direct nitration of HBIW to afford HNIW is impractical for the framework disintegration of HBIW and the competing nitration of phenyl rings, and thereby the debenzylation of HBIW by catalytic hydrogenolysis prior to nitration becomes necessary.[15] HBIW is first reductively acylated to form 2,6,8,12-tetraacetyl-4,10-dibenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADBIW, Scheme 1),[14] which could be converted to different nitration precursors under different reaction conditions (Scheme 1): nitrosation of TADBIW will lead to 2,6,8,12-tetraacetyl-4,10-dinitroso-2,4,6,8,10,12-hexaazaisowurtzitane (TADNSOIW);[14] catalytic hydrogenolysis of TADBIW in formic acid will lead to 2,6,8,12-tetraacetyl-4,10-diformyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADFIW),[16,17] and catalytic hydrogenolysis of TADBIW in acetic acid will lead to 2,6,8,12-tetraacetyl-

2,4,6,8,10,12-hexaazaisowurtzitane (TAIW).[18] Among all the nitration precursors, TAIW has appeared as a favorable compound in terms of product purity and a certain degree of process economy.[19−22] Besides, the larger amount of catalysts required in preparing TAIW than for preparing TADBIW makes this process a priority of research for cost reduction in HNIW production.

Catalytic hydrogenolysis of TADBIW is traditionally carried out using batch reactors, with the highest reported yield being 92%.[18] Further improvement based on the reported high yield seemed to be difficult with such batch-type synthetic method. Besides, batch reactions bring many practical disadvantages such as removal of air from the reactor, treatment of the pyrophoric and toxic catalysts, safety concern from the large amount of available hydrogen gas storage, poor mass and heat transfer of the three-phase reaction due to poor mixing (this is more pronounced at the scaled-up stage). Batch-type catalytic hydrogenolysis of TADBIW is therefore a time-consuming and hazardous process.

Additionally, increased levels of environmental awareness dictate that it has provided thrust to research in complicated chemistry survey free from pollution.[23−28] Conventional batch reactions are subject to rapid change, and readily accessible technologies that support automation and green synthesis are attracting increasing interest of chemists.

The development of high-yielding and green hydrogenolysis technology that can be relatively easily handled for use would

Scheme 1. Practicable synthetic routes for preparing HNIW[a]
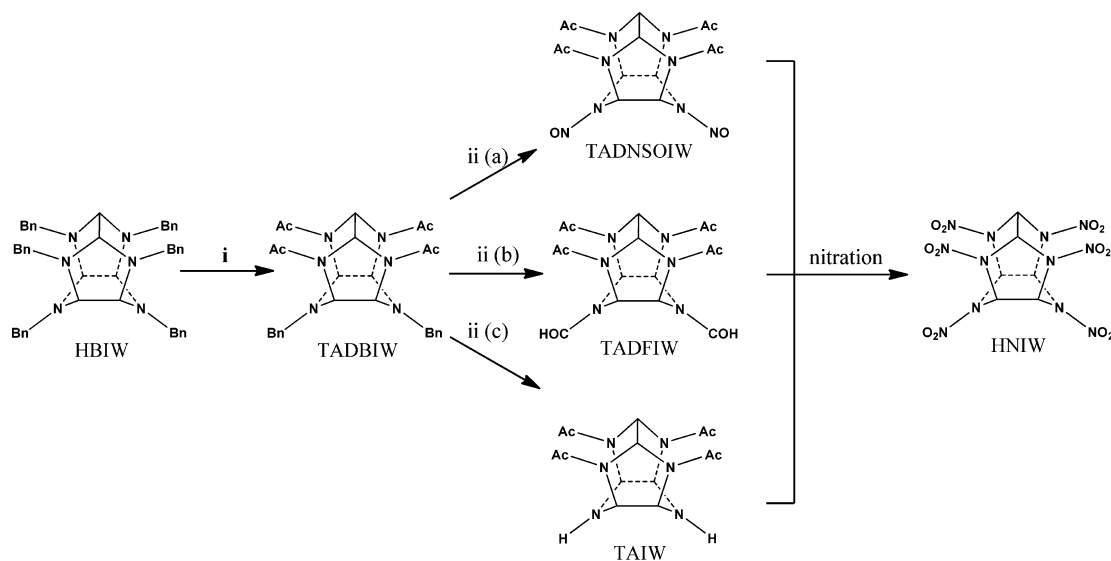
[a]Reaction conditions: i. DMF, Ac_2O, PhBr; H_2; Pd catalyst; ii. (a) NOBF_4 or N_2O_4; (b) HCOOH; H_2; Pd catalyst; (c) AcOH, H_2O; H_2; Pd catalyst.

therefore be a highly valued tool in chemical synthesis. In recent years, continuous flow systems have emerged as increasingly accepted methods, and the advantages of continuous flow synthesis, especially its high-yielding synthesis and easy scale-up, have been discussed extensively.[29−38] Although various continuous flow reactors have been designed and applied in chemical research, many of them could not achieve ideal automaticity or high efficiency.[39−45] In this work, the commercially available H-Cube Pro (Figure S1, Supporting Information [SI]), a continuous flow reactor that showed its unique advantages in recent studies,[46−50] was used for improving the synthesis of TAIW. First, the inventory of hydrogen gas in the H-Cube Pro was minimal but still remained at a high ratio versus substrate, which eliminated the security risk of hydrogen gas storage, and risk of hydrogen gas starvation in the hydrogenolysis process. Second, in the continuous flow reactor, the reactant solution was passed through a catalyst cartridge, and the product solution without catalysts was obtained, achieving automatic isolation of the catalyst and the product. Third, a small flow in this system could provide high surface to volume ratio that allowed for excellent heat and mass transfer, especially for scaled-up applications. Last but not least, the H-Cube Pro was convenient for condition control, which facilitated the optimization of preparing TAIW, and the requirement for less reactant made it more economic and eco-friendly.

Herein, we report a green and high-yielding synthetic method of preparing TAIW under continuous flow conditions, using the commercially available H-Cube Pro reactor. Several variables (i.e., temperature, flow rate, and pressure) and the stability of the system for the hydrogenolysis of TADBIW were investigated to optimize the reaction conditions.

2. Results and Discussion. The reactant solution flowed continuously into the H-Cube Pro equipped with an HPLC pump for hydrogenolysis reaction. It is worth noting that dilution of the reactant solution would be adverse to the improvement of the production efficiency, while concentrated reactant solution was difficult to obtain due to the poor solubility or dissolution rate of the substrate in acetic acid. The solution with a concentration of 40 mg/mL was selected for

our experimental protocol in view of both solubility and efficiency, because TADBIW could be dissolved in acetic acid with the aid of ultrasonic treatment in a relatively short period of time. The two-line inlet valve attached to the HPLC pump helped realize the aim of switching between solvent and reactant without sucking air into the system (the remaining air bubbles in the inlet lines were removed before the experiment). The high-purity hydrogen gas was generated by in-situ high-pressure electrolysis of deionized water, and the maximum production rate of hydrogen gas (approximate 60 mL/min) was used in this work. The hydrogen gas and the reactant solution were mixed, preheated, and transferred to a catalyst cartridge, which was preloaded with 330 mg 10%Pd/C (approximate 65% water wet) catalysts and had two filter systems at either end. The filter systems could allow liquid flow in and out and keep the catalysts in the catalyst cartridge. The product solution then flowed out of the cartridge and was collected in a vial for HPLC analysis. Our exploratory investigation on the stability of the reaction process based on the conversion and the yield helped us achieve good feedback, which provided the basis for our sampling the flow for HPLC analysis. The passage of the reactant solution and the design of the H-Cube Pro are shown in the SI (Figures S2 and S3). Ou et al. reported 2,6,8,12-tetraacetyl-4-monobenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (TAMBIW, Scheme 2) as the final product of TADBIW hydrogenolysis in acetic acid,[51] which did not meet our previous experimental results.[18] This work has indicated that TAMBIW is an intermediate of TADBIW hydrogenolysis to prepare TAIW in acetic acid (Scheme 2), and TAMBIW has been characterized by HPLC−MS analysis (SI, Figure S5).

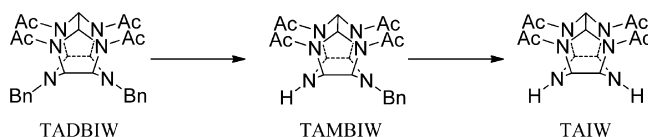**Scheme 2. Hydrogenolysis of TADBIW in acetic acid and water**

Table 1. Effects of investigated variables of the system on the hydrogenolysis of TADBIW under continuous flow conditions[a]

entry	flow rate (mL/min)	T (°C)	P (MPa)	conv. (%)	selectivity (%)[b]		production rate (g/h)[c]
					TAMBIW	TAIW	
1	0.3	40	1	95	27	69	–
2	0.3	40	2	99.4	10	88	–
3	0.3	45	1	100	<1	97	–
4	0.3	45	2	100	0	99	0.46
5	0.3	50	1	100	0	98	0.46
6	0.3	60	1	100	0	99	0.46
7	0.5	50	1	92.2	22	73	–
8	0.5	50	3	99.7	3	96	–
9	0.5	50	4	99.9	2	97	–
10	0.5	50	5	100	0	99	0.77
11	0.5	60	1	99	3	96	–
12	0.5	60	2	100	0	98	0.77
13	0.5	70	1	100	0	97	0.76
14	0.8	70	1	100	0	94	1.18
15	0.8	90	1	100	0	94	1.18

[a]The data was collected by sampling and analyzing the product flow by HPLC analysis. [b]Selectivity is calculated on the basis of the consumed TADBIW. The selectivity of TAIW is equal to its yield in complete reactions. [c]The production rate of TAIW is calculated as follows: Flow rate (mL/min) × (40 × M_{TAIW}/M_{TADBIW}) (mg/mL) × selectivity × 60 (min/h) × 0.001 (g/mg)

Temperature Investigation. Temperature normally acts as an important reaction parameter, and the experimental results given in Table 1 (entries 1, 3, 5−7, 11, 13−15) have shown the effect of temperature as the single variable on the hydrogenolysis of TADBIW. Initially the pressure was set at 1 MPa, and the effect of changing temperature was studied at different flow rates. That is, entries 1, 3, 5, 6 have studied the effects of 40, 45, 50, 60 °C on this reaction at 1 MPa and 0.3 mL/min (case 1), in which case the lowest flow rate of the H-Cube Pro was chosen; entries 7, 11, 13 have studied the effects of 50, 60, 70 °C on this reaction at 1 MPa and 0.5 mL/min (case 2); entries 14, 15 have studied the effects of 70, 90 °C on this reaction at 1 MPa and 0.8 mL/min (case 3). We found that the minimum temperatures for complete reaction of the above three cases were 50, 70, 70 °C, respectively. After further decrease of the temperature for each case, the 40 mg/mL solution could not react completely after one run of flow through the 330 mg catalysts, resulting in TADBIW or TAMBIW remaining. All the yields of TAIW under continuous flow conditions were higher than the reported highest yield under batch conditions, and the highest yields in this work could reach 98−99%. However, the yield was on a declining trend as the reaction was implemented above 70 °C, indicating that high temperature was adverse for the reaction.

Flow Rate Investigation. Flow rate behaves as a valuable parameter to improve the production efficiency. In particular, the flow rate could be increased accordingly in order to increase the output in large-scale applications, as a larger catalyst cartridge will be used. Thus, the effect of flow rate was then investigated. The pressure was set at 1 MPa, and the effect of changing flow rate was studied. The experimental results are given in Table 1 (entries 5, 7, 11, 13, 14). We found that as the flow rate was increased, the reaction was more difficult to complete. For instance, hydrogenolysis of TADBIW could give 100% conversion at 0.3 mL/min, 50 °C and 1 MPa, but the conversion was decreased from 100% to 92.2% as the flow rate was increased from 0.3 mL/min to 0.5 mL/min. The best result was given as the temperature was increased to 70 °C at 0.5 mL/min and 1 MPa. It was well understood because the flow rate is inversely proportional to the residence time, and higher flow rates refer to reduced reaction time, resulting in a tendency for incomplete reaction. The production rates at different flow rates under the optimized conditions were also calculated and are given in Table 1.

Pressure Investigation. The H-Cube Pro provides easy methods for the experimental control of the pressure, and the effect of pressure on the reaction was investigated (entries 1−4 and 7−12). As the experimental results show in Table 1, the pressure was also an important influencing factor in the catalytic hydrogenolysis of TADBIW, and increasing pressure was beneficial to the reaction. Taking entries 7−10 for example, the conversion of TADBIW increased from 92.2% to 100% as the pressure was increased from 1 MPa to 5 MPa, and no negative impact was generated at the same time. Entries 4 and 12 have also proved this point. These results were meaningful because the production efficiency of TAIW could be improved by increasing the flow rate and pressure at moderate temperature, while avoiding the negative impact of high temperature on the reaction.

Catalyst Performance over Time at the Optimized Conditions. The catalyst cartridge of the H-Cube Pro could accommodate 330 mg 10%Pd/C (approximate 65% water wet) catalysts, and the 40 mL/ml reactant solution flows continuously into the cartridge for reaction. The catalyst performance over time of this continuous process was studied to prove the stability of the system. One of the optimized reaction conditions, namely, 0.3 mL/min, 60 °C, and 1 MPa was selected as the object of investigation by sampling the flow at set intervals, and the experimental process was tracked by HPLC analysis. The conversion and yield over time are shown in Figure 1. Hydrogenolysis of TADBIW could proceed in full conversion and high yield for >120 h without any deactivation, during which process the yield was slightly floating but within the error range allowed.

3. CONCLUSION

Continuous flow synthesis of TAIW by catalytic hydrogenolysis of TADBIW was first implemented using the commercially available H-Cube Pro. Several variables and the catalyst stability of the system have been investigated to optimize the operating
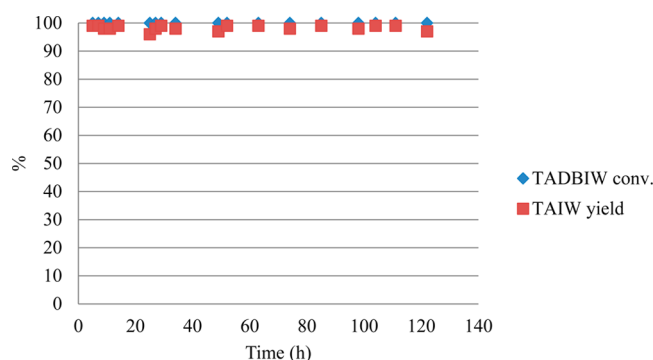
Figure 1. Conversion of TADBIW and the yield of TAIW over time in the hydrogenolysis of TADBIW under continuous flow conditions.

conditions. The hydrogenolysis conditions that afford full conversion and high yield under this continuous flow process have been obtained, and this process could continue to work for long periods of time without any deactivation of the catalysts. This attractive flow mode presents several distinct advantages over the batch process. To be specific, the excellent mixing and heat and mass transfer properties afford the synthesis of TAIW particular high yield. The requirement for less hydrogen gas storage and reactant solution for reaction optimization makes the continuous flow hydrogenolysis of TADBIW safer and more eco-friendly. The research process is highly efficient for the simplification of processing operations, and the H-Cube Pro facilitates the control of the reaction variables studied. The research results in this work provide guidance for the scaled-up hydrogenolysis of TADBIW under continuous flow conditions, and continuous flow synthesis of TAIW has potential applications in improving the production technologies of HNIW.

4. EXPERIMENTAL SECTION

General Method. The equipment for continuous flow hydrogenolysis was an H-Cube Pro 1.00 model with software version 1.0.0.9. The HPLC pump was a KNAUER Smartline Pump 100. TADBIW and TAIW were self-prepared and recrystallized with glacial acetic acid and water several times before use. The purities of TADBIW and TAIW were examined using the area normalization method. The response factor of TAMBIW was estimated (SI). TAIW and TADBIW concentrations were analyzed by HPLC (Agilent 6100 series) with the standard curve method. TAMBIW concentration was estimated using the response factor. Glacial acetic acid was purchased from Aladdin Reagent Inc., and water was purchased from Watsons Group Ltd.. Reactant solution was prepared through a ratio of 80 mL glacial acetic acid, 20 mL water, and 4g TADBIW. Reactant solvent was prepared through a ratio of 80 mL glacial acetic acid and 20 mL water. Operational parameters were set on the touch screen.

Representative Experimental Process. The catalyst cartridge, which was preloaded with 330 mg 10%Pd/C (approximate 65% water wet) catalysts, was encased in the column holder. The two inlet lines were inserted into the prepared solution and solvent, respectively. The flow rate was set at 1 mL/min, and the air bubbles in the two inlet lines were removed from the air outlet using the special needle tubing, after which the flow rate was stopped. Then the hydrogen gas production rate, temperature, pressure, and flow rate were set at 100%, 50 °C, 1 MPa, 0.3 mL/min, respectively, on the touch

screen, and the passage line was set at "Solvent" and "Waste" before clicking the "Start" button. After a while, the touch screen showed "Stable" after clicking the "Start" button, which implied that all the selected parameters were ready, followed by switching the passage line to "Reactant" and "Product". The product flow of the first several hours was discarded to avoid cross contamination, and the product flow of the later several hours was collected for HPLC analysis, resulting in 100% conversion and 98% yield.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
H-Cube Pro photo and schematic design, HPLC/MS methods, calculation methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Sikder, A. K.; Sikder, N. *J. Hazard. Mater.* **2004**, *112*, 1−15.
(2) Li, Y. C.; Qi, C.; Li, S. H.; Zhang, H. J.; Sun, C. H.; Yu, Y. Z.; Pang, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 12172−12173.
(3) Zhang, Y. Q.; Parrish, D. A.; Shreeve, J. n. M. *J. Mater. Chem.* **2012**, *22*, 12659−12665.
(4) Dippold, A. A.; Klapötke, T. M. *J. Am. Chem. Soc.* **2013**, *135*, 9931−9938.
(5) Simpson, R. L.; Urtiew, P. A.; Ornellas, D. L.; Moody, G. L.; Scribner, K. J.; Hoffman, D. M. *Propellants, Explos., Pyrotech.* **1997**, *22*, 249−255.
(6) Geetha, M.; Nair, U. R.; Sarwade, D. B.; Gore, G. M.; Asthana, S. N.; Singh, H. *J. Therm. Anal. Calorim.* **2003**, *73*, 913−922.
(7) Talawar, M. B.; Sivabalan, R.; Anniyappan, M.; Gore, G. M.; Asthana, S. N.; Gandhe, B. R. *Combust. Explos. Shock Waves* **2007**, *43*, 62−72.
(8) Badgujar, D. M.; Talawar, M. B.; Asthana, S. N.; Mahulikar, P. P. *J. Hazard. Mater.* **2008**, *151*, 289−305.
(9) Zhao, X. Q.; Fang, T.; Sun, C. H. *Acta Armamentarii* **2004**, *25*, 354−358.
(10) Pang, S. P.; Yu, Y. Z.; Zhao, X. Q. *Propellants, Explos., Pyrotech.* **2005**, *30*, 442−444.
(11) Herve, G.; Jacob, G.; Gallo, R. *Chem.—Eur. J.* **2006**, *12*, 3339−3344.
(12) Gong, X. B.; Sun, C. H.; Pang, S. P.; Zhang, J.; Li, Y. C.; Zhao, X. Q. *Chin. J. Org. Chem.* **2012**, *32*, 486−496.
(13) Bayat, Y.; Hajimirsadeghi, S. S.; Pourmortazavi, S. M. *Org. Process Res. Dev.* **2011**, *15*, 810−816.
(14) Nielsen, A. T.; Chafin, A. P.; Christian, S. L.; Moore, D. W.; Nadler, M. P.; Nissan, R. A.; Vanderah, D. J. *Tetrahedron* **1998**, *54*, 11793−11812.
(15) Bellamy, A. J. *Tetrahedron* **1995**, *51*, 4711−4722.
(16) Agrawal, J. P.; Hodgson, R. D. *Organic Chemistry of Explosives*; John Wiley & Sons: Chichester, U.K., 2007.
(17) Koskin, A. P.; Simakova, I. L.; Parmon, V. N. *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 2370−2375.

(18) Sun, C. H.; Feng, Z. W.; Fang, T.; Zhao, X. Q. *Chin. J. Struct. Chem.* **2005**, *24*, 204−208.

(19) Sun, C. H.; Fang, T.; Yang, Z. Y.; Bai, J. H.; Feng, Z. W. *Chin. J. Energ. Mater.* **2009**, *17*, 161−165.

(20) Mandal, A. K.; Pant, C. S.; Kasar, S. M.; Soman, T. *J. Energ. Mater.* **2009**, *27*, 231−246.

(21) Nair, U. R.; Asthana, S. N.; Rao, A. S.; Gandhe, B. R. *Def. Sci. J.* **2010**, *60*, 137−151.

(22) Bayat, Y.; Mokhtari, J.; Farhadian, N.; Bayat, M. *J. Energ. Mater.* **2012**, *30*, 124−134.

(23) Constable, D. J. C.; Curzons, A. D.; Freitas dos Santos, L. M.; Geen, G. R.; Hannah, R. E.; Hayler, J. D.; Kitteringham, J.; McGuire, M. A.; Richardson, J. E.; Smith, P.; Webb, R. L.; Yu, M. *Green Chem.* **2001**, *3*, 7−9.

(24) Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chem.* **2001**, *3*, 1−6.

(25) Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002**, *4*, 521−527.

(26) Andraos, J. *Org. Process Res. Dev.* **2005**, *9*, 404−431.

(27) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267−278.

(28) Leahy, D. K.; Tucker, J. L.; Mergelsberg, I.; Dunn, P. J.; Kopach, M. E.; Purohit, V. C.. *Org. Process Res. Dev.* **2013**, *17*, 1099−1109.

(29) Anderson, N. G. *Org. Process Res. Dev.* **2001**, *5*, 613−621.

(30) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300−2318.

(31) Kulkarni, A. A.; Nivangune, N. T.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. *Org. Process Res. Dev.* **2008**, *12*, 995−1000.

(32) Wiles, C.; Watts, P. *Eur. J. Org. Chem.* **2008**, 1655−1671.

(33) Kulkarni, A. A.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. *Org. Process Res. Dev.* **2009**, *13*, 999−1002.

(34) Huang, W. Y.; Liu, J. H. C.; Alayoglu, P.; Li, Y. M.; Witham, C. A.; Tsung, C. K.; Toste, F. D.; Somorjai, G. A. *J. Am. Chem. Soc.* **2010**, *132*, 16771−16773.

(35) Baumann, M.; Baxendale, I. R.; Kuratli, C.; Ley, S. V.; Martin, R. E.; Schneider. *J. Comb. Sci.* **2011**, *13*, 405−413.

(36) Calabrese, G. S; Pissavini, S. *AIChE J.* **2011**, *57*, 828−834.

(37) Pesti, J. *Org. Process Res. Dev.* **2012**, *16*, 843−843.

(38) Petersen, T. P.; Larsen, A. F.; Ritzen, A.; Ulven, T. *J. Org. Chem.* **2013**, *78*, 4190−4195.

(39) Stephenson, P.; Licence, P.; Ross, S. K.; Poliakoff, M. *Green Chem.* **2004**, *6*, 521−523.

(40) Clark, P.; Poliakoff, M.; Wells, A. *Adv. Synth. Catal.* **2007**, *349*, 2655−2659.

(41) Kulkarni, A. A.; Nivangune, N. T.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. *Org. Process Res. Dev.* **2008**, *12*, 995−1000.

(42) Kulkarni, A. A.; Kalyani, V. S.; Joshi, R. A.; Joshi, R. R. *Org. Process Res. Dev.* **2009**, *13*, 999−1002.

(43) Kelly, C. B.; Lee, C. X.; Mercadante, M. A.; Leadbeater, N. E. *Org. Process Res. Dev.* **2011**, *15*, 717−720.

(44) Grego, S.; Aricò, F.; Tundo, P. *Org. Process Res. Dev.* **2013**, *17*, 679−683.

(45) Nishioka, M.; Miyakawa, M.; Daino, Y.; Kataoka, H.; Koda, H.; Sato, K.; Suzuki, T. M. *Ind. Eng. Chem. Res.* **2013**, *52*, 4683−4687.

(46) Jones, R.; Gödörházy, L.; Szalay, D.; Gerencsér, J.; Dormán, G.; Ürge, L.; Darvas, F. *QSAR Comb. Sci.* **2005**, *24*, 722−727.

(47) Jones, R. V.; Godorhazy, L.; Varga, N.; Szalay, D.; Urge, L.; Darvas, F. *J. Comb. Chem.* **2006**, *8*, 110−116.

(48) Kovacs, I.; Jones, R. V.; Niesz, K.; Csajagi, C.; Borcsek, B.; Darvas, F.; Urge, L. *JALA* **2007**, *12*, 284−290.

(49) Clapham, B.; Wilson, N. S.; Michmerhuizen, M. J.; Blanchard, D. P.; Dingle, D. M.; Nemcek, T. A.; Pan, J. Y.; Sauer, D. R. *J. Comb. Chem.* **2008**, *10*, 88−93.

(50) Cooper, C. G. F.; Lee, E. R.; Silva, R. A.; Bourque, A. J.; Clark, S.; Katti, S.; Nivorozhkin, V. *Org. Process Res. Dev.* **2012**, *16*, 1090−1097.

(51) Ou, Y. X.; Xu, Y. J.; Chen, J. T.; Chen, B. R.; Zheng, F. P.; Jia, H. C.; Wang, C. *Chem. J. Chin. Univ.* **1999**, *20*, 561−564.