JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

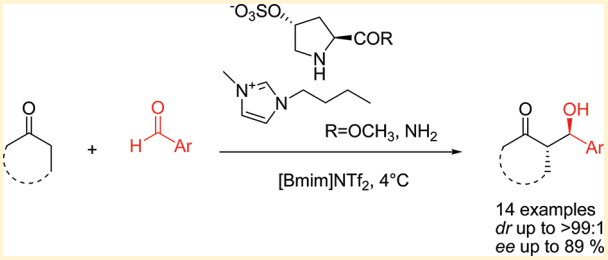
Asymmetric Aldol Reaction Catalyzed by the Anion of an Ionic Liquid

Vincent Gauchot and Andreea R. Schmitzer*

Department of Chemistry, Université de Montréal, C.P. 6128 Succursale Centre-ville, Montréal, Québec, H3C 3J7, Canada

Supporting Information

ABSTRACT: Herein we report the synthesis of a chiral imidazolium salt derived from *trans*-L-hydroxyproline and its applications as a catalyst for the asymmetric aldol reaction. By performing the aldol reaction in [Bmim]NTf_2 as a solvent, we report excellent isolated yields of the aldol product (up to 99%), as well as modest to excellent selectivities (dr superior to 99:1. ee up to 89%). Mechanistic insights and the origins of the selectivity of the aldol reaction are discussed on the basis of the results obtained with two catalytic imidazolium salts having different H-bonding potential.



INTRODUCTION

Organocatalysis, through the use of readily available small chiral molecules as catalysts, has become a field of major interest in the stereocontrolled preparation of chiral adducts.[1−4] Over the last 10 years, the wide application range of organocatalysis has been described through various examples, such as organocatalyzed cycloaddition reactions, desymmetrization reactions, and total synthesis.[5−9] The aldol reaction is one of the most important carbon−carbon bond-forming reactions for the preparation of small optically active molecules. Since Hajos and Parrish described the first organocatalyzed aldol reaction using (*S*)-proline as the catalyst, various examples involving proline and its derivatives demonstrated their efficiency as catalysts for stereoselective organic reactions.[10,11] However, there remain issues regarding the use of environmentally unfriendly solvents such as DMF or DMSO and the difficulties of recycling large quantities of catalysts.

Over the past decade, ionic liquids (ILs) have attracted growing attention as they are becoming greener alternatives to classical organic solvents.[12−14] Several examples have described efficient aldol reactions carried out in IL as solvents.[15−18] More recently, the design and the use of these ionic liquids in combination with chiral catalysts has provided excellent yields and diastereoselectivities. Many examples of functionalized imidazolium cations as catalytic species have been reported in the literature,[19] but so far only two examples of asymmetric aldol reactions catalyzed by a chiral anion have been reported. While the first example reported an enantiomeric excess below 10%,[20] Wang et al. recently described an imidazolium salt catalyst with L-proline as the anion.[21] Using their [Emim][Pro] catalyst, they reported modest to excellent yields and very good selectivities in the aldol reaction.

We present here the supramolecular assistance of the anion of an imidazolium salt in an asymmetric aldol reaction performed in an ionic liquid medium. Using two differents catalysts derived from *trans*-L-hydroxyproline, we discuss mechanistic insights of the reaction, the importance of the functionalization of the carboxylic group of the proline and its role on the stereoselective outcome of the reaction. Carrying out the aldol reaction in [Bmim]NTf_2 using 30 mol % of catalyst led to very good results in terms of yields (up to 99%) and selectivities (dr > 99:1. ee up to 89%). To the best of our knowledge, this is the second example of an asymmetric aldol reaction catalyzed by an anion-modified catalytic ionic liquid providing satisfying conversion and selectivity. The use of ionic liquids both as solvent and catalyst make this methodology attractive in terms of atom economy and green chemistry.

RESULTS AND DISCUSSIONS

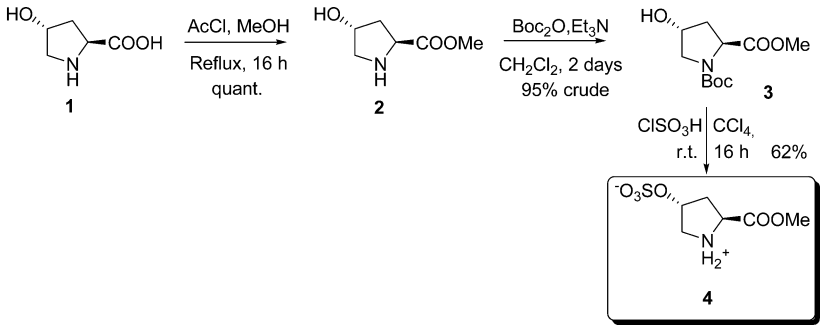
Starting with the readily available *trans*-L-hydroxyproline, the carboxylic acid moiety was first esterified under classic conditions (Scheme 1). Because of solubility issues, protection of the *trans*-L-hydroxyproline methyl ester **2** with a Boc group was necessary in order to proceed to the sulfonation reaction in CCl_4. Sulfonation of the hydroxyl group allowed the simultaneous deprotection of the Boc group, leading to the ester zwitterion **4**. Crystals of **4** suitable for X-ray crystal structure determination were obtained by diffusion of ether to a methanol solution (see the Supporting Information).

Since typical anion metathesis was unsuccessful, the formation of [Bmim]OH as a nonisolable intermediate was required for the anion exchange. The preparation of [Bmim]-OH was performed using an Amberlite IRA-400 hydroxide form resin, and the anion metathesis was then performed (Scheme 2).

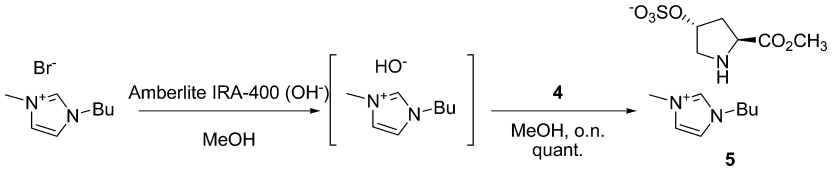
A typical aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone was carried out in several solvents using 30 mol % catalyst loading, according to the previously described conditions for this type of reaction.[21] Whether the reaction was carried out in typical organic solvents or IL, a very long reaction

Received: November 16, 2011
Published: May 14, 2012

Scheme 1. Synthesis of the Anion

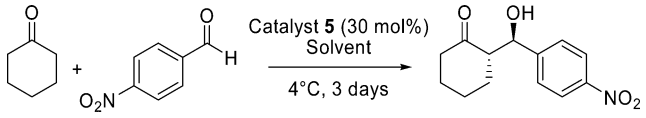


Scheme 2. Preparation of the Catalyst



time was required (Table 1). TLC analysis revealed that some reactions were still incomplete after 5 days.

Table 1. Solvent Screening[a]



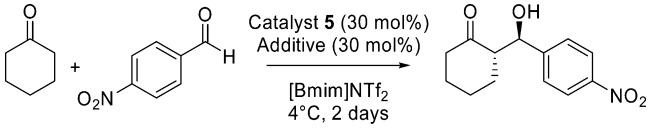
entry	solvent	yield (%)	dr (anti/syn)[b]	ee (anti)[c] (%)
1	[Bmim]BF_4	37 (82)[d]	66:34 (71:29)[d]	46 (55)[d]
2	[Bmim]PF_6	51 (82)[d]	76:24 (73:27)[d]	60 (52)[d]
3	[Bmim]NTf_2	53 (89)[d]	76:24 (75:25)[d]	57 (55)[d]
4	MeOH	53 (73)[d]	62:38 (68:32)[d]	22 (30)[d]
5	DCM	41 (66)[d]	75:25 (76:24)[d]	40 (30)[d]
6	DMSO	22 (73)[d]	72:28 (64:36)[d]	34 (40)[d]
7	DMF	20 (16)[d]	71:29 (73:27)[d]	79 (75)[d]
8	neat	82 (98)[d]	59:41 (58:42)[d]	44 (60)[d]

[a]Conditions: A solution of cyclohexanone (0.3 mmol) and catalyst (30 mol %) in solvent (0.3 mL) was stirred for 30 min at 4 °C. *p*-Nitrobenzaldehyde (0.1 mmol) was added, and the mixture was stirred for 72 h at 4 °C. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC. [d]Results in parentheses were obtained when acetic acid was used as an additive; reaction time was 48 h.

ILs led to better enantioselectivites than common organic solvents. As it was previously demonstrated that the formation of the enamine intermediate should be enhanced by a catalytic source of acid, a solvent screening study was performed using acetic acid (30 mol %) as an additive. As shown in Table 1, the overall trend for the addition of acid was to reduce the reaction time, though selectivity was unchanged. Increasing solvent polarity had little effect on diastereoselectivity, but generally offered a slight improvement of ee. Performing the reaction in neat conditions predictably afforded excellent yields, but poor selectivity. Within this series, the ionic liquids ([Bmim]BF_4, [Bmim]PF_6, and [Bmim]NTf_2), offered the best combination of good yields and selectivities. Best results were achieved in [Bmim]PF_6, and [Bmim]NTf_2, but since PF_6-derived ILs are known to release HF,[22] we further explored the [Bmim]NTf_2 system by improving the reaction conditions and recyclability.

With the goal of optimizing the reaction conditions, various acidic additives were tested for the aldol reaction (Table 2).

Table 2. Influence of Acidic Additives



entry	additive	yield (%)	dr (anti/syn)[a]	ee (anti)[b] (%)
1	none	43	76:24	57
2	*p*-TSA	6	57:43	rac
3	TFA	11	75:25	rac
4	3,5−DNBA	63	74:26	47
5	benzoic acid	64	71:29	41
6	acetic acid	72	75:25	52

[a]Determined by ^{1}H NMR. [b]Determined by chiral HPLC.

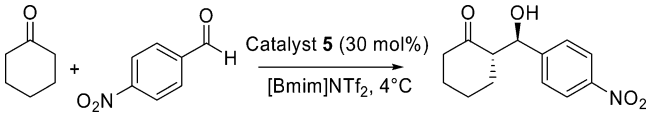
With the exception of acetic acid, the decrease of selectivity in spite of a shorter reaction time suggests a kinetic control of the reaction, where the formation of the racemate is favored, instead of one particular enantiomer. Another indication of kinetic control was the lower selectivity observed when performing the reaction at room temperature. Strong inhibition of the aldol reaction was observed in the presence of TFA and *p*-TSA: these acids are strong enough to protonate the counteranion of the catalyst (pK_a of 0.3 and −2.8, respectively), leading to anion metathesis and destruction of the catalyst, explaining the poor yields, and selectivities.

A variation of the medium concentration was also tested using [Bmim]NTf_2 as solvent with catalyst **5**. As a general trend, it was observed that increasing the concentration of the reaction medium reduced the reaction time was, and led to better selectivities (Table 3). In an attempt to further decrease the reaction time, the reaction was carried out at the highest concentration tested, using acetic acid as additive, and we were surprised to observe that enantioselectivity plummeted.

Based on reaction results in neat conditions, we observed that adding 10 equiv of cyclohexanone instead of 3 allowed the reaction to be completed in 2 days, with higher dr (86:14) and

dx.doi.org/10.1021/jo300737u | J. Org. Chem. 2012, 77, 4917−4923

Table 3. Concentration Studies[a]

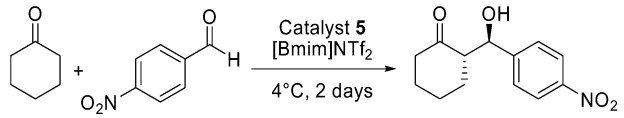


entry	[aldehyde] (mol·L^{-1})	dr (anti/syn)[b]	ee (anti)[c] (%)
1	0.33	76:24	57
2	0.40	75:25	65
3	0.50	76:24	71
4	0.66	81:19	69
5	1	89:11	73
6[d]	1	71:29	29
7[e]	1	86:14	86

[a]All reactions were arbitrarily stopped after 16 h. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC. [d]Reaction was carried out using acetic acid as a additive (30 mol %). [e]10 equiv of cyclohexanone; reaction time was 2 days

ee (86%) (entry 7). Using these optimized conditions, a lower catalyst loading only resulted in a longer reaction time and lower selectivities (Table 4).

Table 4. Influence of Catalyst Loading



entry	catalyst loading (%)	yield (%)	dr (anti/syn)[a]	ee (anti)[b] (%)
1	30	83	86:14	86
2	20	35	83:17	81
3	10	17	73:27	75

[a]Determined by ^{1}H NMR. [b]Determined by chiral HPLC.

To broaden the scope of our catalyst **5**, we performed the asymmetric aldol reaction for different cyclic ketones under the optimized conditions, using *o*-, *m*-, or *p*-nitrobenzaldehydes. As shown in Table 5 (entries 1−6), apart from cycloheptanone, the reaction proceeded with good yields and generally good ee However, when performing the aldol reaction with other aldehydes, no aldol product was observed, probably due to both the lower reactivity of these aldehydes and the steric hindrance induced by the methyl group of the catalyst.

Based on these observations, we designed another catalyst anion bearing a hydrogen bond donor functional group. Zwitterion **6** was obtained by dissolving **4** in concentrated NH_4OH, and catalyst **7** was prepared using the same conditions used for catalyst **5** (Scheme 3). We expected this new catalyst **7** to be more efficient toward less reactive aldehydes through activation by hydrogen bonding with these aldehydes and to have the properties required to participate and control the stereoselectivity of the reaction.

Carrying out the aldol reaction with less activated aldehydes and catalyst **7** gave access to aldol products that catalyst **5** could not produce, with good to excellent yields, as well as excellent selectivities (Table 5, entries 7−13). Less reactive aldehydes, such as 2-naphtaldehyde or 2-thiophenecarboxaldehyde gave only low to moderate yields, even after longer reaction times, but still led to the aldol product with excellent diastereo- and enantioselectivities. These results highlighted the assistance of the amide group in the reaction, by activating the aldehydes through hydrogen bonding. Nonetheless, when catalyst **7** was used in our model reaction of cyclohexanone with *p*-nitrobenzaldehyde, a qualitatively faster reaction was observed, but with a lower selectivity. Catalyst **5** gave a complexe mixture of regioisomers when using linear ketones, but using catalyst **7** with 2-butanone as substrate, only one regioisomer was obtained in good yields and selectivities (entry 14).

In terms of mechanism, our first hypothesis was that the steric hindrance of the methyl group of the ester moiety on the anion was the main source of the selectivity of the reaction when using catalyst **5** (Figure 1 (1)). The methyl group should be bulky enough to hinder the approach of aldehyde to the enamine intermediate, and favor the approach by the opposite face. However, catalyst **7**, able to form H-bonds with the aldehyde (Figure 1 (2)) and direct its approach, led to the same major enantiomer and a 3-fold shorter reaction time (16 h instead of 48 h). The amide group, by hydrogen bonding, may be responsible for directing the approach of the aldehyde toward the enamine while activating the aldehyde. It is reasonable to propose a similar transition state using catalyst **5**, but steric hindrance of the ester moiety may be the source of the lower reactivity. None of our experiments confirmed the implication of the imidazolium cation in the transition state, as proposed previously.[21]

As the major obtained stereoisomers are the same using either the ester or the amide catalyst, discrimination between the two faces of the reaction intermediate when approaching the aldehyde could be attributed to the position of the imidazolium cation close to the sulfonate group (Figure 1 (3)). The imidazolium cation, being localized near the negative charge on the proline derivative, may block the approach of the aldehyde on this side and allow the formation of the *anti* diastereomer.

Molecular modeling was performed to confirm the proposed transition states and, as shown in Figure 2(2), the resulting models support the experimental results. The imidazolium cation is close to the negative charge of the sulfate group (1), which sterically hinders the approach of the aldehyde (2) on this side.

The possibility to recycle the catalyst and the ionic liquid was also proven for cyclohexanone and *p*-nitrobenzaldehyde reaction(Table 6). Up to five catalytic runs were achieved, with only a small decrease in the catalytic efficiency of our system.

■ CONCLUSION

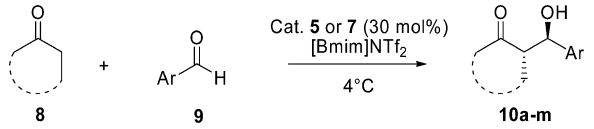
In conclusion, we report the supramolecular assistance of an imidazolium-based chiral catalyst in asymmetric organic synthesis. The mechanistic insights of the asymmetric aldol reaction allow us to propose that the same proline-based catalyst can be used in other reactions involving enamine intermediates, such as the Michael addition. Up to five catalytic cycles were performed using the same conditions, illustrating the recyclability of this setup. The ease of switching the anion encouraged us to develop a new recycling method, as well as the design of other catalytic anions are currently underway in our group.

■ EXPERIMENTAL SECTION

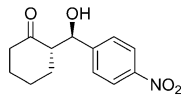
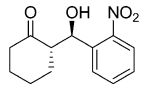
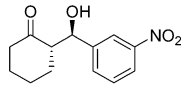
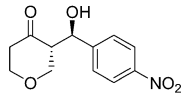
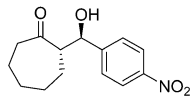
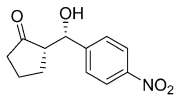
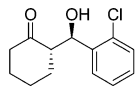
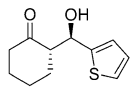
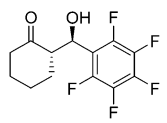
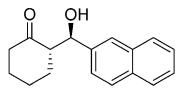
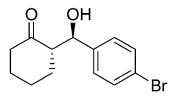
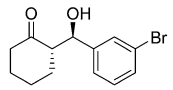
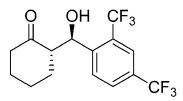
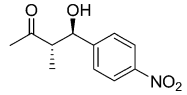
Materials. All organic compounds were obtained commercially and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on 400, 300, 100, and 75 MHz spectrometers, respectively, in the indicated solvent. Chemical shifts are reported in ppm with internal reference to TMS, and *J* values are given in Hertz. All HPLC

dx.doi.org/10.1021/jo300737u | J. Org. Chem. 2012, 77, 4917−4923

Table 5. Substrate Scope



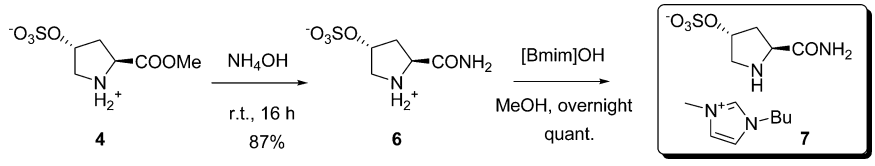
8 9 10a-m

Entry		Product	Catalyst	Time	Yield	*dr* (anti:syn)[a]	*ee.*(anti)[b]
10a	1		**5**	2 days	83%	84:16	4%/86% (syn/anti)
			7	16h	82%	75:25	76%
10b	2		**5**	2 days	82%	97:3	69%
10c	3		**5**	2 days	77%	85:15	67%
10d	4		**5**	2 days	99%	83:17	56%
10e	5		**5**	5 days	33%	66:34	16%
10f	6		**5**	2 days	71%	37:63	16%
10g	7		**7**	2 days	93%	>99:1	89%
10h	8		**7**	5 days	11%	95:5	85%
10i	9		**7**	2 days	92%	>99:1	88%
10j	10		**7**	4 days	38%	84:16	77%
10k	11		**7**	2 days	49%	98:2	83%
10l	12		**7**	2 days	70%	78:22	75%
10m	13		**7**	2 days	80%	>99:1	88%
10n	14		**7**	2 days	58%	62:38	76%

[a]Determined by ^{1}H NMR. [b]Determined by chiral HPLC.

dx.doi.org/10.1021/jo300737u | *J. Org. Chem.* 2012, 77, 4917−4923

Scheme 3. Preparation of Catalyst 7



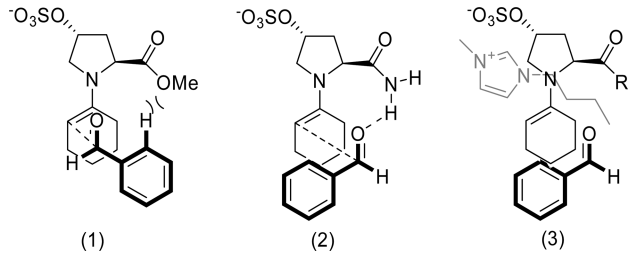


Figure 1. Proposed transition states.

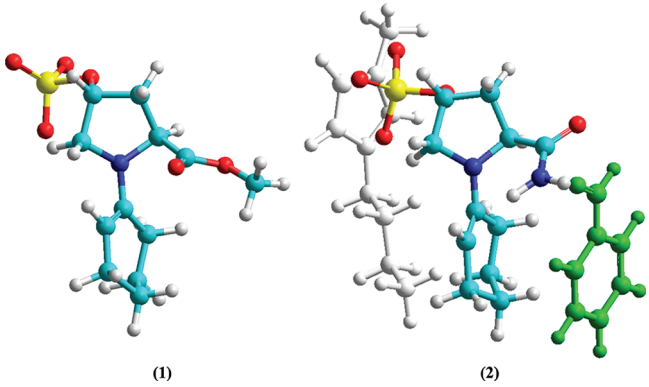


Figure 2. Theoretical calculation of the enamine intermediate obtained with MOPAC, PM6 method. Carbon atoms are represented in blue, oxygen in red, and sulfur in yellow. The aldehyde is represented in green and the imidazolium cation in gray.

Table 6. Recycling Studies

catalytic run	reaction time (days)	conversion[a] (%)
1	2	97
2	2.5	91
3	3	87
4	3	99
5	4	85

[a]Determined by chiral HPLC.

analysis were done using Chiralpak AD or OD columns and absolute configurations of the aldols products were based on previously reported literature.[23−25] Ionic liquids used as solvents were prepared as already described.[26]

Molecular Modeling. In order to assess the energy content for various molecules designed, semiempirical quantum calculations were undertaken using the PM6 method in gas phase or in aqueous solution (MOPAC2009TM; Stewart Computational Chemistry). All structures were optimized to a gradient inferior to 0.1 using the eigenvector following method.

*(2S,4R)-Methyl-4-hydroxypyrrolidine-2-carboxylate Hydrochloride (**2**).* *trans*-4-Hydroxy-L-proline (5.0 g) was suspended in methanol (40 mL) and cooled to 0 °C. Acetyl chloride (4.08 mL, 1.5 equiv) was slowly added, and the reaction was stirred at reflux for 16 h. The reaction mixture was then cooled to room temperature. Ether was added and the reaction medium filtered to afford compound **2** (6.92 g, quant) as white crystals. ^{1}H NMR (D_2O, 400 MHz): δ = 4.53−4.66 (m, 2H), 3.76 (s, 3H), 3.28−3.52 (m, 2H), 2.41 (dd, J = 14.1, 7.7 Hz, 1H), 2.12−2.29 (m, 1H). ^{13}C NMR (D_2O, 100 MHz): δ = 171, 70.2, 58.9, 54.6, 54.2, 37.4. HRMS (ESI): calcd for $C_6H_{12}NO_3$ 146.08117, found 146.08111. Mp: 161.8−162.2 °C.

*(2S,4R)-1-tert-Butyl-2-methyl-4-hydroxypyrrolidine-1,2-dicarboxylate (**3**).* Compound **2** (4 g) was suspended in methylene chloride and cooled to 0 °C. Triethylamine (9.21 mL, 3 equiv) and di-*tert*-butyl dicarbonate (5.29 g, 1.1 equiv) were added, and the mixture was stirred at room temperature for 2 days. The solution was first washed with an aqueous solution of 1 N HCl, washed with a saturated aqueous solution of $NaHCO_3$, and finally washed with brine. The organic phase was dried on magnesium sulfate, filtered, and concentrated under vacuum to give the crude product **3** as a pale yellow oil (5.13 g, 95% crude). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.49 (bs, 1H), 4.40 (t, J = 8 Hz, 1H), 3.74 (s, 3H), 3.44−3.65 (m, 2H), 2.22−2.35 (m, 1H), 3.03−2.12 (m, 1H). HRMS (ESI): calcd for $C_{11}H_{19}NO_5Na$ 268.11554, found 268.11652.

*(3R,5S)-5-(Methoxycarbonyl)pyrrolidin-3-yl Hydrogen Sulfate (**4**).* Under inert atmosphere, crude **3** (4.835 g) was solubilized in 40 mL of carbon tetrachloride and then cooled to 0 °C. Chlorosulfonic acid (1.57 mL, 1.2 equiv) was added dropwise to the reaction mixture under strong stirring. The reaction medium was then stirred vigorously at room temperature overnight. The solvent was removed under vacuum, the residue was triturated in methanol and then filtered to give **4** as a white powder (2.73 g, 62%). ^{1}H NMR (D_2O, 400 MHz): δ = 5.12 (s, 1H), 4.65 (dd, J = 10.6, 7.9 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 1H), 3.55−3.62 (m, 1H), 2.69−2.79 (m, 1H), 2.37 (s, 1H). ^{13}C NMR (D_2O, 100 MHz): δ = 170.4, 77.83, 58.93, 54.68, 52.44, 35.64. HRMS (ESI): calcd for $C_6H_{12}NO_6S$ 226.03798, found 226.03795.

*(3R,5S)-5-Carbamoylpyrrolidin-3-yl Hydrogen Sulfate **6**.* Compound **4** (1 g, 4.44 mmol) was dissolved in concentrated ammonium hydroxide (10 mL), and the reaction medium was stirred overnight at room temperature. The solvent was evaporated under vacuum and the residue was suspended and triturated in methanol. Filtration of the mixture afforded compound **6** as a white powder (809.2 mg, 87%). ^{1}H NMR (D_2O, 400 MHz): δ = 5.12 (t, J = 4.2 Hz, 1H), 4.45 (dd, J = 10.4, 7.7 Hz, 1H), 3.45−3.66 (m, 2H), 2.74 (dd, J = 14.5, 7.7 Hz, 1H), 2.17−2.29 (m, 1H). ^{13}C NMR (D_2O, 100 MHz): δ = 172.8, 79.1, 59.2, 52.6, 37.1. HRMS (ESI): calcd for $C_5H_{11}N_2O_5S$ 211.03832, found 211.03886.

General Procedure for the Synthesis of the Imidazolium Catalysts. 1-Butyl-3-methylimidazolium bromide (450 mg) was dissolved in 24 mL of methanol and passed through a glass column containing 12 g of activated Amberlite IRA400 hydroxide form resin. The column was then washed twice with 15 mL of methanol. The collected fractions were assembled in a 100 mL round-bottom flask, and zwitterion **4** or **6** was added (1.15 equiv). The mixture was allowed to stir at room temperature overnight. The solvent volume was reduced under vacuum, cooled down to 0 °C for 3 h, and filtered through a Celite pad to remove excess zwitterion. The filtrate was evaporated under vacuum and dried under vacuum overnight to afford catalyst **5** or **7** as a viscous pale yellow oil (quant.).

*1-Butyl-3-methylimidazolium (3R,5S)-5-(Methoxycarbonyl)-pyrrolidin-3-yl Sulfate (**5**).* ^{1}H NMR (D_2O, 400 MHz): δ = 8.60 (s, 1H), 7.37 (s, 1H), 7.32 (s, 1H), 4.87−4.97 (m, 1H), 4.09 (t, J = 7.1 Hz, 2H), 4.02 (t, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.00−3.20 (m, 2H), 2.33−2.48 (m, 1H), 2.03−2.18 (m, 1H), 1.64−1.81 (m, 2H), 1.21 (d, J = 7.7 Hz, 2H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (D_2O, 100 MHz): δ = 175, 135.4, 123, 121.7, 79.6, 57.5, 52.4, 51.5, 48.8, 35.8, 35.1, 30.8, 18.3, 12.1. HRMS (+ESI): calcd for $C_8H_{15}N_2$ 139.12297, found 139.12347; (-ESI) calcd for $C_6H_{10}NO_6S$ 224.02343, found 224.02324.

dx.doi.org/10.1021/jo300737u | J. Org. Chem. 2012, 77, 4917−4923

1-Butyl-3-methylimidazolium (3R,5S)-5-Carbamoylpyrrolidin-3-yl Sulfate (7). ^{1}H NMR (D_2O, 400 MHz): δ = 8.63 (s, 1H), 7.38−7.43 (m, 1H), 7.36 (t, J = 1.7 Hz, 1H), 4.92−4.97 (m, 1H), 4.12 (t, J = 7.1 Hz, 2H), 3.94 (t, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.05−3.22 (m, 2H), 2.44 (dd, J = 14.5, 7.9 Hz, 1H), 2.00 (ddd, J = 14.3, 9.1, 5.3 Hz, 1H), 1.72−1.83 (m, 2H), 1.19−1.31 (m, 2H), 0.85 (t, J = 7.4 Hz, 3H). ^{13}C NMR (D_2O, 100 MHz): δ = 179.3, 136.40, 124.2, 123.0, 81.6, 59.4, 53.1, 50.0, 37.9, 36.4, 32.0, 19.5, 13.4. HRMS (+ESI): calcd for $C_8H_{15}N_2$ 139.12297, found 139.12323; (−ESI) calcd for $C_5H_9N_2O_5S$ 209.02377, found 209.02279.

(S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)cyclohexanone (10a): General Representative Procedure for the Asymmetric Aldol Reaction. Cyclohexanone (103.5 μL, 10 equiv) was introduced in a vial containing the catalyst (10.9 mg, 30% mol) in [Bmim]NTf_2 (0.1 mL), and the mixture was stirred 30 min a 4 °C before *p*-nitrobenzaldehyde (15.12 mg, 1 equiv) was added to the reaction medium. The mixture was vigorously stirred at 4 °C until completion (monitored by TLC). The mixture was then directly purified by flash chromatography (hexanes/ethyl acetate: 9/1 then 65/35) to give the product as a white solid (20.69 mg, 83%, mp: 98−99 °C). Diastereomeric ratio (89:11) was determined by ^{1}H NMR spectroscopy and enantiomeric excess (syn/anti: 4%/86%) was determined by chiral HPLC (Chiralpak AD column, hexanes/2-propanol 90/10, flow rate: 1.0 mL·min^{-1}, λ = 254 nm). t_R (*syn* isomer) = 18.07 (minor), 22.24 (major); t_R (*anti* isomer) = 24.48 (minor), 32.45 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.19−8.27 (m, 2H), 7.47−7.58 (m, 2H), 4.92 (d, J = 8.4 Hz, 1H), 2.57−2.66 (m, 1H), 2.48−2.57 (m, 1H), 2.33−2.44 (m, 1H), 2.09−2.18 (m, 1H), 1.81−1.92 (m, 1H), 1.66−1.79 (m, 1H), 1.51−1.66 (m, 2H), 1.36−1.47 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{-1}, λ = 254 nm) t_R (*anti* isomer) = 22.01 (minor), 29.76 (major), t_R (*syn* isomer) = 16.08 (minor), 19.75 min (major). HRMS (ESI): calcd for $C_{13}H_{15}NO_4Na$ 272.08933, found 272.08959.

(S)-2-((R)-Hydroxy(2-nitrophenyl)methyl)cyclohexanone (10b). White solid. Yield: 20.4 mg, 82%. Mp: 116−118 °C. dr (*anti/syn*): 97:3, *ee* (*anti/syn*): 69%/−. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.87 (dd, J = 8.1, 1.3 Hz, 1H), 7.79 (dd, J = 8.0, 1.4 Hz, 1H), 7.62−7.71 (m, 1H), 7.40−7.51 (m, 1H), 5.47 (d, J = 7.0 Hz, 1H), 2.72−2.84 (m, 1H), 2.43−2.53 (m, 1H), 2.30−2.42 (m, 1H), 2.07−2.20 (m, 1H), 1.83−1.94 (m, 1H), 1.48−1.83 (m, 4H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 85/15, flow rate = 0.5 mL·min^{-1}, λ = 254 nm) t_R (*anti* isomer) = 26.38 (minor), 24.52 min (major). HRMS (ESI): calcd for $C_{13}H_{15}NO_4Na$ 272.08933, found 272.08995.

(S)-2-((R)-Hydroxy(3-nitrophenyl)methyl)cyclohexanone (10c). Pale yellow solid. Yield: 18.9 mg, 77%. Mp: 69−71 °C. dr (*anti/syn*): 85:15. ee (*anti/syn*): 67%/15%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.10−8.28 (m, 2H), 7.64−7.74 (m, 1H), 7.50−7.61 (m, 1H), 4.92 (d, J = 8.4 Hz, 1H), 2.60−2.71 (m, 1H), 2.48−2.56 (m, 1H), 2.33−2.47 (m, 1H), 2.08−2.19 (m, 1H), 1.81−1.93 (m, 1H), 1.52−1.79 (m, 3H), 1.34−1.48 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 92/8, flow rate = 1.0 mL·min^{-1}, λ = 254 nm) t_R (*anti* isomer) = 27.91 (minor), 21.90 (major), t_R (*syn* isomer) = 17.87 (minor), 19.70 min (major). HRMS (ESI): calcd for $C_{13}H_{15}NO_4Na$ 272.08933, found 272.09007.

(S)-Tetrahydro-3-((R)-hydroxy(4-nitrophenyl)methyl)pyran-4-one (10d). Pale yellow oil.Yield: 24.9 mg, 99%. dr (*anti/syn*): 83:17. ee (*anti/syn*): 67%/15%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.19−8.29 (m, 2H), 7.48−7.59 (m, 2H), 5.01 (d, J = 8.1 Hz, 1H), 4.17−4.35 (m, 1H), 3.68−3.83 (m, 2H), 3.48 (dd, J = 11.3, 9.9 Hz, 1H), 2.87−3.00 (m, 1H), 2.65−2.80 (m, 1H), 2.44−2.61 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{-1}, λ = 254 nm) t_R (*anti* isomer) = 48.72 (minor), 57.36 (major), t_R (*syn* isomer) = 30.63 (minor), 37.60 min (major). HRMS (ESI): calcd for $C_{12}H_{13}NO_5Na$ 274.06859, found 274.06922.

(R)-2-((S)-Hydroxy(4-nitrophenyl)methyl)cycloheptanone (10e). Colorless oil. Yield: 8.5 mg, 32%. dr (*anti/syn*): 66:34. ee (*anti/syn*): 16%/9%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.24 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 5.32 (d, J = 2.0 Hz, 1H), 2.89 (dt, J = 10.5, 2.8 Hz, 1H), 2.41−2.75 (m, 2H), 1.18−2.00 (m, 8H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 80/20, flow rate = 0.5 mL·min^{-1}, λ = 254 nm) t_R (*anti* isomer) = 39.93 (minor), 19.80 (major), t_R (*syn* isomer) = 14.10 (minor), 16.57 min (major). HRMS (ESI): calcd for $C_{14}H_{17}NO_4Na$ 286.10498, found 286.10443..

(S)-2-((S)-Hydroxy(4-nitrophenyl)methyl)cyclopentanone (10f). Yellow solid. Yield: 8.5 mg, 71%. Mp: 88−90 °C. dr (*anti/syn*): 37:63. ee (*anti/syn*): 16%/rac. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.18−8.28 (m, 2H), 7.49−7.61 (m, 2H), 5.44 (d, J = 2.9 Hz, 1H), 2.35−2.54 (m, 2H), 2.10−2.23 (m, 1H), 1.92−2.09 (m, 1H), 1.68−1.80 (m, 2H), 1.50−1.63 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol =95/5, flow rate =1.0 mL·min^{-1}, λ = 254 nm) t_R (*anti* isomer) = 42.35 (minor), 45.73 (major), t_R (*syn* isomer) = 33.70 (minor), 23.90 min (major). HRMS (ESI): calcd for $C_{12}H_{13}NO_4Ag$ 341.989, found 341.98983.

(S)-2-((R)-(2-Chlorophenyl)(hydroxy)methyl)cyclohexanone (10g). Colorless oil. Yield: 22.1 mg, 93%. dr (*anti/syn*): >99:1. ee (*anti/syn*): 89%/−. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.54−7.60 (m, 1H), 7.30−7.39 (m, 2H), 7.19−7.27 (m, 1H), 5.37 (d, J = 8.2 Hz, 1H), 2.65−2.75 (m, 1H), 2.45−2.54 (m, 1H), 2.31−2.42 (m, 1H), 2.06−2.16 (m, 1H), 1.80−1.88 (m, 1H), 1.51−1.78 (m, 4H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{-1}, λ = 215 nm) t_R (*anti* isomer) = 11.92 (minor), 10.49 min (major). HRMS (ESI): calcd for $C_{13}H_{15}ClO_2Na$ 261.06528, found 261.0649.

(S)-2-((R)-Hydroxy(thiophene-2-yl)methyl)cyclohexanone (10h). Pale yellow oil. Yield: 2.4 mg, 11%. dr (*anti/syn*): 95:5. ee (*anti/syn*): 85%/−. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.27−7.33 (m, 1H), 6.96−7.01 (m, 2H), 5.10 (d, J = 8.4 Hz, 1H), 2.64−2.73 (m, 1H), 2.47−2.55 (m, 1H), 2.33−2.44 (m, 1H), 2.09−2.18 (m, 1H), 1.56−1.89 (m, 4H), 1.37 (qd, J = 12.8, 3.7 Hz, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{-1}, λ = 215 nm) t_R (*anti* isomer) = 15.18 (minor), 13.75 min (major). HRMS (ESI): calcd for $C_{11}H_{14}O_2SNa$ 233.06067, found 233.06033.

(S)-2-((R)-Hydroxy(perfluorophenyl)methyl)cyclohexanone (10i). White solid. Yield: 27 mg, 92%. Mp: 85−87 °C. dr (*anti/syn*): >99:1. ee (*anti/syn*): 88%/−. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.34 (d, J = 9.7 Hz, 1H), 2.96−3.08 (m, 1H), 2.50−2.59 (m, 1H), 2.42 (td, J = 13.0, 6.2 Hz, 1H), 2.09−2.25 (m, 1H), 1.82−1.96 (m, 1H), 1.55−1.77 (m, 3H), 1.35 (qd, J = 12.6, 3.7 Hz, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 0.5 mL·min^{-1}, λ = 215 nm) t_R (*anti* isomer) = 18.74 (minor), 14.86 min (major). HRMS (ESI): calcd for $C_{13}H_{11}F_5O_2Na$ 317.05714, found 317.0561.

(S)-2-((R)-Hydroxy(naphthalen-3-yl)methyl)cyclohexanone (10j). Colorless oil. Yield: 9.6 mg, 38%. dr (*anti/syn*): 84:16. ee (*anti/syn*): 77%/17%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.82−7.90 (m, 3H), 7.78 (s, 1H), 7.46−7.54 (m, 3H), 4.99 (d, J = 8.8 Hz, 1H), 2.75 (ddd, J = 13.1, 7.9, 5.1 Hz, 1H), 2.50−2.57 (m, 1H), 2.35−2.47 (m, 1H), 2.06−2.16 (m, 1H), 1.49−1.84 (m, 4H), 1.32−1.43 (m, 1H). HPLC: (Chiralpak OD column, hexanes/2-propanol = 85/15, flow rate = 1.0 mL·min^{-1}, λ = 210 nm) t_R (*anti* isomer) = 15.18 (minor), 12.10 (major), t_R (*syn* isomer) = 6.67 (minor), 10.62 min (major). HRMS (ESI): calcd for $C_{17}H_{18}O_2Na$ 277.1199, found 277.11917.

(S)-2-((R)-(4-Bromophenyl)(hydroxymethyl)cyclohexanone (10k). Colorless oil. Yield: 13.9 mg, 49%. dr (*anti/syn*): 98:2. ee (*anti/syn*): 83%/−. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.46−7.52 (m, 2H), 7.19−7.25 (m, 2H), 4.77 (d, J = 8.8 Hz, 1H), 2.54−2.63 (m, 1H), 2.47−2.54 (m, 1H), 2.32−2.43 (m, 1H), 2.07−2.16 (m, 1H), 1.78−1.87 (m, 1H), 1.50−1.75 (m, 3H), 1.27−1.38 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 0.8 mL·min^{-1}, λ = 215 nm) t_R (*anti* isomer) = 18.64 (minor), 22.70 min (major). HRMS (ESI): calcd for $C_{13}H_{15}BrO_2Na$ 305.01476, found 305.01351.

(S)-2-((R)-(3-Bromophenyl)(hydroxymethyl)cyclohexanone (10l). Colorless oil. Yield: 19.8 mg, 70%. dr (*anti/syn*): 78:22. ee (*anti/syn*): 75%/13%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.51 (d, J = 1.8 Hz, 1H), 7.44 (dt, J = 7.1, 1.9 Hz, 1H), 7.21−7.26 (m, 2H), 4.76 (d, J = 8.8 Hz, 1H), 2.55−2.64 (m, 1H), 2.47−2.54 (m, 1H), 2.32−2.44 (m, 1H), 2.08−2.16 (m, 1H), 1.79−1.88 (m, 1H), 1.51−1.77 (m, 4H), 1.29−1.39 (m, 1H). HPLC: (Chiralpak AD column, hexanes/2-propanol = 98/2, flow rate = 0.5 mL·min^{-1}, λ = 215 nm) t_R (*anti* isomer) = 74.51 (minor), 69.73 (major), t_R (*syn* isomer) = 47.75 (minor), 39.50 min

dx.doi.org/10.1021/jo300737u | J. Org. Chem. 2012, 77, 4917−4923

(major). HRMS (ESI): calcd for $C_{13}H_{15}BrO_2Na$ 305.01476, found 305.01424.

*(S)-2-((R)-(2,4-Bis(trifluoromethyl)phenyl)(hydroxymethyl)-cyclohexanone (**10m**).* Colorless oil. Yield: 27.1 mg, 80%. dr (*anti/syn*): >99:1. ee (*anti/syn*): 88%/−. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.85−7.95 (m, 3H), 5.32−5.39 (m, 1H), 2.70−2.81 (m, 1H), 2.50−2.59 (m, 1H), 2.34−2.46 (m, 1H), 2.08−2.19 (m, 1H), 1.82 (dd, J = 13.2, 1.3 Hz, 1H), 1.70 (qt, J = 13.0, 3.9 Hz, 1H), 1.50−1.63 (m, 1H), 1.36−1.48 (m, 2H). ^{13}C NMR (CD_3OD, 100 MHz): δ =212.6, 146.6, 130.7, 130.3−130 (d, J = 24.7 Hz), 129.4 (d, J = 2.3 Hz), 128.9−128.6 (d, J = 23.2 Hz), 125.3−125.2 (d, J = 7.7 Hz), 1226−122.5 (d, J = 6.1 Hz), 122.3, 67.4, 57.9, 42.6, 31.5, 28.7, 24.8. HPLC: (Chiralpak AD column, hexanes/2-propanol = 90/10, flow rate = 1.0 mL·min^{-1}, λ = 215 nm) t_R (*anti* isomer) = 6.92 (minor), 8.08 min (major). HRMS (ESI): calcd for $C_{15}H_{14}F_6O_2Na$ 363.07902, found 363.07848.

*(3S,4R)-4-Hydroxy-3-methyl-4-(4-nitrophenyl)butan-2-one (**10n**).* Colorless oil. Yield: 12.9 mg, 58%. dr (*anti/syn*): 62:38. ee (*anti/syn*): 76%/42%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.22−8.25 (m, 2H), 7.53−7.57 (m, 2H), 4.89 (d, J = 7.8 Hz, 1H), 2.93 (qt, 1H), 2.83−2.85 (m, 1H), 2.49−2.51 (m, 1H), 2.23 (s, 3H), 1.05 (t, J = 7.4 Hz, 3H), HPLC: (Chiralpak AD column, hexanes/2-propanol = 70/30, flow rate = 0.5 mL·min^{-1}, λ = 215 nm) t_R (*anti* isomer) = 22.01 (minor), 18.19 (major), t_R (*syn* isomer) = 16.78 (minor), 20.83 min (major). HRMS (ESI): calcd for $C_{11}H_{13}NO_4Na$ 246.07368, found 246.07356.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra, HPLC traces, and crystallographic data for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ar.schmitzer@umontreal.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Fonds Québécois de la Recherche sur la Nature et les Technologies, the Centre of Green Chemistry and Catalysis, the Canada Foundation for Innovation, and the Université de Montréal. We thank Augusto César Hernandez Perez for the 2-naphthaldehyde and our colleagues for careful discussions of this manuscript.

■ REFERENCES

(1) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748.
(2) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416−5470.
(3) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569.
(4) S. Bertelsen, B.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178−2189.
(5) Wang, Y.; Li, H. M.; Wang, Y. Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364−6365.
(6) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett.* **2006**, *8*, 2217−2220.
(7) Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 9652−9654.
(8) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849−1851.
(9) Knowles, R. R.; Carpenter, J.; Blakey, S. B.; Kayano, A.; Mangion, I. K.; Sinz, C. J.; MacMillan, D.W. C. *Chem. Sci.* **2011**, *2*, 308−311.
(10) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621.
(11) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703−4832.
(12) Welton, T. *Chem. Rev.* **1999**, *99*, 2071−2084.
(13) Parvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615−2665.
(14) Sowmiah, S.; Srinivasadesikan, V.; Tseng, M.-C.; Chu, Y.-H. *Molecules* **2009**, *14*, 3780−3813.
(15) Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 6425−6428.
(16) Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 3689−3692.
(17) Lombardo, M.; Pasi, F.; Easwar, S.; Trombinia, C. *Adv. Synth. Catal.* **2007**, *349*, 2061−2065.
(18) Guo, H. M.; Cun, L. F.; Gong, L. Z.; Mi, A. Q.; Jiang, Y. Z. *Chem. Commun.* **2005**, *11*, 1450−1452.
(19) Bica, K.; Gaertner, P. *Eur. J. Org. Chem.* **2008**, 3235−3250.
(20) Hu, S.; Jiang, T.; Zhang, Z.; Zhu, A.; B. Han, B.; Song, J.; Xie, Y.; Li, W. *Tetrahedron Lett.* **2007**, *48*, 5613−5617.
(21) Qian, Y.; Zheng, X.; Wang, Y. *Eur. J. Org. Chem.* **2010**, 3672−3677.
(22) Swatloski, R. P.; Holbrey, J. D.; Rogers, R. D. *Green Chem.* **2003**, *5*, 361−363.
(23) Hernandez, J. G.; Juaristi, E. *J. Org. Chem.* **2011**, *76*, 1464−1467.
(24) Wu, C.; Fu, X.; Li, S. *Eur. J. Org. Chem.* **2011**, 1291−1299.
(25) Yang, H.; Mahapatra, S.; Cheong, P. H.-Y.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 7279−7290.
(26) Gauchot, V.; Kroutil, W.; Schmitzer, A. R. *Chem.—Eur. J.* **2010**, *16*, 6748−6751.