UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF PROLINE-BASED CHIRAL IONIC LIQUID ORGANOCATALYST FOR ASYMMETRIC MICHAEL REACTION UNDER MICROWAVE IRRADIATION

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DOCTOR OF PHILOSOPHY
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By

EMMY MARYATI OMAR

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of

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Chairman : Professor Mohd Basyaruddin Abdul Rahman, PhD

Faculty : Science

Recent developments in organocatalysis have shown that chiral ionic liquid organocatalysts can be advantageously performed in various organic solvents and ionic liquids. Along with the good catalytic performance especially in Michael reaction, some drawbacks such as high catalyst loading, large excess of substrates and long reaction time need to be improved in the reaction processes. In this thesis, four aspects of the title objectives were studied. In the first part, eight proline derived amino acids were successfully screened for good catalytic activity and selectivity towards Michael products. L-proline amino acid has been identified as the most active organocatalyst and selective small organic molecule in the Michael reaction of aldehydes to nitrostyrenes. A high percentage yield (> 92%), moderate enantioselectivity (28% ee) and high diastereomeric ratio (90/10) were obtained using 30 mol% catalyst loading, 2 aldehyde equivalent ratio and 9 hours reaction time in isopropanol solvent at room temperature. Beside organic solvent, the uses of environmentally-friendly ionic liquids were explored. The 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([Bmim][NTf_2]) ionic liquid was found to be the best solvent media compared to other ten more ionic liquids. The results obtained with high percentage yield (90%), slightly increased in enantioselectivity (38% ee) and high diastereomeric ratio (91/9). In order to develop the catalytic activity, microwave irradiation technique was used to shorten the Michael reaction time. The time was successfully reduced from 8-9 hours to 5-40 min at temperature 60 ^{o}C with almost similar results as in room temperature and conventional heating conditions. The [Bmim][NTf_2] ionic liquid was reused five times, representing an economic alternative to conventional organic solvents.

The synthetic reaction was optimized by Response Surface Methodology (RSM) approach. Design of experiments based on Central Composite Design (CCD) was used to

evaluate the interactive effects of the reaction parameters including catalyst loading, substrate equivalent ratio and reaction time. By RSM optimization, a catalyst loading could be reduced from 30 to 10 mol% with high percentage yield (97%) and moderate enantioselectivity (37% ee). Large excess of aldehyde (normally 10-20 equiv ratio) that has been used in organocatalysis field was also successfully reduced to 2 equivalent ratio indicating that the RSM approach can be applied effectively to optimize the Michael reaction of aldehyde to *ß*-nitrostyrene.

The proline-based chiral ionic liquid (CIL) organocatalysts were designed and synthesized in order to overcome some of the drawbacks by L-proline. These chiral ionic liquids contain a chiral pyrrolidine (proline-based) backbone and incorporated with ionic species. Without any additive, the reaction of CIL imidazolium (*S*)-pyrrolidine sulfonamide organocatalyst was found to be very effective in isopropanol at room temperature in giving excellent yields (up to 90%), shorten time constraint (3-5 hours), and high diastereoselectivities (95/5). The results also demonstrated that [Bmim][NTf_2] ionic liquid was not suitable solvent as it reduced the catalytic activity not only at room temperature but also under microwave irradiation. However, the reaction of CIL imidazolium (*S*)-pyrrolidine sulfonamide organocatalyst was found to be effective under microwave irradiation in isopropanol with very high yield (99%) with slightly increased in enantioselectivity (42% ee) in 10 min reaction time.

The understanding of the stereoselectivity on the mechanism catalyzed by CIL imidazolium (*S*)-pyrrolidine sulfonamide organocatalyst was also investigated by General Atomic and Molecular Electronic Structure System (winGAMESS) software in the last part of the thesis. This approach indicated that the N−H acidic hydrogen from the CIL imidazolium (*S*)-pyrrolidine sulfonamide organocatalyst plays an important role in the reaction by forming a hydrogen bond to the nitrostyrene substrate that leads to C−C bond formation by the enamine mechanism. The computational results agree quite well with the observed stereoselectivity of chiral ionic liquid organocatalyst for the Michael reaction of aldehyde to nitrostyrene.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PEMBANGUNAN CECAIR IONIK KIRAL BERASASKAN SEBATIAN PROLINA SEBAGAI PEMANGKINAN ORGANIK UNTUK TINDAKBALAS TIDAK SIMETRI MICHAEL DI BAWAH IRADIASI GELOMBANG MIKRO

Oleh

EMMY MARYATI OMAR

Disember 2013

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Pembangunan terkini dalam bidang pemangkinan organik menunjukkan bahawa mangkin cecair ionik kiral boleh memberikan kesan yang bagus ke atas pelarut organik dan pelarut ionik. Sehubungan dengan itu, dalam tindak balas Michael, terdapat beberapa kelemahan seperti, penggunaan jumlah pemangkinan yang tinggi, kadar nisbah reaktan dan masa tindak balas yang panjang seharusnya diberikan perhatian. Oleh yang demikian, kajian yang telah dihuraikan di dalam tesis ini memfokuskan kepada empat bahagian utama. Pada bahagian pertama, lapan asid amino telah berjaya dikenal pasti. Di dalam tindak balas Micheal dari aldehida ke nitrostirena, asid amino L-prolina telah dikenalpasti sebagai molekul organik kecil yang aktif dan juga selektif. Hasil produk yang tinggi (>92%), enantioselektiviti yang sederhana (28 ee%) dan kadar diastereomerik yang tinggi (90/10) telah berjaya diperoleh menggunakan mangkin L-prolina sebanyak 30 mol%, aldehida dengan kadar 2 nisbah reaktan dalam masa tindak balas selama 9 jam dalam pelarut isopropil alkohol pada suhu bilik. Selain daripada pelarut organik, penggunaan pelarut yang dikatakan mesra alam seperti cecair ionik juga diterokai. Cecair ionik [Bmim][NTf_2] didapati sebagai pelarut media yang terbaik berbanding dengan sepuluh cecair ionik yang lain. Keputusan yang diperoleh menunjukkan peratusan hasil produk yang tinggi (90%), kenaikan enantioselektiviti (38% ee) dan juga kadar diastereometrik yang tinggi (91/9). Dalam menghasilkan aktiviti pemangkinan yang lebih efektif, teknik iradiasi gelombang mikro telah digunapakai untuk mempercepatkan masa tindakbalas Micheal. Jumlah masa berjaya dikurangkan daripada 8-9 jam kepada 5-40 minit pada suhu 60 ^{o}C. Keputusan ini sangat bertepatan dengan keputusan pada suhu bilik dan kondisi pemanasan yang konvensional. Cecair ionik [Bmim][NTf_2] telah digunakan semula sebanyak 5 kali dan boleh dijadikan sebagai salah satu media alternatif yang komersial berbanding dengan pelarut organik.

Tindak balas sintetik telah dioptimumkan melalui kaedah *Response Surface Methodology* (RSM). Rekabentuk eksperimen adalah berdasarkan kepada *Central Composite Design* (CCD) yang telah digunakan untuk menilai kesan interaktif untuk beberapa parameter termasuk jumlah pemangkin, kadar nisbah reaktan dan masa tindakbalas. Melalui keputusan hasil data RSM yang optimum, jumlah mangkin dapat dikurangkan daripada 30 kepada 10 mol% dengan peratusan hasil produk yang tinggi (97%) dan enantioselektiviti yang sederhana (37% ee). Lebihan aldehida yang tinggi (kadar nisbah reaktan normal 10-20) yang digunakan dalam bidang pemangkinan organik telah berjaya dikurangkan kepada kadar nisbah 2, menunjukkan bahawa RSM adalah kaedah yang boleh diaplikasi secara efektif untuk mengoptimumkan tindak balas Micheal aldehida ke nitrostirena.

Beberapa mangkin cecair ionik kiral (CIL) berasaskan sebatian prolina telah dibentuk dan disintesiskan untuk mengatasi beberapa kelemahan yang wujud oleh L-prolina. Cecair ionik kiral ini mempunyai tulang belakang kiral pirrolidina yang telah digabungkan dengan spesis ionik. Tanpa bahan tambahan, tindak balas mangkin CIL imidazol (*S*)-pirrolidina sulfonamida telah didapati sangat efektif dalam pelarut isopropil alkohol pada suhu bilik dengan peratusan hasil yang sangat memberangsangkan (sehingga 90%), masa yang singkat (3-5 jam) dan kadar diastereoselektif yang tinggi (95/5). Hasil kajian ini juga menunjukkan bahawa cecair ionik [Bmim][NTf_2] tidak sesuai menjadi pelarut kepada mangkin organik kerana ia mengurangkan aktiviti pemangkinan bukan hanya pada suhu bilik, tetapi juga di bawah teknik iradiasi gelombang mikro. Walaubagaimanapun, tindak balas mangkin CIL imidazol (*S*)-pirrolidina sulfonamida didapati memberi kesan yang efektif di bawah keadaan radiasi gelombang mikro di dalam pelarut isopropil alkohol dengan peratusan hasil produk yang sangat tinggi (99%) dengan sedikit kenaikan pada enantioselektif (42% ee) dalam masa 10 minit.

Perisian General Atomic and Molecular Electronic Structure System (winGAMESS) digunakan dalam bahagian akhir thesis bagi memahami mekanisma streoselektif. Kaedah yang digunakan ini menunjukkan bahawa ikatan hidrogen N-H yang bersifat asidik memainkan peranan penting dalam tindak balas melalui penghasilan ikatan hidrida kepada nitrostirena yang akan membawa kepada penghasilan ikatan C-C melalui mekanisma enamina. Perisian komputer juga menunjukkan keputusan streoselektif yang didapati hampir sama dengan pemerhatian sebenar oleh cecair ionik kiral untuk tindakbalas Micheal dari aldehida ke nitrostirena.

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Emmy Omar

I certify that a Thesis Examination Committee has met on 3rd December 2013 to conduct the final examination of Emmy Maryati Omar on her thesis entitled "Development of

[1] *Azhar,Nora, Zati,Naimah, Asrul,Rizal, Peter, Ieja, Uswatun, Maha, Lim, K.syila, Malahat, Naz, Sok Han, Hanim, Casey, Fariza, Nana, Saadi, Wasiew, Mohamad, Ahmad, Dave and many more…millions thanks!!!!!*

Proline-based Chiral Ionic Liquid Organocatalyst for Asymmetric Michael Reaction Under Microwave Irradiation" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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Date : 19 December 2013

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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DECLARATION

Declaration by Graduate Student

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