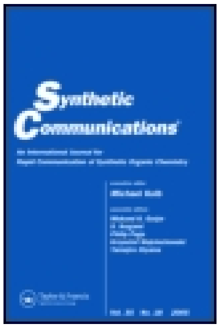
This article was downloaded by: [Georgetown University]
On: 19 August 2013, At: 14:38
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Catalytic Microwave-Promoted Direct Aldol Condensation Using Resin-Bound Secondary Amine

Fu Xu Liao [a] , Yu Guang Wang [a] & Qing Zhu [a]

[a] College of Biological and Environmental Engineering, Zhejiang University of Technology , Hangzhou , Zhejiang , P. R. of China

Accepted author version posted online: 15 Aug 2013.

To cite this article: Synthetic Communications (2013): Catalytic Microwave-Promoted Direct Aldol Condensation Using Resin-Bound Secondary Amine, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI: 10.1080/00397911.2013.793775

To link to this article: http://dx.doi.org/10.1080/00397911.2013.793775

Disclaimer: This is a version of an unedited manuscript that has been accepted for publication. As a service to authors and researchers we are providing this version of the accepted manuscript (AM). Copyediting, typesetting, and review of the resulting proof will be undertaken on this manuscript before final publication of the Version of Record (VoR). During production and pre-press, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal relate to this version also.

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the “Content”) contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

ACCEPTED MANUSCRIPT

Catalytic Microwave-Promoted Direct Aldol Condensation Using Resin-Bound Secondary Amine

Fu Xu Liao[1], Yu Guang Wang[1], Qing Zhu[1,]

[1]College of Biological and Environmental Engineering, Zhejiang University of Technology, Hangzhou, Zhejiang, P. R. of China

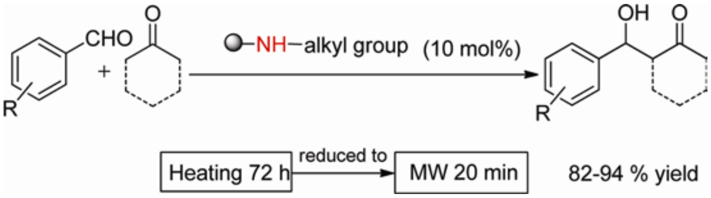
Address correspondence to Qing Zhu, College of Biological and Environmental Engineering, Zhejiang University of Technology, Hangzhou, Zhejiang 310014, P. R. of China. Tel.: +86-571-88320781; E-mail: zhuq@zjut.edu.cn

Downloaded by [Georgetown University] at 14:38 19 August 2013

Abstract

A series of polystyrene-supported imino group-bearing catalysts were prepared. Highly efficient combination of recyclable catalysts and microwave was developed as a green protocol for the direct aldol reaction. Notably, MW greatly shorten the reaction times to only 20 min and improved the yield significantly，meanwhile, catalyst loading was reduced as well. Different aromatic aldehydes as aldol donors were subjected to our catalyst system and afforded the corresponding products in satisfactory yields. Additionally, the polymer-supported catalysts could be recovered by simple filtration and were reusable for at least four times without significant loss of reactivity.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



ACCEPTED MANUSCRIPT

KEYWORDS: Aldol reaction; polymer-supported reagents; imino group; microwave; recyclability

Downloaded by [Georgetown University] at 14:38 19 August 2013

INTRODUCTION

The aldol reaction, one of the most important carbon-carbon bond-forming reactions, was widely employed in synthetic organic chemistry.[1–4] Its products, β-hydroxyl carbonyl compounds or α, β-unsaturated carbonyl compounds, had served as important building blocks for the synthesis of polyfunctional compounds and natural products.[5] In recent years, studies of organocatalysts for the aldol reaction, such as proline and its derivatives or analogues, have attracted great attentions due to their simple structures and being free of metals.[6–12] For example, List and Barbas reported that the direct intermolecular aldol reaction could be performed under mild catalysis of proline.[13] More recently, secondary amines were found to have distinct or better catalytic abilities in direct aldol reaction and Michael addition due to the formation of enamine, whereas proline-based catalysts showed no activity.[14–17] This mechanism proposed that the imino group plays an indispensable role in promoting the condensation with an aldol acceptor.[6,18–22] However, these homogeneous catalysts were not beneficial to the purification process.[23,24] Few years ago, K. Sakthivel et al. developed a heterogeneous catalyst by the immobilization of proline on silica gel, which offered good yield and purity.[6] Unfortunately, the major disadvantages of these heterogeneous catalysts included the long reaction times, high catalyst loading but delivering varied yields,[25] and the large amount addition of additives (such as acetic acid,[26] DiMePEG,[27] diols or diphenols[28]). Moreover, this class of catalysts was not robust for the direct aldol condensation due to low stability caused by the non-covalent bond between the catalysts and solid support.[29] To overcome these shortcomings, herein, we investigated a microwave-assisted direct aldol condensation catalyzed by resin-bound secondary amine.

RESULTS AND DISCUSSION

A series of cross-linked PS resin-supported secondary amines were prepared according to the synthetic route outlined in Scheme 1. Four kinds of amine were attached to the polymer via a simple two-step reaction to give heterogeneous catalysts. The loadings were determined by gravimetry.

Secondary Amine Resin-Catalyzed Aldol Reaction Under The Enhancement Of MW Irradiation

Microwave irradiation has become a useful tool in organic synthesis. It is reported that the MW irradiation could shorten the reaction time and increase the product yield compared to conventional thermal approach.[30,31] To optimize the MW conditions, we initially studied the model reaction of *p*-nitrobenzaldehyde with cyclohexanone catalyzed by the four kinds of resin (20 mol%) in methanol. Firstly, the reaction was carried out with a temperature-controlled program. In methanol, only 20% of conversion was achieved after 20 min at 70℃ with 20 mol% resin **2a** (entry 1, Table 1). For other groups, the temperature was increased to 90℃ or 110℃, and 46% or 92% yields were obtained after 20 min (entry 2 and 3, Table 1). Once the temperature was above 130℃, *p*-nitrobenzaldehyde was totally consumed after 20 min. However, a large amount of bis-

Downloaded by [Georgetown University] at 14:38 19 August 2013

ACCEPTED MANUSCRIPT

aldol and by-products (methylal) were detected (entry 4, Table 1). Moreover, at the temperature of 110 ℃, a comparable yield could be obtained by using half amount of the resin-catalyst (entry 5, Table 1). The catalytic performances of other three kinds of resin were also investigated under the same conditions (entries 6, 7, 8, Table 1), in general, the yields obtained were not as good as that obtained by resin **2a**. Based on these results further examinations were made using resin **2a**.

Downloaded by [Georgetown University] at 14:38 19 August 2013

Substrate Scope And The Resin Reusability Studies

After the optimization of microwave conditions, the substrate scope was extended to other aldehydes and ketones. As shown in Table 2, both of the results with and without the assistance of MW were listed. As for the trials without MW enhancement, benzaldehydes with strong electron-withdrawing groups, such as *p*-fluorobenzaldehyde (entry 6, Table 2), *p*-nitrobenzaldehyde (entry 11, Table 2), *p*-chlorobenzaldehyde (entry 8, Table 2) could be converted to the corresponding aldol products in good yields. On the other hand, benzaldehydes with electron-donating groups such as methoxyl group, gave a relatively poor conversion (entry 10, Table 2). Different substitutent positions on benzene ring also affected the yields of Aldol reactions. For example, *p*-tolualdehyde with smaller steric hindrance compared to *o*-tolualdehyde and *m*-tolualdehyde, gave the highest yield (entries 3~5, Table 2). It is also interesting to note that cyclohexanone offered β-hydroxyl ketone rather than the corresponding α, β-unsaturated carbonyl compound, which may result from the great steric hindrance on the ring (entry 1, Table 2). However, this time-consuming and relatively less efficient method was far from ideal, though the reusablity of the catalyst. Once the MW irradiation was applied, the results were totally improved.

ACCEPTED MANUSCRIPT

Most of the substrates gave yields of more than 82% in only 20 min. Under this innovative catalyst system, most kinds of aldehydes were transformed into the corresponding aldol products with higer conversion and yield, and only 20 min was required compared with that by means of conventional heating. Thus, the use of the MW technique offered a great advantage in the secondary amine resin-catalyzed aldol condensation reaction.

Downloaded by [Georgetown University] at 14:38 19 August 2013

Next, the recycling of these resin-catalysts was investigated. As shown in Table 2, the recovered resin **2a** could catalyze the aldol reaction of *p*-nitrobenzaldehyde with cyclohexanone in good yields even after five consecutive trials (entries 12~15, Table 2).

A Possible Mechanism For Direct Aldol Condensation

Based on the above results, we proposed the following enamine-mediated mechanism (Scheme 2). Firstly, the imino group launched a nucleophilic attack, and the consequent dehydration and deprotonation of the corresponding intermediates led to the formation of another crucial intermediate enamine (**a**, Scheme 2). Next, the carbon-carbon bond-forming reaction between acetone enamine and aldehydes occurred and resulted in intermediate **c**. After the subsequent effect of water, it was converted to **d**, which was transformed to β-hydroxyl-ketone (**e**) quickly. The α, β-unsaturated carbonyl compound (**f**) was generated after the release of one molecule of water. Obviously, MW irradiation could promote the secondary amine-catalyzed aldol reactions probably due to the specific interaction of the electric field with the polar reaction species. [32, 33]

ACCEPTED MANUSCRIPT

CONCLUSION

A novel kind of catalyst system has been established by the use of MW and recyclable resin catalyst. Reaction times and the required catalysts loading were reduced significantly after the assistance of the MW irradiation. The combination of MW energy and secondary amine resin-bound catalysts could constitute a new type of highly reliable and recyclable catalyst system, which, as far as we know, has not been reported previously. This approach is potentially applicable to a number of reactions catalyzed by proline and its analogues as organocatalysts.

Downloaded by [Georgetown University] at 14:38 19 August 2013

EXPERIMENTAL

All the Aldol products were known compounds and identified by using a combination of their NMR and mass spectra, and compared with data given in the literature and from the data library of Agilent GC-MS workstation.

The full experimental details and characterization data for the preparation of reusable catalysts are provided in the Supplementary Information.

General Procedure For Aldol Reaction (Conventional Method).

Resin was added to a suspension of aldehyde (0.5 mmol), ketone (1.0 mmol) in 4 mL solvent in a sealed tube. The reaction mixture was stirred for 72 h at 50℃, and HPLC or GC-MS were employed to determine the conversions and yields.

Typical Procedure For Aldol Reaction Under MW Irradiation.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

To a 10 mL vessel were introduced resin, aldehyde (0.5 mmol), solvent (4 mL) and finally ketone (1.0 mmol). The vessel was sealed with a septum and placed into the microwave cavity. The microwave source was then turned on. After the time was out, HPLC or GC-MS were employed to determine the conversions and yields.

Recycling Of The Catalytic System.

After the reaction was completed, the organic reaction solution was vacuum-filtered through a sintered-glass funnel. The small balls were washed successively with THF, water and methanol until there were no residual compounds. After the recovered catalyst was dried under vacuum for four hours, it was directly used in the next cycle without further purification.

Downloaded by [Georgetown University] at 14:38 19 August 2013

Characterization Of Typical Compounds.

2-(Hydroxy(4-Nitrophenyl)Methyl)Cyclohexanone(5a):[34]

^{1}H NMR (400 MHz, $CDCl_3$) δ8.13 (s, 2H), 7.41 (s, 2H), 4.82 (d, J = 8.4 Hz, 1H), 2.54 (s, 1H), 2.31 (dd, J = 14.7, 4.5 Hz, 2H), 1.77 (s, 3H), 1.63 (d, J = 9.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 151.3, 147.1, 128.5, 123.3, 76.4, 56.6, 39.4, 29.2, 25.6, 23.6. HPLC: t_R: 9.75 min. MS(EI): *m/z* 250[M^++H]. Anal. Calcd. For: $C_{13}H_{15}NO_4$: C 62.64, H 6.07, N 5.62, O 25.67, found: C 62.61, H 6.08, N 5.66, O 25.65.

The Full experimental detail, data of ^{1}H, ^{13}C NMR spectra, retention time in HPLC or GC and ESI-MS characterization of products **5b-l** together with the IR spectra of prepared catalysts(**1a-d**) are available in the Supplementary Information.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

REFERENCES

1. Alcaide, B.; Almendros, P. The direct catalytic asymmetric aldol reaction. *Eur. J. Org. Chem.* **2002**, 1595-1601.

2. Saito, S.; Yamamoto, H. Design of acid-base catalysis for the asymmetric direct Aldol reaction. *Acc. Chem. Res.* **2004**, *37*, 570-579.

3. Palomo, C.; Oiarbide, M.; Garcı´a, J. M. Current progress in the asymmetric Aldol addition reaction. *Chem. Soc. Rev.***2004**, *33*, 65-75.

4. Dalko, P. I.; Moisan, L. In the golden age of organocatalysis. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175.

5. Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. An especially convenient stereoselective reduction of β-hydroxy ketones to anti 1,3-diols using samarium diiodide. *J. Org. Chem.* **1999**, *64*, 2172-2173.

6. Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. Amino acid catalyzed direct asymmetric Aldol reactions: A bioorganic approach to catalytic asymmetric carbon-carbon bond-forming reactions. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267.

7. Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas III, C. F. A highly enantioselective amino acid-catalyzed route to functionalized α-amino acids. *J. Am. Chem. Soc.***2002**, *124*, 1842-1843.

8. Michelangelo G.; Francesco G.; Renato N. Supported proline and proline-derivatives as recyclable organocatalysts. *Chem. Soc. Rev.* **2008**, *37*, 1666-1688.

9. Giacalone, F.; Gruttadauria, M.; Marculescu, A. M.; Anna F. D.; Noto, R. Polystyrene-supported proline as recyclable catalyst in the Baylis–Hillman reaction of arylaldehydes and methyl or ethyl vinyl ketone. *Catal. Commun.* **2008**, *9,* 1477-1481.

Downloaded by [Georgetown University] at 14:38 19 August 2013

ACCEPTED MANUSCRIPT

10. Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas III, C. F. A way to highly enantiomerically enriched aza-Morita-Baylis-Hillman-Type products. *Angew.Chem. Int. Ed.* **2007**, *46*, 1878-1880.

11. List, B. Proline-catalyzed asymmetric reactions. *Tetrahedron.* **2002**, *58*, 5573-5590.

12. Jarvo, E. R.; Miller, S. J. Amino acids and peptides as asymmetric organocatalysts. *Tetrahedron.* **2002**, *58*, 2481-2495.

13. List, B.; Lerner, R. A.; Barbas III, C. F. Proline-catalyzed direct asymmetric aldol reactions. *J. Am. Chem. Soc*. **2000**, *122*, 2395-2396.

14. Kim, H.; MacMillan, D. W. C. Enantioselective organo-SOMO catalysis: The α-vinylation of aldehydes. *J. Am. Chem. Soc.* **2008**, *130*, 398-399.

15. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. Diphenylprolinol silyl ethers as efficien organocatalysts for the asymmetric Michael reaction of aldehydes and nitroalkenes. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.

16. Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. Design of an axially chiral amino acid with a binaphthyl backbone as an organocatalyst for a direct asymmetric Aldol reaction. *Angew. Chem. Int. Ed.* **2005**, *44*, 3055-3057.

17. Xiao, J.; Lu, Y. P.; Liu, Y. L.; Wong, P. S.; Loh, T. P. A new class of structurally rigid tricyclic chiral secondary amine organocatalyst: Highly enantioselective organocatalytic Michael addition of aldehydes to vinyl sulfones. *Org. Lett.* **2011**, *13*, 876-879.

18. Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Meo, P. L.; Riela, S.; Noto, R. Hydrophobically directed aldol reactions: Polystyrene-supported L-proline as a

Downloaded by [Georgetown University] at 14:38 19 August 2013

recyclable catalyst for direct asymmetric aldol reactions in the presence of water. *Eur. J. Org. Chem.* **2007**, 4688-4698.

19. Mase, N.; Tanaka, F.; Barbas, III, C. F. Rapid fluorescent screening for bifunctional amine-acid catalysts: Efficient syntheses of quaternary carbon-containing Aldols under organocatalysis. *Org. Lett.* **2003**, *5,* 4369-4372.

20. Nakadai, M.; Saito, S.; Yamamoto, H. Diversity-based strategy for discovery of environmentally benign organocatalyst: Diamine-protonic acid catalysts for asymmetric direct aldol reaction. *Tetrahedron*. **2002**, *58,* 8167-8177.

21. Tang, Z.; Jiang, F.; Yu, L.; Cui, X.; Gong, L.; Mi, A.; Jiang, Y.; Wu. Y. Novel small organic molecules for a highly enantioselective direct aldol reaction. *J. Am. Chem. Soc.* **2003**, *125*, 5262-5263.

22. Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List. B. Quantum mechanical predictions of the stereoselectivities of proline-catalyzed asymmetric intermolecular aldol reactions. *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479.

23. Cozzi, F. Immobilization of organic catalysts: When, why, and how. *Adv. Synth. Catal.* **2006**, *348*, 1367-1390.

24. Benaglia, M.; Puglisi, A.; Cozzi, F. Polymer-supported organic catalysts. *Chem. Rev.* **2003**, *103*, 3401-3429.

25. Fraile, J. M.; Garcia, J. I.; Mayoral, J. A. Noncovalent immobilization of enantioselective catalysts. *Chem. Rev.* **2009**, *109*, 360-417.

26. Chen, J. R.; Lu, H. H.; Li, X. Y.; Cheng, L.; Wan, J.; Xiao, W.J. Readily tunable and bifunctional L-prolinamide derivatives: Design and application in the direct enantioselective Aldol reactions. *Org. Lett.* **2005**.*7,* 4543-4545.

Downloaded by [Georgetown University] at 14:38 19 August 2013

ACCEPTED MANUSCRIPT

27. Font, D.; Jimeno, C.; Perica`s, M. A. Polystyrene-supported hydroxyproline: An insoluble, recyclable organocatalyst for the asymmetric Aldol reaction in water. *Org. Lett.* **2006**. *8*, 4653-4655.

28. Luo, J.; Tan, R.; Yu, K.; Li, C.Y.; Yin, D.H. Effect of additives on L-proline catalyzed direct asymmetric Aldol reactions. *Chin. J. Catal.* **2012**, *33*, 1133-1138.

29. Wang, Z.; Yan, J.; Zhang, X.; Wang, L. Merrifield resin supported ionic liquids/L-proline as efficient and recyclable catalyst systems for asymmetric Aldol reaction. *Synthesis*, **2009**, *22,* 3744-3750.

30. Bruckmann, A.; Krebs, A.; Bolm, C. Organocatalytic reactions: effects of ball milling, microwave and ultrasound irradiation. *Green Chem.* **2008**, *10*, 1131-1141.

31. Dondoni, A.; Massi, A. Asymmetric organocatalysis: From infancy to adolescence. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638-4660.

32. Perreux, L.; Loupy, A. A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations. *Tetrahedron*. **2001**, *57*, 9199-9223.

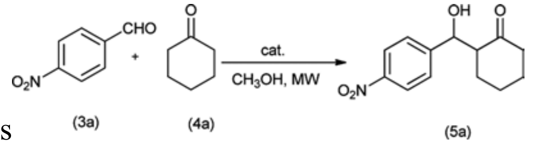
33. Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C.O. Microwave-assisted asymmetric organocatalysis. A probe for nonthermal microwaveeffects and the concept of simultaneous cooling. *J. Org. Chem.* **2007**, *72*, 1417-1424.

34. Córdova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.W. Acyclic amino acid-catalyzed direct asymmetric aldol reactions: alanine, the simplest stereoselective organocatalyst. *Chem. Commun*. **2005**, 3586-3588.

Downloaded by [Georgetown University] at 14:38 19 August 2013

ACCEPTED MANUSCRIPT

Table 1. MW-assisted aldol reactions under the catalysis of solid-phase calysts



Entry	Catalyst	t/min	mol%	T/°C	Con./%[a]	Y./%[b]
1	2a	20	20	70	23	19
2	2a	20	20	90	55	46
3	2a	20	20	110	96	92
4	2a	20	20	130	99	45
5	2a	20	10	110	94	90
6	2b	20	10	110	79	74
7	2c	20	10	110	75	69
8	2d	20	10	110	75	58
9[c]	2a	4320	20	50	78	75

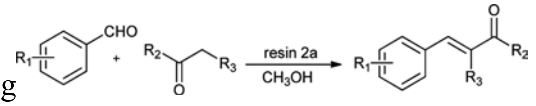
[a] Conversion based on 5, and determined by HPLC;

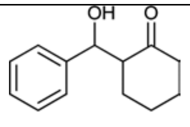
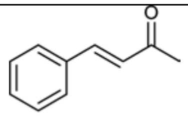
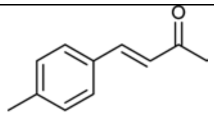
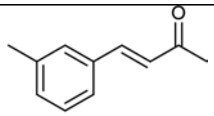
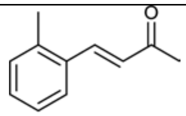
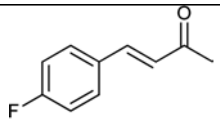
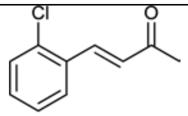
[b] Yields were determined by HPLC.

[c] In comparison with the performance without the assistance of MW irradiation.

Downloaded by [Georgetown University] at 14:38 19 August 2013

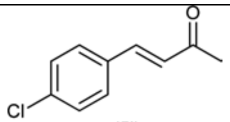
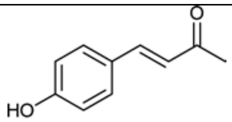
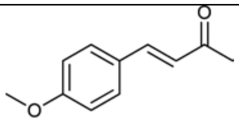
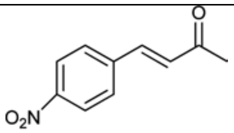
Table 2. Comparison of the direct aldol reactions between microwave irradiation and conventional heating



Entry	Product	Conventional method[a]			Microwave method[b]		
		t/min	Con./%[c]	Y./%[d]	t/min	Con.%[c]	Y./%[d]
1	 (5b)	4320	53	47	20	89	86
2	 (5c)	4320	66	62	20	93	90
3	 (5d)	4320	63	60	20	86	85
4	 (5e)	4320	44	38	20	88	84
5	 (5f)	4320	39	32	20	83	80
6	 (5g)	4320	82	69	20	98	94
7	 (5h)	4320	53	46	20	86	83

Downloaded by [Georgetown University] at 14:38 19 August 2013

ACCEPTED MANUSCRIPT

8	 (5i)	4320	74	69	20	93	89
9	 (5j)	4320	18	10	20	83	80
10	 (5k)	4320	32	28	20	85	84
11	 (5l)	4320	73	66	20	87	82
12	First reuse of resin 1	4320	74	70	20	92	90
13	Second reuse of resin 1	4320	72	66	20	89	86
14	Third reuse of resin 1	4320	75	65	20	88	87
15	Fourth reuse of resin 1	4320	69	67	20	83	82

[a] entries 1~15, 20mol% of resin 2a;

[b] entries 1~15, 10mol% of resin 2a, MW 110°C;

[c] Conversion based on the aldehyde and determined by HPLC or GC-MS;

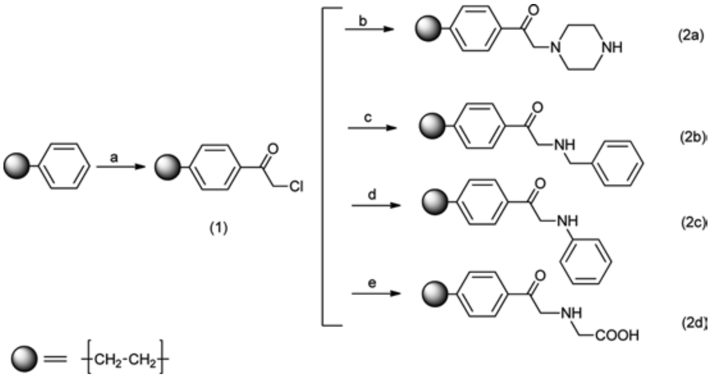
[d] determined by HPLC or GC-MS;

Downloaded by [Georgetown University] at 14:38 19 August 2013

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

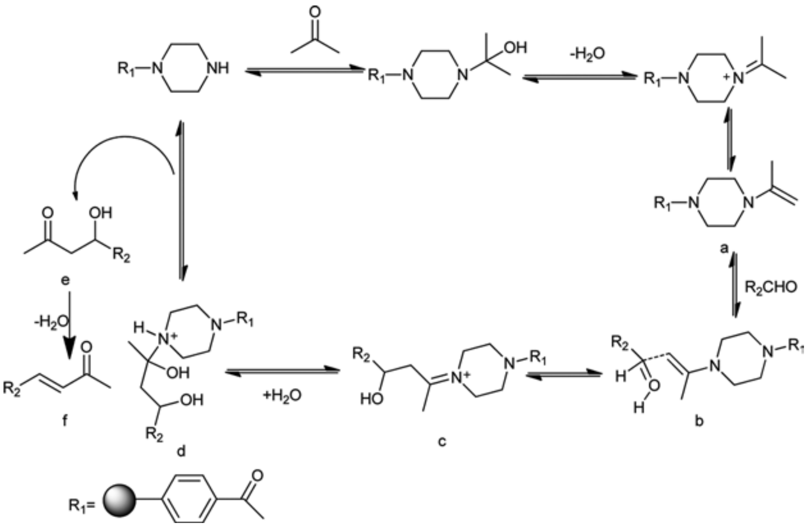
Scheme 1. Synthesis of the resin-catalysts. Reagents and conditions: (a):$ClCH_2COCl$, $AlCl_3$, CH_2Cl_2, r.t.; (b): piperazine, K_2CO_3, DMF, 80℃; (c): benzylamine, DBU, DMSO, r.t. ; (d): aniline, DBU, DMSO, r.t. ; (e): glycine, DBU, DMSO, r.t.



Downloaded by [Georgetown University] at 14:38 19 August 2013

ACCEPTED MANUSCRIPT

Scheme 2. Proposed enamine mechanism of aldol reaction catalyzed by imino group-bearing organocatalysts



Downloaded by [Georgetown University] at 14:38 19 August 2013