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Resin-Immobilized Pyrrolidine-Based Chiral Organocatalysts for Asymmetric Michael Additions of Ketones and Aldehydes to Nitroolefins

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Abstract: Based on the electrostatic adsorption between acidic resins and organocatalysts, a series of resin-supported chiral organocatalysts were designed and synthesized. They were evaluated for the asymmetric Michael addition of cyclohexanone with nitrostyrene, in which, catalyst **3** (Figure 1) exhibited the best catalytic performance. This reaction proceeded under catalyst **3** smoothly at room temperature without any solvent or additive and could give product with high yield (95%) and good stereoselectivity (90% ee, 98:2 dr). Encouragingly, catalyst **3** was easily isolated and reused for 16 consecutive runs without obvious loss of reaction enantioselectivity. Furthermore, it was successfully applied to catalyze the reactions of a series of ketones and aldehydes with nitroolefins.

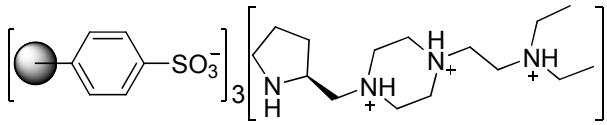

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Fig. 1. The structure of catalyst **3**

Key Words: Organocatalysis; Asymmetric Michael addition; Immobilization; Environmental friendliness

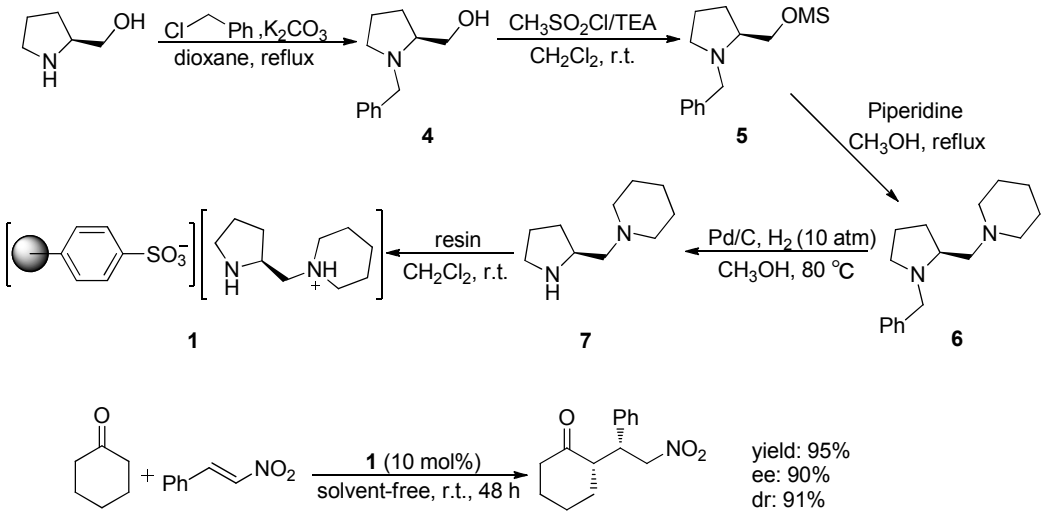
Michael addition is one of the most important carbon-carbon bond-forming reactions in organic synthesis.[1] Organocatalytic asymmetric Michael addition has attracted intensive attention in recent years due to its environmental friendliness and the generation of multiple stereogenic centers in a single step.[2] Pyrrolidine-based derivatives have been demonstrated to be effective asymmetric catalysts for the asymmetric Michael additions of aldehydes and ketones with nitroolefins.[3] Number of highly stereoselective catalysts have been developed and applied for these reactions.[3]

Normally, organocatalysts are difficult to be separated and recycled.

Environmental concerns associated with chemical processes have encouraged the development of environmental friendly methodologies for organic reactions. Recently, immobilization of chiral organocatalysts on supports has received more and more interests,[4] just because immobilized catalysts are easier to be recycled. However, most of them suffered from low efficiency, poor stereoselectivity and short lifespan.

In 2008, Sanzhong Luo et al. designed and synthesized a series of noncovalently supported chiral amine catalysts for asymmetric direct aldol and Michael addition reactions.[5] In this report, the organocatalysts were immobilized on the acidic supporter by electrostatic force. Then, in 2011, a comprehensive review of non-covalent immobilization of asymmetric organocatalysts was provided by Long Zhang.[6] This strategy inspired us greatly.

Thus, we chose ion-exchange resins as supports and synthesized a resin-immobilized organocatalyst **1** (Scheme 1), whose structure was similar to the catalyst reported by Sanzhong Luo in 2008. It was employed to catalyze the Michael reaction of cyclohexanone with trans-*β*-nitrostyrolene (molar ratio 10:1) smoothly at room temperature in high yield (95%), good diastereoselectivity (97:3 dr) and enantioselectivity (90% ee) without any solvent or additive.



Scheme 1. Synthesis of catalyst **1** and its application in the Michael addition

The catalytic mechanism of catalyst **1** is similar to many other proline derivative catalysts which have been reported.[7] A possible transition state model is proposed as

Fig.2. The secondary amine of the pyrrolidine ring activates the cyclohexanone through the formation of an enamine intermediate. The hydrogen bond donor between the nitro group and the tertiary amine, directs the nitrostyrene to attack the *re*-face of the enamine.

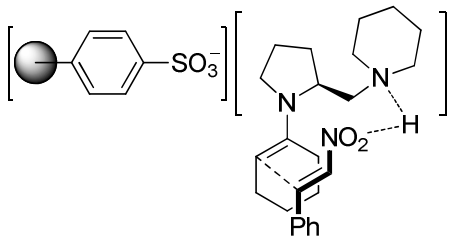
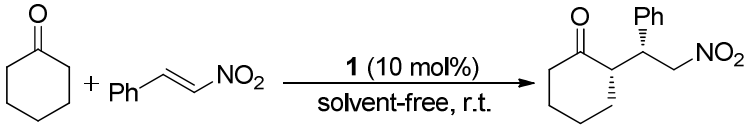


Fig. 2. A possible transition state

After completion of the reaction, catalyst **1** was simply separated from the reaction mixture by filtration, washed by CH_2Cl_2 (10 mL*3) and dried at 40 □ for 1 h. Unfortunately, when catalyst **1** was recycled for 2nd and 3rd runs, its activity declined dramatically (Table 1).

Table 1. Successive trials by using recyclable catalyst **1**.[a]



Trial	Time (h)	Yield (%)[b]	ee (%)[c]	dr[d]
1	48	95	90	97:3
2	72	86	89	97:3
3	96	63	89	97:3

[a] Cylcohexanone (10.0 mmol), nitrostyrene (1.0 mmol), reused **1** (contains 0.10 mmol of active loading), solvent-free, room temperature. [b] Isolated yields. [c] Determined by HPLC using chiralpak AS-H column. [d] Determined by ^{1}H NMR.

In order to figure out the way by which catalyst **1** deactivated so quickly, we concentrated the filtrate after the filtration of catalyst **1**. As a result, compound **7** was detected by TLC (thin-layer chromatography) and was determined by ^{1}H NMR. This result illustrated that catalyst **1** was unstable, its active component: compound **7,** partly leaked from the resin and dissolved in the liquid phase.

Then, what was the percentage of the loss of effective ingredients? With the purpose of figuring out this problem, pure and enough compound **6** which was got with the method in Scheme 1, was applied to make up 0.1 mol/L, 0.2 mol/L, 0.3 mol/L and 0.4 mol/L methanol solutions. Keeping the injected volume as 10 μL, the four levels of solutions were tested on HPLC using Agilent Prep-C18 Scalar PN440910-902 column. By peak area as X-axis and concentration of solution as Y-axis, a straight line $\mathbf{L_1}$ was fitted (Figure 3).

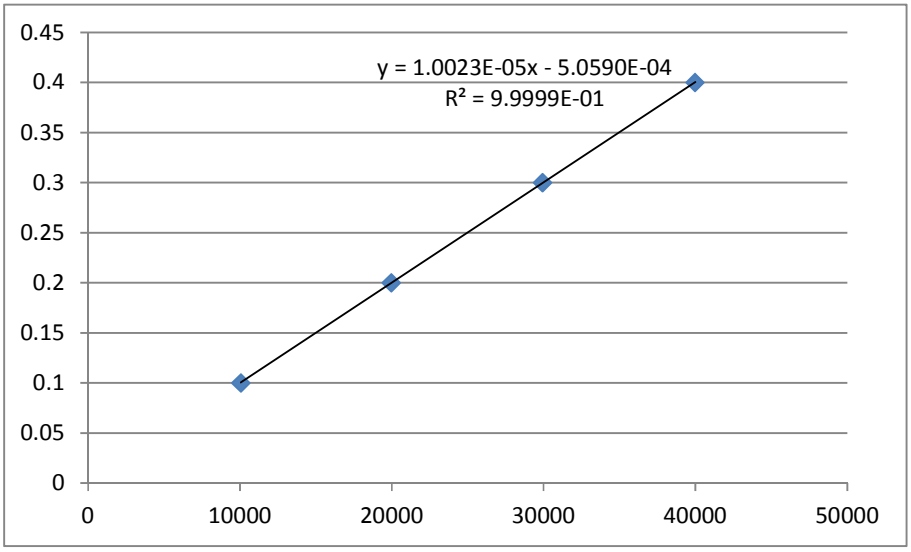
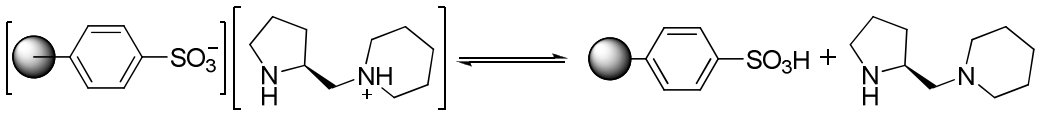


Fig. 3. The fitting line $\mathbf{L_1}$

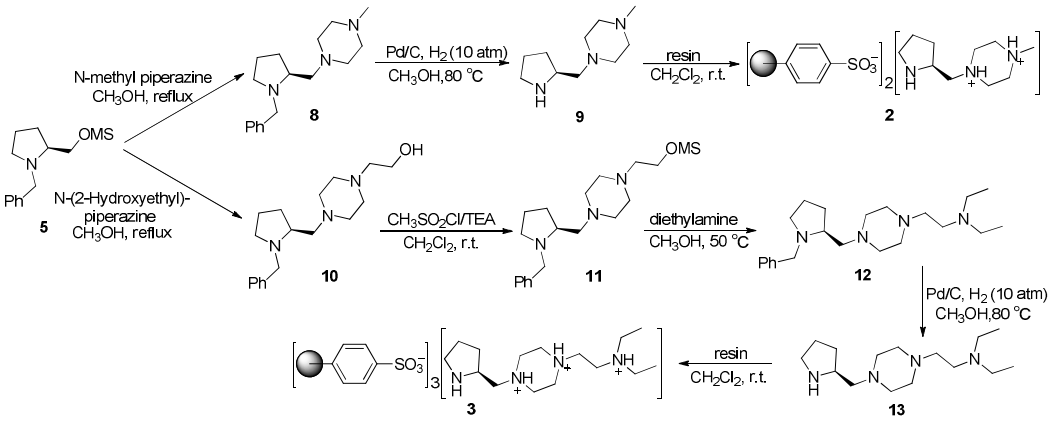
Concurrently, we increased the amount of the above Michael addition reaction by 10 times (cylcohexanone 100 mmol, nitrostyrene 10mmol, catalyst **1** containing 1mmol active loading). After completion of the reaction, the mixture was filtered, washed by CH_2Cl_2 (100 mL*3), and purified by column chromatography to afford compound **7**. Then, it was employed to react with plenty of benzyl chloride, purified by column chromatography to obtain compound **6**, and 1 mL methanol was added. Then, It was tested on HPLC (injected volume: 10 μL). From the equation of $\mathbf{L_1}$ and the peak area of the sample, the concentration of the sample was calculated effortlessly. Thus, there were 20.29% compound **7** leaking from catalyst **1**.

As we knew, in catalyst **1**, the linkage between the organocatalyst and the support was electrostatic force, which was weaker than covalent bond. In the reaction mixture, there was probably an adsorption-desorption equilibrium (Scheme 2).



Scheme 2. The adsorption-desorption equilibrium in the reaction mixture

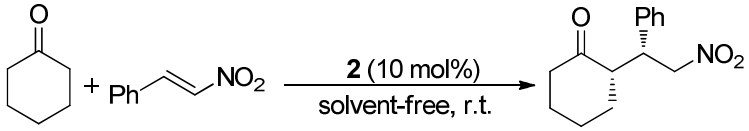
Then, if the number of tertiary nitrogen-atom of the organocatalyst was increased, the binding sites between the support and organocatalyst would be increased. In this way, the linkage would be enhanced, and the equilibrium would move left, so the service life of catalyst would be prolonged. Therefore, we additionally designed and synthesized two resin-immobilized organocatalysts **2** and **3** (Scheme 3).



Scheme 3. Synthesis of catalysts **2** and **3**

Then, catalysts **2** and **3** were empolyed to catalyze the asymmetric Michael addition of cyclohexanone with trans-*β*-nitrostyrolene. We were pleased to find that, under the same reaction conditions, **2** could be used for 5 runs (Table 2), meanwhile, **3** exhibited much better catalytic performance and could be used for 16 consecutive runs without significant loss of reaction enantioselectivity (Table 3).

Table 2. Successive trials by using recyclable catalyst **2**.[a]

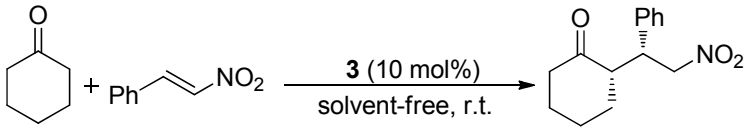


Trial	Time (h)	Yield (%)[b]	ee (%)[c]	dr[d]
1	48	95	91	97:3

2	72	95	90	98:2
3	72	93	90	97:3
4	96	93	91	97:3
5	96	88	89	97:3

[a] Cylcohexanone (10.0 mmol), nitrostyrene (1.0 mmol), reused **2** (contains 0.10 mmol of active loading) under solvent-free reaction conditions at room temperature. [b] Isolated yields. [c] Determined by HPLC using chiralpak AS-H column. [d] Determined by ^{1}H NMR.

Table 3. Successive trials by using recyclable catalyst **3**.[a]



Trial	Time (h)	Yield (%)[b]	ee (%)[c]	dr[d]
1	48	95	90	98:2
2	48	95	91	97:3
3	48	92	90	98:2
4	72	93	90	97:3
5	72	93	91	97:3
6	72	92	91	97:3
7	72	90	90	97:3
8	72	89	89	98:2
9	72	90	90	97:3
10	96	92	90	97:3
11	96	92	91	97:3
12	96	90	89	97:3
13	96	89	89	97:3
14	96	90	90	97:3
15	96	88	90	97:3
16	96	85	90	97:3

[a] Cylcohexanone (10.0 mmol), nitrostyrene (1.0 mmol), reused **3** (contains 0.10 mmol of active loading) under solvent-free reaction conditions at room temperature. [b] Isolated yields. [c] Determined by HPLC using chiralpak AS-H column. [d] Determined by ^{1}H NMR.

We analyzed the filtrate after the first run of catalysts **2** and **3**, just like what we

did to catalyst **1**. However, we could not find the compound **9** or **12** by TLC, perhaps because it was only a trace of active component leaking from the support.

Then, we studied that how much the loss of effective ingredients was, by using the "fitting line" method (Figure 4). Compound **8** was applied to make up 0.025 mol/L, 0.05 mol/L, 0.075mol/L and 0.10 mol/L methanol solutions, and other conditions were same with that of testing catalyst **1**. As a result, there were 5.42% compound **9** leaking from the support of catalyst **2**.

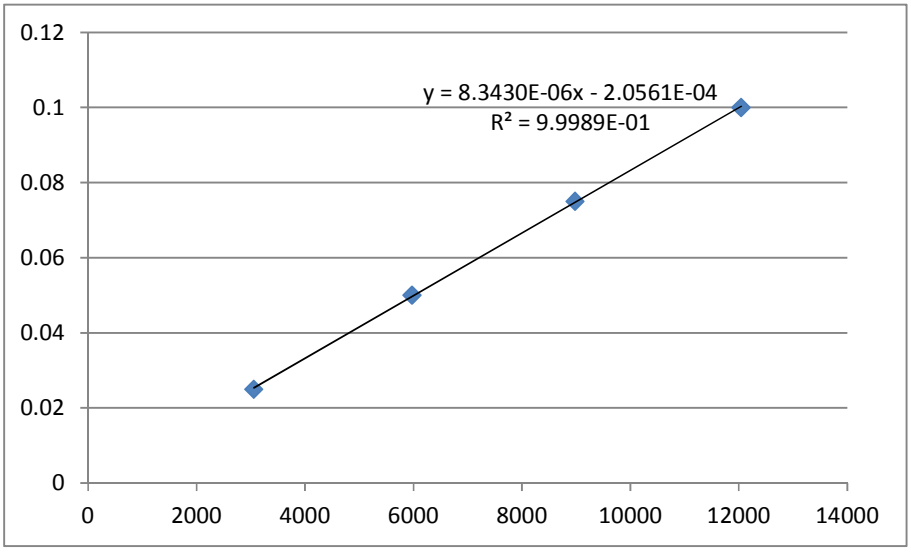


Fig. 4. The fitting line $\mathbf{L_2}$

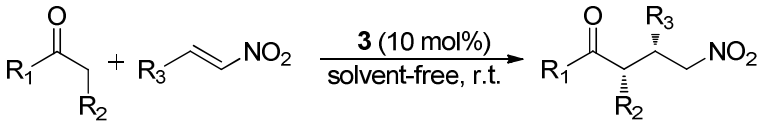
We also attempted to provide the percentage of the loss of active components of catalyst **3** with the similar method. However, there was so little compound **12** that we could not isolate it from the filtrate.

As the above results showed, we could conclude that increasing the number of tertiary nitrogen-atom of organocatalyst indeed enhanced the linkage between resin and organocatalyst, and thus the stability of the catalyst was effectively improved.

Based on the excellent performance of catalyst **3**, we applied it for a wide range of Michael addition reactions between ketones and aldehdyes to nitroolefins, the obtained results were summarized in Table 4. It was obvious that catalyst **3** displayed satisfied results for all the Michael additions of cyclohexanone with nitroolefins. Dihydro-2*H*-pyran-4(3*H*)-one also showed to be an efficient Michael donor with high yield (92%) and good enantioselectivity (79% ee) (Table 4, entry 11). With the increase of the length of side chain of the ketone, the enantioselectivity of the Michael

addition process was improved (Table 4, entries 12-13). The nitroolefin bearing nitro group at *p*-position of benzene ring yielded the adduct in excellent enantioselectivity (99% ee) and diastereoselectivity (99:1 dr) (Table 4, entry 9), much better than that of nitroolefins with chlorine or bromine (Table 4, entries 4-8), electron-donating groups (Table 4, entries 2-3) or nitro group at *o*-position (Table 4, entry 10). However, cyclopentanone, cycloheptanone, propanal and *n*-butyraldehyde only presented the adducts with moderate diastereoselectivities (Table 4, entries 14-17).

Table 4. Asymmetric Michael addtions of ketones and aldehydes to nitroolefins[a]



Entry	R_1	R_2	R_3	Yield (%)[b]	ee (%)[c]	dr[d]
1	-$(CH_2)_4$-		Ph	95	90	98:2
2	-$(CH_2)_4$-		4-Me-Ph	95	85	99:1
3	-$(CH_2)_4$-		4-MeO-Ph	96	75	95:5
4	-$(CH_2)_4$-		4-Cl-Ph	95	88	93:7
5	-$(CH_2)_4$-		3-Cl-Ph	95	80	96:4
6	-$(CH_2)_4$-		2-Cl-Ph	94	84	99:1
7	-$(CH_2)_4$-		2,4-Cl-Ph	94	70	99:1
8	-$(CH_2)_4$-		4-Br-Ph	95	73	96:4
9	-$(CH_2)_4$-		4-NO_2	95	99	99:1
10	-$(CH_2)_4$-		2-NO_2	95	85	99:1
11	-$(CH_2CH_2OCH_2)$		Ph	92	79	99:1
12	Me	H	Ph	88	15	--
13	Et	Me	Ph	70	90	99:1
14	-$(CH_2)_3$-		Ph	61	50	80:20
15	-$(CH_2)_5$-		Ph	64	18	96:4
16	H	Me	Ph	82	25	95:5
17	H	Et	Ph	83	32	56:44

[a] Ketones or aldehydes (10.0 mmol), nitroolefins (1.0 mmol), catalyst **3** (contains 0.10 mmol of active loading) under solvent-free reaction conditions at room temperature. [b] Isolated yields. [c] Determined by HPLC using chiralpak AS-H column. [d] Determined by ^{1}H NMR.

In summary, a series of resin-immobilized pyrrolidine-based chiral organocatalysts have been developed for asymmetric Michael additions of cyclohexanone with nitrostyrene. Among them, catalyst **3** exhibited outstanding performance and presented products with high yield (95%) and good stereoselectivities (90% ee, 98:2 dr) at room temperature without any solvent or additive. Moreover, **3** can be easily isolated and reused for 16 consecutive runs without significant loss of reaction enantioselectivity. It could also be applied for a series of Michael additions of ketones and aldehydes to nitroolefins. These advantages make **3** a potential catalyst for industrial applications.

References and notes:

1. (a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.*, *2002*, 1877; (b) J. Christoffers, A. Baro, *Angew. Chem. Int. Ed.*, 2003, **15**, 1688.
2. T. Miao, L. Wang, *Tetrahedron Letters*, 2008, **13**, 2173.
3. (a) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.*, 2003, **5**, 2559; (b) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.*, 2004, **126**, 9558; (c) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biomol. Chem.*, 2005, **3**, 84; (d) E. Reyes, J. L. Vicario, D. Badia, L. Carrillo, *Org. Lett.*, 2006, **8**, 6135; (e) B. Ni, Q. Zhang, A. D. Headley, *Tetrahedron: Asymmetry*, 2007, **18**, 1443; (f) D. -Q. Xu, L. -P. Wang, S. -P. Luo, Y. -F. Wang, S. Zhang, Z. -Y. Xu, *Eur. J. Org. Chem*., 2008, 1049; (g) B. Ni, Q. -Y. Zhang, K. Dhungana, A. D. Headley, *Org. Lett*., 2009, **11**, 1037; (h) Z. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.*, 2010, **132**, 50.
4. (a) E. Alza, X. C. Cambeiro, C. Jimeno, M. A. Pericàs, *Org. Lett.*, 2007, **9**, 3717; (b) L. T. Shukron, M. Portnoy, *Adv. Synth. Catal.*, 2009, **351**, 541; (c) P. H. Li, L. Wang, M. Wang, Y. C. Zhang, *Eur. J. Org. Chem*., 2008, 1157; (d) B. G. Wang, B. C. Ma, Q. Wang, W. Wang, *Adv. Synth. Catal.*, 2010, **352**, 2923; (e) E. Alza, S. Sayalero, P. Kasaplar, D. Almasi, M. A. Pericàs, *Chem. Eur. J.*, 2011, **17**, 11585; (f) P. Kasaplar, P. Riente, C. Hartmann, M. A. Pericàs, *Adv. Synth. Catal.*, 2012, **354**, 2905.
5. S. Z. Luo, J. Y. Li, L. Zhang, H. Xu, J. P. Cheng, *Chem. Eur. J.*, 2008, **14**, 1273.
6. L. Zhang, S. Z. Luo, J. P. Cheng, *Catal. Sci. Technol.*, 2011, **1**, 507.
7. (a) N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas III, *Org. Lett.*, 2004, **6**, 2527; (b) B. Ni, Q. Y. Zhang, A. D. Headley, *Tetrahedron Letters*, 2008, **49**, 1249; (c) X. H. Cao, G. Wang, R. C. Zhang, Y. Y. Wei, W. Wang, H. C. Sun, L. G. Chen,

Org. Biomol. Chem., 2011, **9**, 6487; (d) S. V. Pansare, K. Pandy, *J. Am. Chem. Soc.*, 2006, **128**, 9624; (e) W. Wang, J. Wang, H. Li, *Angew. Chem. Int. Ed.*, 2005, **44**, 1369.