

# RSC Advances



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this is available.

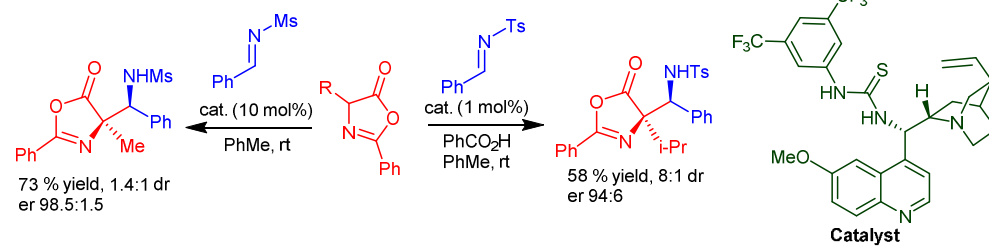
You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Graphical abstract for

## Enantioselective Addition of Oxazolones to *N*-Protected Imines Catalysed by Chiral Thioureas

M. Žabka, A. Malastová, R. Šebesta\*



Chiral thiourea-catalysed Mannich-type addition of oxazolones to imines, which provide highly functionalized amino oxazolones with quaternary stereogenic centres.

## COMMUNICATION

# Enantioselective Addition of Oxazolones to *N*-Protected Imines Catalysed by Chiral Thioureas

Cite this: DOI: 10.1039/x0xx00000x

Matej Žabka,<sup>a</sup> Andrea Malastová<sup>a</sup> and Radovan Šebesta<sup>\*a</sup>

Received 00th January 2012,

Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

**Hydrogen bond-catalysed aza-Mannich addition of oxazolones to various protected aldimines has been developed. The resulting, highly functionalized, oxazolones contain quaternary stereogenic centre and can serve as precursors for chiral  $\alpha,\beta$ -diamino acids with different protecting groups on each amino group. The process benefits from the versatile bifunctional thiourea catalysts, which affects the formation of these products in high yields and stereoselectivities.**

Enantiomerically pure  $\alpha$ -substituted  $\alpha,\beta$ -diamino acids constitute a group of useful building blocks for chiral auxiliaries and biologically active compounds, including peptides with antibiotic activity.<sup>1</sup> A number of reports have recently appeared dealing with the preparation of enantiopure  $\alpha,\beta$ -diamino acids by the Mannich reaction starting from oxazolones.<sup>2, 3</sup> Oxazol-5(4*H*)-ones are masked amino acid fragments,<sup>4, 5</sup> widely used in the construction of quaternary  $\alpha$ -amino acids.<sup>6-15</sup> These procedures, utilizing e.g. TMS-quinine,<sup>16</sup> chiral ion-pair catalysts including phosphonium salts,<sup>17, 18</sup> binaphthyl betaines,<sup>19</sup> phosphoric acid derivatives,<sup>20</sup> and gold complexes<sup>21</sup> give products in excellent yields and stereoselectivities. However, quite complex catalysts or high catalyst loadings are, usually, required. Catalysis using chiral hydrogen-bond donors, particularly thioureas and squaramides, has recently emerged as a frontier of research in asymmetric organocatalysis.<sup>22-25</sup> Chiral, bifunctional thiourea catalysts are capable of activating both the electrophile and the nucleophile, leading to an enantioenriched product.<sup>26-28</sup> Moreover, they offer superior advantages with respect to their stability and cost. Therefore, we decided to evaluate a series of easily prepared bifunctional thioureas to address the issue of stereoselective formation of  $\alpha,\beta$ -diamino acids by the Mannich reaction between oxazolones and imines.

In this context, we present chiral thiourea catalyzed Mannich type reaction of oxazolones with *N*-protected aldimines. Such additions have not been described with hydrogen-bonding catalysts so far.

Figure 1 depicts nine thioureas **1-3**,<sup>29-32</sup> **4-5**,<sup>33</sup> and which have been used in this study.

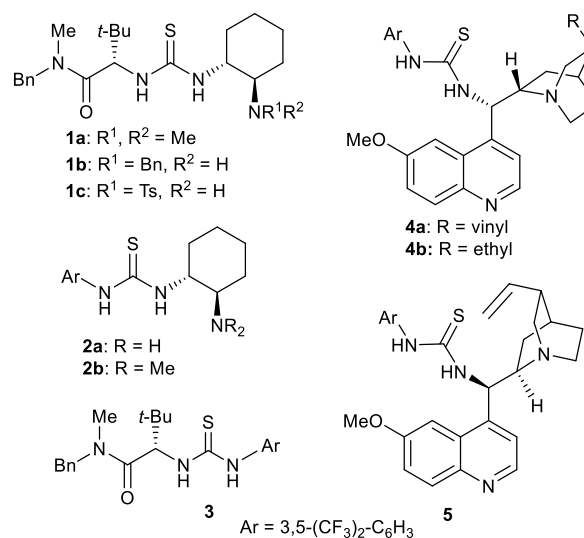


Figure 1. Thiourea catalysts used in this study.

Figure 2 depicts two squaramide catalysts **6** and **7**.<sup>34, 35</sup>

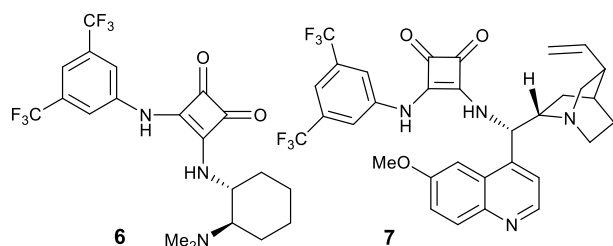
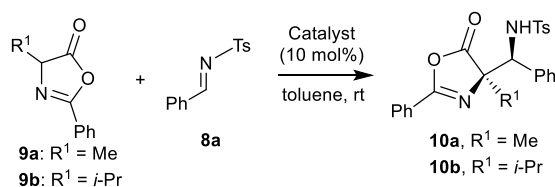


Figure 2. Squaramide catalysts used in this study.

We first screened the reaction between imine **8a** and oxazolone **9a** and planned to utilize several bifunctional thiourea catalysts, with different amine functionalities (Figure 1). We tested Jacobsen-type catalysts **1a-c** in toluene, which afforded product **10a** with poor enantioselectivity (Scheme 1, Table 1, entries 2-4). Excellent yield and a moderate enantioselectivity were achieved by using Takemoto catalyst (entry 6). Catalyst **3** with no amine functionality did not perform well. These results suggest that both tertiary or secondary amine functional group and an activating, electron-withdrawing substituent on the thiourea resulting in higher acidity are necessary for the good performance of the catalyst.<sup>36</sup> Thus cinchona-alkaloid catalyst **4a** gave the product in excellent yield and good enantioselectivity (Table 1, entry 9). We have also found that a small excess of the oxazolone (1.2 eq.) was beneficial for the reaction (Table 1, cf. entries 8-10). Structurally similar catalyst **4b** with an ethyl group instead of a vinyl group performed equally well as catalyst **4a**.



Scheme 1

Table 1. Screening of catalysts in the addition of oxazolone **9a** to imine **8a**.<sup>a</sup>

Entry	Catalyst	Yield (%) <sup>b</sup>	dr <sup>c</sup>	er <sup>d</sup>
1	<b>DABCO</b>	76	4.1:1	0
2	<b>1a</b>	71	2.1:1	51:49
3	<b>1b</b>	49	5.2:1	63:37
4	<b>1c</b>	18 <sup>g</sup>	1.5:1	54:46
5	<b>2a</b>	20 <sup>g</sup>	1.4:1	53:47
6	<b>2b</b>	99	3.7:1	17:83
7	<b>3</b>	25 <sup>g</sup>	0.9:1	59:41
8	<b>4a<sup>e</sup></b>	65	1.6:1	77:23
9	<b>4a</b>	82	3:1	90:10
10	<b>4a<sup>f</sup></b>	80	3.3:1	79:21
11	<b>4b</b>	78	3:1	90:10
12	<b>5</b>	64	1.5:1	37:63

<sup>a</sup> Experimental conditions: imine **6a** (0.1 mmol), oxazolone **7a** (1.2 eq.), catalyst (10 mol %), toluene (0.5 mL), rt, 18 h. <sup>b</sup> Combined isolated yield of both diastereomers; <sup>c</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>d</sup> er of the major diastereomer determined by HPLC analysis. <sup>e</sup> 1 eq. oxazolone was used. <sup>f</sup> 1.5 eq. oxazolone was used. <sup>g</sup> Conversion determined by <sup>1</sup>H NMR.

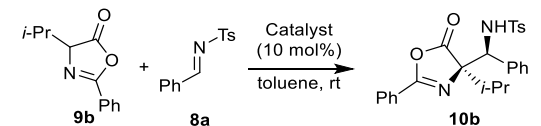
Our next goal was to screen solvents and evaluate concentration effects to achieve higher stereoselectivity. Experiments were typically conducted at 0.2 M concentration. Running the reaction at lower concentration (0.1 M) resulted in lower yield, but the selectivity did not improve (Table 2, entry 1). By using different, non-polar solvents, however, only small change was observed in terms of diastereo- and enantioselectivity (Table 2, entries 3-6). Use of acetonitrile as a more polar solvent led to inferior enantioselectivity, as this solvent can partially disrupt hydrogen bonds (Table 2, entry 7).

Table 2. Screening of solvents in the addition of oxazolone **9a** to imine **8a**.<sup>a</sup>

Entry	Solvent	Yield (%)	dr <sup>b</sup>	er <sup>c</sup>
1	PhMe <sup>d</sup>	55	2.3:1	89:11
2	PhMe <sup>e</sup>	43	2.6:1	89:11
3	CH <sub>2</sub> Cl <sub>2</sub>	53	2.3:1	87:13
4	xylenes	63	3:1	88:12
5	Et <sub>2</sub> O	72	3.5:1	90:10
6	CHCl <sub>3</sub>	64	2.6:1	84:16
7	MeCN	64	3:1	70:30

<sup>a</sup> Experimental conditions: imine **8a** (0.1 mmol), oxazolone **9a** (1.2 eq.), catalyst **4b** (10 mol %), solvent (0.5 mL), rt, 18 h. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup> er of the major diastereomer determined by HPLC analysis. <sup>d</sup> 0.1 M solution. <sup>e</sup> -35 °C to rt.

We then proceed to evaluate the reaction with more sterically demanding oxazolone **9b**. This substrate provided product **10b** with excellent diastereo- and enantioselectivity with catalyst **4a** at -5 °C (Table 3, entry 2). Increasing the concentration or adding molecular sieves (4A) did not have any effect on the selectivity (Table 3, entries 3 and 4). Lower catalyst loading (1 and 5 mol%) decreased the yield of product **10b** but its diastereomeric and enantiomeric purity remained high (Table 3, entries 5-6). Catalyst **4b** afforded slightly inferior result in comparison to catalyst **4a** (Table 3, entry 7). The catalyst **5**, which is the pseudo-enantiomer of catalyst **4a**, provided the product with the opposite stereochemistry in equally high enantiomeric ratio (Table 3, entry 8). Use of the squaramide-derived catalyst **6**, analogous to the Takemoto catalyst **2b**, led to inferior results (Table 3, entry 9). Squaramide catalyst **7**, derived from quinine, also gave the product with slightly lower enantioselectivity (Table 3, entry 10).

Table 3. Catalyst screening in the reaction with oxazolone **9b**.<sup>d</sup>


Entry	Catalyst	Yield (%)	dr <sup>b</sup>	er <sup>c</sup>
1	<b>4a</b>	58	8:1	88:12
2	<b>4a<sup>d</sup></b>	67	12:1	96:4
3	<b>4a<sup>e</sup></b>	78	12:1	93:7
4	<b>4a<sup>f</sup></b>	78	8:1	93:7
5	<b>4a<sup>g</sup></b>	58	8:1	94:6
6	<b>4a<sup>h</sup></b>	48	8:1	97:3
7	<b>4b</b>	50	8:1	92:8
8	<b>5</b>	82	8:1	10:90
9	<b>6</b>	67	3:1	33:67
10	<b>7</b>	44	4:1	86:14

<sup>a</sup> Experimental conditions: imine **8a** (0.1 mmol), oxazolone **7b** (1.2 eq.), catalyst **4a** (10 mol %), toluene (0.5 mL), rt, 18 h. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup> er of the major diastereomer determined by HPLC analysis. <sup>d</sup> -5 °C, 3 days. <sup>e</sup> 0.4 M solution. <sup>f</sup> MS 4A (50 mg) added. <sup>g</sup> 1 mol %; <sup>h</sup> 5 mol %.

We noticed that the product from oxazolone **9b** was formed with good enantioselectivity only if it was contaminated by benzoic anhydride impurity. Benzoic anhydride may remain in the oxazolone from its synthesis and it probably forms benzoic acid under the reaction conditions. It is difficult to completely remove it from the oxazolones. When particular care was taken to remove it, the reaction surprisingly proceeded without any stereoselectivity (Table 4, entry 1). The acid may facilitate nucleophile formation from oxazolone as well as activate the imine. In terms of stereoselectivity, the acid helps in better organization of the transition state. Therefore, we screened several acid co-catalysts. Indeed, we found that acid additive is necessary for the good performance of the catalyst, otherwise only racemic mixture was obtained. Benzoic acid afforded the best results in terms of diastereomeric and enantiomeric purity of the product **10b** (Table 4, entry 2). Interestingly, use of sodium benzoate also improved the reaction to certain degree (Table 4, entry 3). This indicates involvement of the benzoate anion in the enantio-determining step of the reaction. No improvement was achieved using different acids with varying acidities (entries 4-9). Interestingly, chiral mandelic acid gave the same result when used as racemate or enantiomerically pure. This suggests that the influence of the anion of acid is in overall steric volume rather than any specific interactions in the transition state. A similar, but less pronounced effect of the acid co-catalyst was observed in an aldol addition.<sup>37</sup>

Table 4. Screening of acid additives in the reaction of oxazolone **9b** with imine **8a**.<sup>d</sup>

Entry	Additive	Yield (%)	dr <sup>b</sup>	er <sup>c</sup>
1	-	52	1.2:1	49:51
2	PhCO <sub>2</sub> H	54	13:1	95:5
3	PhCO <sub>2</sub> Na	62	4:1	73:27
4	AcOH <sup>d</sup>	36	6.3:1	91:9
5	TFA	48	5.5:1	85:15
6	2-IC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	65	3:1	77:23
7	4-BrC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	43	5.5:1	85:15
8	( <i>RS</i> )-mandelic acid	35	9:1	93:7
9	( <i>R</i> )-mandelic acid	35	9:1	93:7
10	PhCH <sub>2</sub> CO <sub>2</sub> H	68	6.5:1	86:14

<sup>a</sup> Experimental conditions: imine **6a** (0.1 mmol), oxazolone **7b** (1.2 eq.), catalyst **4a** (10 mol %), additive (10 mol %), toluene (0.5 mL), rt, 18 h. <sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup> er of the major diastereomer determined by HPLC analysis. <sup>d</sup> 100 mol % used.

Next, we varied the sulfonyl protecting group at the imine. Mesyl-protected imine **8b** provided product **10c** in high yield with excellent enantioselectivity. Differently substituted oxazolones **9b** (*i*-Pr) and **9c** (Bn) gave inferior results with mesyl imine **8b**. High diastereoselectivity was achieved with naphthyl imine **8c** while the enantioselectivity remained high. More sterically demanding imines **8d-e** (2,4,6-trimethylphenyl and 2,4,6-tri(isopropyl)phenyl) gave products with high enantiomeric ratios only with oxazolone **9b**, rather than with **9a**. Figure 3 depicts structures of all products **10**.

These results show that in order to achieve high selectivity, steric demands of substrates must match. It seems that oxazolones with less sterically demanding substituents (e.g. **9a**) should be combined with imines containing smaller protecting group, such as mesyl (**8b**). On the other hand, more sterically demanding oxazolones need imines with bigger protecting groups.

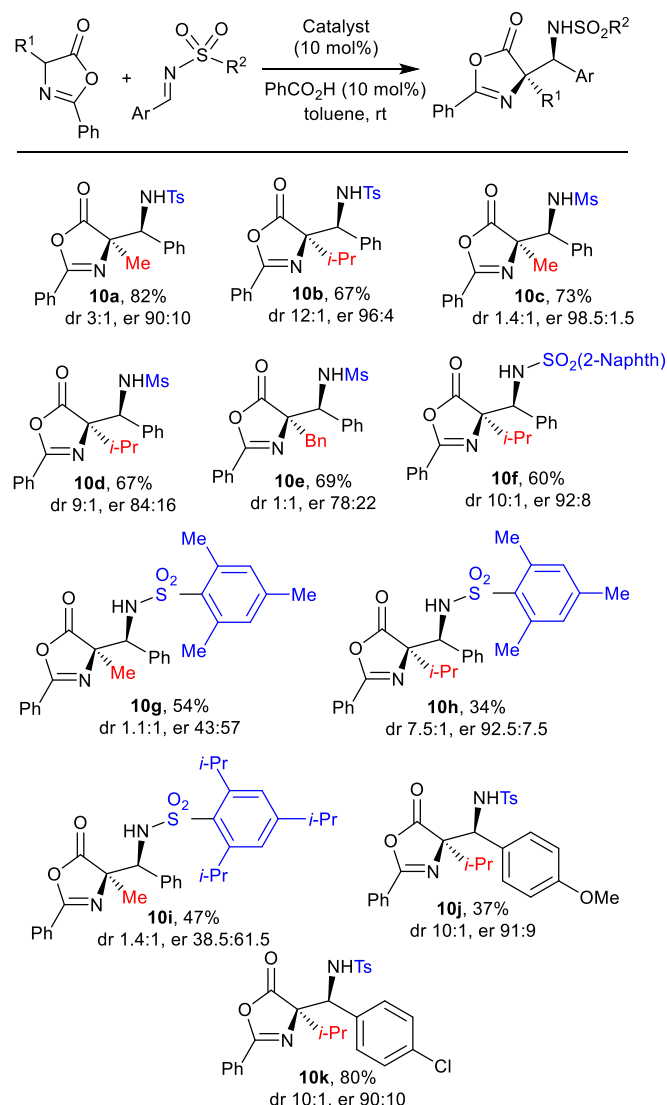


Figure 3. Oxazolones **10a-k** obtained by the reactions of imine **8** (0.1 mmol), oxazolone **9** (1.2 eq.), catalyst **4a** (10 mol %), PhCO<sub>2</sub>H (10 mol %), toluene (0.5 mL), rt, 18 h.

We have confirmed absolute configuration of compounds **10a** and **10b** to be (*S,R*) by comparison of its electronic CD spectra with theoretically calculated ones. Figure 4 shows spectra for compound **10b**; for more details see Supporting information.

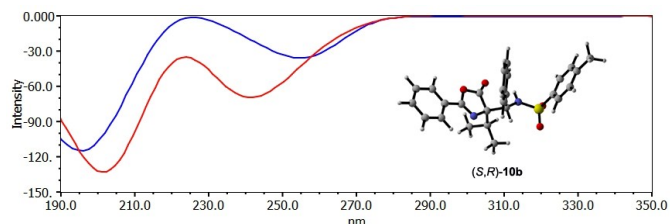
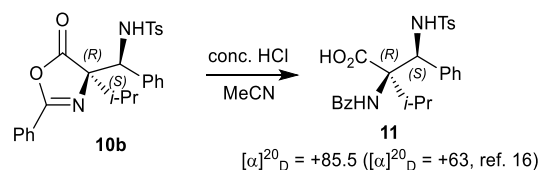


Figure 4. Comparison of theoretical and experimental ECD spectra of derivative (*S,R*)-**10b**; red curve - experimental spectrum; blue curve - calculated conformationally averaged spectrum (DFT, M06/def2\_TZVP).

With the help of quantum-chemical calculations (HF, 3-21G), we also proposed a possible model of transition state for the addition, which explains observed stereochemistry of products (see Supporting Information).

Azlactones **10** can be cleaved in acidic medium to  $\alpha,\beta$ -diamino acids. The compound **10b** afforded acid **11** in quantitative yield (Scheme 2). By comparison of the sign of its optical rotation with literature data, we further confirmed absolute configuration of the azlactone products.<sup>16</sup>



Scheme 2.

## Conclusions

Hydrogen bond-catalysed Mannich-type addition of oxazolones to protected imines affords highly functionalized oxazolones. These compounds contain quaternary stereogenic centre and can afford chiral  $\alpha,\beta$ -diamino acids with orthogonally protected amino groups. The products were obtained in medium to high yields and stereoselectivities, which depend on the substitution pattern of the starting materials. Relative and absolute configurations of products were determined by NMR and comparison of calculated and measured CD spectra. Stereochemical course of the addition was explained with the help of quantum-chemical calculations.

We acknowledge support from the Slovak Grant Agency Vega, grant no.: 1/0543/11.

## Notes and references

<sup>a</sup> Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University, Mlynská Dolina CH-2, SK-842 15 Bratislava, Slovakia.

Electronic Supplementary Information (ESI) available: experimental procedures, characterisation data, and computational details. See DOI: 10.1039/c000000x/

1. A. Viso, R. Fernández de la Pradilla, A. García and A. Flores, *Chem. Rev.*, 2005, **105**, 3167-3196.
2. R. G. Arrayás and J. C. Carretero, *Chem. Soc. Rev.*, 2009, **38**, 1940-1948.
3. J. M. M. Verkade, L. J. C. V. Hemert, P. J. L. M. Quaedflieg and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29-41.
4. A.-N. R. Alba and R. Rios, *Chem. Asian J.*, 2011, **6**, 720-734.
5. J. S. Fisk, R. A. Mosey and J. J. Tepe, *Chem. Soc. Rev.*, 2007, **36**, 1432-1440.
6. A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller and J. Lex, *Angew. Chem. Int. Ed.*, 2005, **44**, 807-811.
7. J. Alemán, A. Milelli, S. Cabrera, E. Reyes and K. A. Jørgensen, *Chem. Eur. J.*, 2008, **14**, 10958-10966.
8. Y. Hayashi, K. Obi, Y. Ohta, D. Okamura and H. Ishikawa, *Chem. Asian J.*, 2009, **4**, 246-249.
9. H. Jiang, M. W. Paixão, D. Monge and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2010, **132**, 2775-2783.
10. A.-N. R. Alba, X. Companyó, G. Valero, A. Moyano and R. Rios, *Chem. Eur. J.*, 2010, **16**, 5354-5361.
11. A.-N. R. Alba, G. Valero, T. Calbet, M. Font-Bardía, A. Moyano and R. Rios, *Chem. Eur. J.*, 2010, **16**, 9884-9889.

12. C. K. De, N. Mittal and D. Seidel, *J. Am. Chem. Soc.*, 2011, **133**, 16802-16805.
13. M. Terada and H. Nii, *Chem. Eur. J.*, 2011, **17**, 1760-1763.
14. C.-W. Cai, X.-L. Zhu, S. Wu, Z.-L. Zuo, L.-L. Yu, D.-B. Qin, Q.-Z. Liu and L.-H. Jing, *Eur. J. Org. Chem.*, 2013, **2013**, 456-459.
15. M. Terada, H. Tanaka and K. Sorimachi, *J. Am. Chem. Soc.*, 2009, **131**, 3430-3431.
16. X. Liu, L. Deng, X. Jiang, W. Yan, C. Liu and R. Wang, *Org. Lett.*, 2010, **12**, 876-879.
17. D. Uraguchi, Y. Ueki and T. Ooi, *J. Am. Chem. Soc.*, 2008, **130**, 14088-14089.
18. D. Uraguchi, K. Yoshioka, Y. Ueki and T. Ooi, *J. Am. Chem. Soc.*, 2012, **134**, 19370-19373.
19. W.-Q. Zhang, L.-F. Cheng, J. Yu and L.-Z. Gong, *Angew. Chem. Int. Ed.*, 2012, **51**, 4085-4088.
20. S.-H. Shi, F.-P. Huang, P. Zhu, Z.-W. Dong and X.-P. Hui, *Org. Lett.*, 2012, **14**, 2010-2013.
21. A. D. Melhado, G. W. Amarante, Z. J. Wang, M. Luparia and F. D. Toste, *J. Am. Chem. Soc.*, 2011, **133**, 3517-3527.
22. R. Ian Storer, C. Aciro and L. H. Jones, *Chem. Soc. Rev.*, 2011, **40**, 2330-2346.
23. S. J. Connon, *Chem. Commun.*, 2008, 2499-2510.
24. B. List and K. Maruoka, *Asymmetric Organocatalysis, Workbench Edition*, Thieme Chemistry, Stuttgart, 2012.
25. J. Alemán, A. Parra, H. Jiang and K. A. Jørgensen, *Chem. Eur. J.*, 2011, **17**, 6890-6899.
26. A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713-5743.
27. W.-Y. Siau and J. Wang, *Catal. Sci. Technol.*, 2011, **1**, 1298-1310.
28. Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.*, 2009, **38**, 1187-1198.
29. A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964-12965.
30. S. E. Reisman, A. G. Doyle and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2008, **130**, 7198-7199.
31. K. Dudziński, A. M. Pakulska and P. Kwiatkowski, *Org. Lett.*, 2012, **14**, 4222-4225.
32. A. Berkessel and B. Seelig, *Synthesis*, 2009, 2113-2115.
33. B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967-1969.
34. H. Konishi, T. Y. Lam, J. P. Malerich and V. H. Rawal, *Org. Lett.*, 2010, **12**, 2028-2031.
35. W. Yang and D.-M. Du, *Org. Lett.*, 2010, **12**, 5450-5453.
36. G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert and P. R. Schreiner, *Org. Lett.*, 2012, **14**, 1724-1727.
37. R. P. Singh, B. M. Foxman and L. Deng, *J. Am. Chem. Soc.*, 2010, **132**, 9558-9560.