BCSJ Bulletin of the Chemical Society of Japan

Asymmetric Michael addition of isobutyraldehyde to nitroolefins using an α,α-diphenyl-(*S*)-prolinol-derived chiral diamine catalyst

Wei Han and Takeshi Oriyama*

Advance Publication on the web May 12, 2020
doi:10.1246/bcsj.20200078

Asymmetric Michael addition of isobutyraldehyde to nitroolefins using an α,α-diphenyl-(*S*)-prolinol-derived chiral diamine catalyst

Wei Han and Takeshi Oriyama*

Department of Chemistry, Faculty of Science, Ibaraki University, 2-1-1 Bunkyo, Mito, Ibaraki 310-8512

E-mail: takeshi.oriyama.sci@vc.ibaraki.ac.jp

Abstract

The enantioselective Michael addition of isobutyraldehyde to nitroolefin analogs was achieved by utilizing an α,α-diphenyl-(*S*)-prolinol-derived chiral diamine catalyst **1b**. In this protocol, catalyst and additive loadings were reduced to 5 mol% respectively, due to the presence of the tertiary amine moiety in **1b**.

Keywords: asymmetric catalysis, Michael addition, chiral diamine

1. Introduction

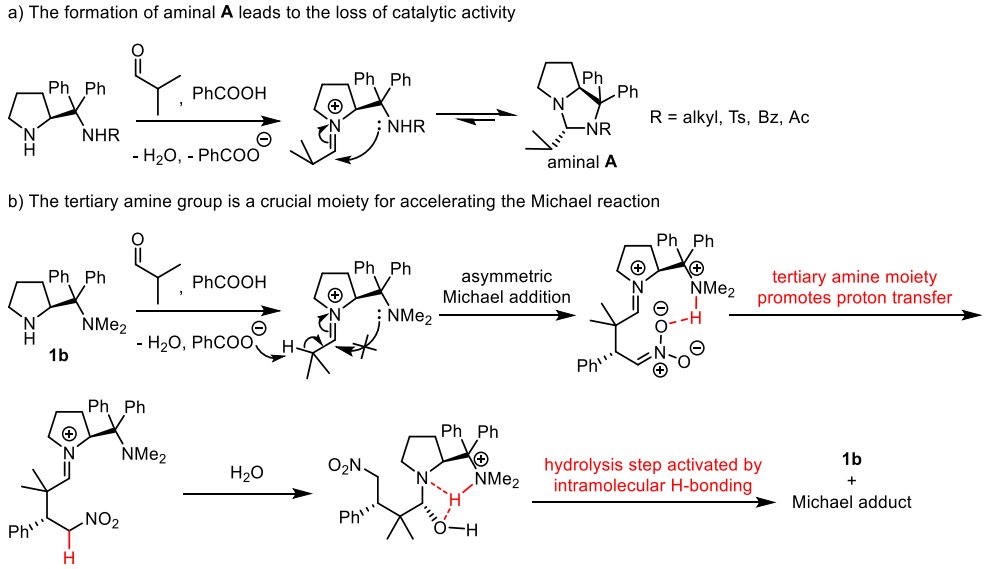
Enamine catalysis is one of the most powerful and successful strategies for asymmetric synthesis.[1] In particular, chiral primary or secondary amine-based organocatalysts are extremely useful for the enantioselective conjugate addition of carbonyl compounds to nitroolefins via activation of the enamine. The optically active γ-nitrocarbonyl products are versatile precursors for constructing bioactive compounds.[2] Although, the organocatalytic asymmetric Michael addition of linear aldehydes/ketones to nitroolefins has been studied extensively,[3] Michael addition reactions using α-branched aldehydes as Michael donors have received little attention owing to the difficulty in generating an all-carbon quaternary center in the γ-nitroaldehyde Michael adducts.

Generally, the construction of chiral compounds containing a quaternary carbon center is a challenging task in asymmetric synthesis. Despite the progress in research on the organocatalytic asymmetric Michael addition of α,α-disubstituted aldehydes to nitroolefins, as reported by Barbas *et al.*,[4] and the effort devoted to investigating this transformation,[5] only a few primary amine catalysts have been shown to achieve high enantioselectivity for the Michael addition of α-branched aldehydes.[5f,5h,6] Moreover, high catalyst or additive loading of 20 mol% or more is often needed in many circumstances.[4,5b,5c,5g,5i,5k,6a,7] To date, procedures for this transformation using the catalyst loading less than 5 mol% are limited.[5o,6b] Thus, research on conducting more efficient asymmetric Michael addition of α,α-disubstituted aldehydes to nitroolefins is still desired.

Among the numerous chiral aminocatalysts currently in use, diaryl-(*S*)-prolinol and the corresponding silyl ether derivatives are known to be effective for various organic reactions, including, asymmetric Michael additions, Mannich, aldol, Diels-Alder, Friedel-Crafts, α-, β- and γ-functionalization of carbonyl compounds, and cyclization reactions.[8] With these chiral aminocatalysts, high to excellent enantioselectivity was achieved in these transformations.

By utilizing nitroolefins, the more catalytically activity diphenyl-(*S*)-prolinol trimethylsilyl ether can be employed to catalyze the asymmetric Michael addition of the α-branched aldehyde, isobutyraldehyde; this results in the Michael product with moderate yield and enantioselectivity (68% ee). Unfortunately, four days are needed to bring this result.[8b]

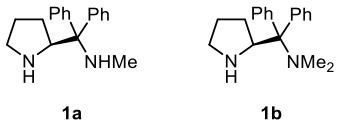
Recently, Juaristi *et al.* reported on the use of diamine analogs derived from α,α-diphenyl-(*S*)-prolinol and their application as organocatalysts in asymmetric Michael and Mannich reactions.[5g] In Juaristi's report, diamine and diamine analogs such as pyrrolidine-based azide, sulfonamide, amino amide salts, and triazole were successfully synthesized and examined via the asymmetric Michael addition of isobutyraldehyde to nitroolefins. However, the catalytic activity of these diamine analogs derived from diphenyl-(*S*)-prolinol was unspectacular as better results could only be obtained after high catalyst and additive loadings (20 mol% of amino azide



Scheme 1. Effect of amino group on the right side of organocatalysts

catalyst and 0.5 equiv. of benzoic acid) and long reaction times (12 days).

According to literatures[9] and Juaristi's research on the mechanism of cyclization for amino amide and amino thiourea catalysts,[5g] it was proposed that these catalysts' loss of activity was due to the generation of an aminal **A,** via an intramolecular attack initiated by the catalysts' amide or the secondary amine moiety (Scheme 1a). It was theorized that introducing a tertiary amino group on the right side of the organocatalyst would circumvent the formation of the catalyst-derived aminal and assist the proton transfer process, thereby accelerating the Michael reaction (Scheme 1b).[5c,5d,7a,7b,7d,10] Furthermore, the utilization of the diamine catalysts **1a** and **1b** (Figure 1), and their analogs for asymmetric synthesis is still rare and challenging task for researchers.[5g,11]



1a **1b**

Figure 1. Diamine catalysts derived from diphenyl-(*S*)-prolinol

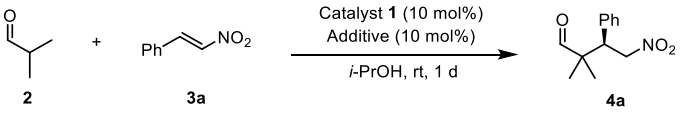
In this context, we report an efficient asymmetric Michael addition of isobutyraldehyde to nitroolefins using a chiral diamine catalyst **1b** derived from α,α-diphenyl-(*S*)-prolinol. Herein, the Michael reaction was achieved with low catalyst and additive loadings of 5 mol%, respectively, due to the presence of the tertiary amine moiety in **1b**.

2. Results and Discussion

The chiral diamine catalysts **1a**[12] and **1b** were initially synthesized according to the reported protocol (Figure 1).[11c] To prove our hypothesis, we explored the catalytic activity of these chiral diamines in the Michael addition of isobutyraldehyde to the nitroalkene **3a** using benzoic acid as an additive (both the catalyst and additive loadings were 10 mol%, respectively) in isopropanol.[5g] When **1a** was used, only trace amounts of the Michael adduct **4a** were observed even though the reaction was conducted over two days; in contrast, catalyst **1b** provided **4a** with moderate yields of 45% and a high enantioselectivity value of 89% ee (Table 1, Entries 1 and 2). Encouraged by these results, we then investigated the use of carboxylic acids such as salicylic acid, chloroacetic acid, and (-)-camphorsulfonic acid (Table 1, Entries 3-5) as possible additives. However, since the best result of these series were obtained with benzoic acid (Table 1, Entry 2), we decided to use **1b** as the catalyst and benzoic acid as the additive to screen other reaction conditions.

Next, the effects of solvents were investigated (Table 2). Here, 4 equiv. of isobutyraldehyde was used instead of the usual 5 or 10 equiv. employed in previously reported studies. Under neat reaction conditions, as well as with CH_2Cl_2 and $CHCl_3$, the Michael product **4a** was obtained with high enantioselectivity 94-95% ee but low yields (Table 2, Entries 1-3). Toluene and water were also examined and found to be unsuitable for the Michael addition (Table 2, Entries 4 and 5). The use of *i*-PrOH as a solvent afforded product **4a** with 91% yield and a high enantioselectivity value of, 93% ee (Table 2, Entry 6). It is worth noting that polar protic solvents such as MeOH and *t*-BuOH exerted significant effects on the overall reactivity. The use of MeOH only slightly reduced enantioselectivity and caused a notable decline in the yield (Table 2, Entries 6 and 7), whereas, the reaction was unsuccessful in *t*-BuOH (Table 2, Entry 8). Although the reason is not unclear, we propose that alcohol solvents effect the nitro group of nitroolefin differently by H-bonding interactions leading to these results.[6c] The use of THF and DMSO showed that polar aprotic solvents were also ineffective for this transformation (Table 2, Entries 9 and 10).

Table 1. Screening of catalysts and acid additives[a]

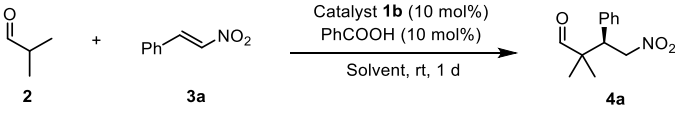


2 **3a** **4a**

Entry	Catalyst	Additive	Yield[b] (%)	ee[c] (%)
1[d]	**1a**	PhCOOH	trace	-
2	**1b**	PhCOOH	45	89
3	**1b**	salicylic acid	43	89
4	**1b**	chloroacetic acid	21	90
5	**1b**	(-)-CSA	NR	-

[a]Reactions were carried out with isobutyraldehyde **2** (0.2 mmol), nitroolefin **3a** (0.1 mmol), catalysts **1a** or **1b**, and the additives in *i*-PrOH (0.2 ml) at room temperature. NR = No reaction. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Reaction time was 2 days.

Table 2. Screening of solvents for asymmetric Michael addition



2 **3a** **4a**

Entry	Solvent	Yield[b] (%)	ee[c] (%)
1[d]	neat	26	95
2	CH_2Cl_2	18	95
3	$CHCl_3$	21	94
4	toluene	trace	-
5	H_2O	NR	-
6	*i*-PrOH	91	93
7	MeOH	40	87
8	*t*-BuOH	NR	-
9	THF	NR	-
10	DMSO	30	77

[a]Reactions were carried out with isobutyraldehyde **2** (0.4 mmol), nitroolefin **3a** (0.1 mmol), catalyst **1b**, and PhCOOH in the relevant solvent (0.2 ml) at room temperature. NR = No reaction. [b]Isolated yield. [c]Determined by chiral HPLC. [d] 8 equiv. of isobutyraldehyde were used.

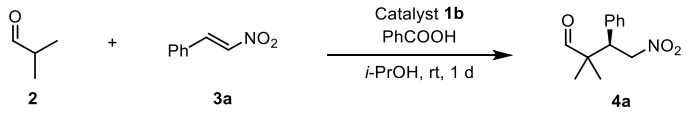
Next, the impact of various catalyst and additive loadings on the Michael addition reaction was investigated (Table 3). The ratio of catalyst **1b** and PhCOOH only slightly affected the Michael addition of isobutyraldehyde to nitroolefin **3a**, as both the yield and the enantiomeric purity were obtained with almost the same degree (Table 3, Entries 1-3). Fortunately, reducing

the amount of catalyst and PhCOOH to 5 mol% respectively, also resulted in successful catalyzation of the Michael reaction (Table 3, Entries 1 and 4). Using 5 mol% **1b** and reducing PhCOOH to 3 mol% afforded the Michael adduct **4a** with excellent enantioselectivity (95% ee), but decreased the yield to 70% (Table 3, Entries 4 and 5). Given this, we stopped reducing the amount of **1b** and PhCOOH altogether and concluded that increasing the amount of isobutyraldehyde from 4 to 5 equiv. provided product **4a** with better yield and higher enantiomeric purity (Table 3, Entries 4 and 6). Therefore, we chose to conduct the Michael addition reactions with 5 equiv. of aldehyde **2**. This was consistent with previous reports in which the influence[13] exerted by the acid additive affected the reaction rate but not the enantioselectivity (Table 3, Entries 6 and 7). From the above results, the optimal reaction conditions were as follows: nitroolefins (0.1 mmol), 5 mol% each of catalyst **1b** and PhCOOH, as well as 5 equiv. of aldehyde **2**, in 0.2 ml *i*-PrOH at room temperature (Table 3, Entry 6).

With the optimized reaction conditions in hand, we next examined various nitroolefins using isobutyraldehyde as a Michael donor (Table 4) and found that nitroolefins bearing an electron-withdrawing 4-cyano group were more reactive than those that had an electron-donating 4-methyl group in the aromatic ring (Table 4, Entries 2 and 3). Although the electronic effect of 4-methyl substitution resulted in long reaction time, the corresponding products **4b** and **4c** were obtained in moderate to good yields of 39% and 78% with high to excellent enantioselectivity values of 90% and 97% ee, respectively (Table 4, Entries 2 and 3). Nitroolefins that contained halogen atoms, such as 4-chloro, 4-bromo, 3-bromo, on the phenyl ring also afforded the Michael adducts **4d-f** in good to excellent yields 66-99% with high enantioselectivity values of 94-96% ee (Table 4, Entries 4-6). It should be noted that the groups substituted at the *ortho* position on the phenyl ring significantly lowered both the reactivity and the enantioselectivity of the nitroolefins, as evidenced by the relatively poor yields and moderate enantiomeric purity of the adduct products **4g-h** (Table 4, Entries 7 and 8 vs. 5 and 6). Fortunately, nitroolefins with a 2-naphthyl group or a heteroaryl ring, such as 2-furyl and 2-thiophenyl groups, afforded the Michael products **4i-k** in 33-97% yields with high enantioselectivity values of 90-91% ee (Table 4, Entries 9-11). In addition to the electronic effect and *ortho*-substituted influence exerted on nitroolefins, it was theorized that their reduced solubility in *i*-PrOH might have led to diminished chemical yields in some cases (Table 4, Entries 5, 7 and 9).

In addition, cyclopentanecarboxaldehyde (cyclic α-branched aldehyde) and 3-methylbutanal (an aliphatic β-branched aldehyde) were also examined as the Michael donors. Cyclopentanecarboxaldehyde reacted with nitroolefin **3a** under the optimized reaction conditions to give the corresponding Michael adduct **4l** in 34% yield with 57% ee after 12 h. The Michael product of 3-methylbutanal (**4m**) was obtained in 80% yield, *syn*/*anti* = 87/13 dr, and 98% ee for the *syn* diastereomer (see supporting information).

Table 3. Optimization of reaction conditions[a]

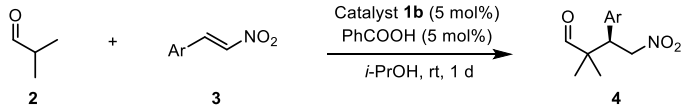


2 3a 4a

Entry	Aldehyde **2** (equiv.)	**1b** (mol%)	PhCOOH (mol%)	Yield[b] (%)	ee[c] (%)
1	4	10	10	91	93
2	4	10	5	97	92
3	4	5	10	94	92
4	4	5	5	94	92
5	4	5	3	70	95
6	5	5	5	96	93
7	5	5	-	39	92

[a]Reactions were carried out with isobutyraldehyde **2**, nitroolefin **3a** (0.1 mmol), catalyst **1b**, and PhCOOH in *i*-PrOH (0.2 ml) at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC.

Table 4. Asymmetric Michael addition of isobutyraldehyde to various nitroolefins[a]



Entry	Ar	Product **4**	Yield[b] (%)	ee[c] (%)
1	Ph	**4a**	96	93
2	4-CNC_6H_4	**4b**	78	97
3[d]	4-MeC_6H_4	**4c**	39	90
4	4-ClC_6H_4	**4d**	95	94
5[e]	4-BrC_6H_4	**4e**	66	96
6	3-BrC_6H_4	**4f**	99	96
7[f]	2-BrC_6H_4	**4g**	26	74
8[f]	2-$MeOC_6H_4$	**4h**	60	81
9[d]	2-naphthyl	**4i**	33	91
10	2-furyl	**4j**	97	91
11	2-thiophenyl	**4k**	78	90

[a]Reactions were carried out with isobutyraldehyde **2** (0.5 mmol), nitroolefin **3a** (0.1 mmol), catalyst **1b**, and PhCOOH in *i*-PrOH (0.2 ml) at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Reaction time was 3 days. [e]Reaction time was 2 days. [f]Reaction time was 4 days.

3. Conclusion

In conclusion, an efficient method for the asymmetric Michael addition of isobutyraldehyde to nitroolefins was achieved via the use of a chiral diamine catalyst derived from α,α-diphenyl-(*S*)-prolinol. In our protocol, the Michael addition was successfully conducted with low catalyst and additive loadings of 5 mol%, respectively, due to the presence of the tertiary amine group in the catalyst **1b**. Moreover, various quaternary carbon containing optically active γ-nitroaldehydes were obtained in good yields (up to 99%) and good to excellent enantioselectivity (up to 97% ee).

Supporting Information: (Experimental data is in the material). This material is available on http://dx.doi.org/10.1246/bcsj.***.

References

1. For selected reviews on enamine catalysis, see: a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471. b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem., Int. Ed.* **2008**, *47*, 6138.
2. A. Y. Sukhorukov, A. A. Sukhanova, S. G. Zlotin, *Tetrahedron* **2016**, *72*, 6191.
3. For a recent review about asymmetric Michael addition of carbonyl compounds to nitroolefins, see: D. A. Alonso, A. Baeza, R. Chinchilla, C. Gómez, G. Guillena, I. M. Pastor, D. Ramón, *Molecules* **2017**, *22*, 895.
4. N. Mase, R. Thayumanavan, F. Tanaka, C. F. Barbas, *Org. Lett.* **2004**, *6*, 2527.
5. For review and selected recent reports of organocatalytic asymmetric Michael addition of α,α-disubstituted aldehydes to nitroolefins, see: a) A. Desmarchelier, V. Coeffard, X. Moreau, C. Greck, *Tetrahedron* **2014**, *70*, 2491. b) A. Avila, R. Chinchilla, B. Fiser, E. Gómez-Bengoa, C. Nájera, *Tetrahedron: Asymmetry* **2014**, *25*, 462. c) T. P. Kumar, K. Haribabu, *Tetrahedron: Asymmetry* **2014**, *25*, 1129. d) J. He, Q. Chen, B. Ni, *Tetrahedron Lett.* **2014**, *55*, 3030. e) T. P. Kumar, *Tetrahedron: Asymmetry* **2015**, *26*, 907. f) X. T. Guo, F. Sha, X. Y. Wu, *Res. Chem. Intermed.* **2016**, *42*, 6373. g) G. Reyes-Rangel, J. Vargas-Caporali, E. Juaristi, *Tetrahedron* **2016**, *72*, 379. h) Z. W. Ma, X. F. Liu, B. Sun, X. H. Huang, J. C. Tao, *Synthesis* **2017**, *49*, 1307. i) T. P. Kumar, M. A. Sattar, S. S. Prasad, K. Haribabu, C. S. Reddy, *Tetrahedron: Asymmetry* **2017**, *28*, 401. j) C. G. Avila-Ortiz, L. Díaz-Corona, E. Jiménez-González, E. Juaristi, *Molecules* **2017**, *22*, 1328. k) R. J. Martínez-Guillén, J. Flores-Ferrándiz, C. Gómez, E. Gómez-Bengoa, R. Chinchilla, *Molecules* **2018**, *23*, 141. l) A. B. Gorde, R. Ramapanicker, *Eur. J. Org. Chem.* **2019**, 4745. m) A. B. Gorde, R. Ramapanicker, *J. Org. Chem.* **2019**, *84*, 1523. n) And the related examples cited by reference 5h. o) F. Hu, C.-S. Guo, J. Xie, H.-L. Zhu, Z.-Z. Huang, *Chem. Lett.* **2010**, *39*, 412.
6. a) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. b) T. C. Nugent, M. Shoaib, A. Shoaib, *Org. Biomol. Chem.* **2011**, *9*, 52. c) Z. W. Ma, Y. X. Liu, W. J. Zhang, Y. Tao, Y. Zhu, J. C. Tao, M. S. Tang, *Eur. J. Org. Chem.* **2011**, 6747.
7. a) X. Zhang, S. Liu, X. Li, M. Yan, A. S. C. Chan, *Chem. Commun.* **2009**, 833. b) X. Zhang, S. Liu, J. Lao, G. Du, M. Yan, A. S. C. Chan, *Tetrahedron: Asymmetry* **2009**, *20*, 1451. c) Y. F. Ting, C. Chang, R. J. Reddy, D. R. Magar, K. Chen, *Chem. –Eur. J.* **2010**, *16*, 7030. d) J. R. Chen, Y. Q. Zou, L. Fu, F. Ren, F. Tan, W. J. Xiao, *Tetrahedron* **2010**, *66*, 5367.
8. For examples and reviews, see: a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2005**, *44*, 794. b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. c) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296. d) A. Lattanzi, *Chem. Commun.* **2009**, 1452. e) A. Wróblewska, *Synlett* **2012**, *23*, 953. f) K. L. Jensen, G. Dickmeiss, H. Jiang, Ł. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248.
9. a) B. J. Knight, E. E. Stache, E. M. Ferreira, *Tetrahedron* **2015**, *71*, 5814. b) Z. Weng, X. Shao, D. Graf, C. Wang, C. D. Klein, J. Wang, G.-C. Zhou, *Eur. J. Med. Chem.* **2017**, *125*, 751. c) B. Xu, M. Y. Ding, Z. Weng, Z. Q. Li, F. Li, X. Sun, Q. L. Chen, Y. T. Wang, Y. Wang, G. C. Zhou, *Bioorg. Med. Chem.* **2019**, *27*, 3879.
10. S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599.
11. a) J. Luis Olivares-Romero, E. Juaristi, *Tetrahedron* **2008**, *64*, 9992. b) N. Hosoda, H. Kamito, M. Takano, Y. Takebe, Y. Yamaguchi, M. Asami, *Tetrahedron* **2013**, *69*, 1739. c) F. Chen, H. X. Ren, Y. Yang, S. P. Ji, Z. B. Zhang, F. Tian, L. Peng, L. X. Wang, *Chirality* **2017**, *29*, 369.
12. Diamine catalyst **1a** was synthesized for the first time by our group. See: supporting information.
13. a) K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta* **2011**, *94*, 719. b) J. Burés, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2011**, *133*, 8822. c) J. Burés, A. Armstrong, D. G. Blackmond, *J. Am. Chem. Soc.* **2012**, *134*, 6741. d) J. Burés, A. Armstrong, D. G. Blackmond, *Acc. Chem. Res.* **2016**, *49*, 214.