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Pyrrolidine–oxyimide catalyzed asymmetric Michael addition of α,α-disubstituted aldehydes to nitroolefins

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ABSTRACT

Organocatalytic enantioselective Michael addition of α,α-disubstituted aldehydes onto nitroolefins using pyrrolidine–oxyimide catalyst was reported. The reaction works effectively under neat conditions with 15 mol % of catalyst and 10 mol % of *p*-nitrobenzoic acid as an additive at 0 °C; this results in the formation of Michael adducts possessing an all-carbon quaternary center with good yields and enantioselectivities.

1. Introduction

Organocatalysis is now realized as a powerful alternative and/or complementary approach to enzymatic and organometallic catalysis. Remarkable advances have been witnessed over the past few years and a large collection of organocatalytic protocols have been added to the vast synthetic chemistry library.[1] Specifically, asymmetric organocatalysis with proline and proline derivatives has been found to be effective in driving the reactions by means of an enamine or iminium mechanism.[2] A large number of asymmetric organocatalytic transformations with a diverse range of substrate combinations have been reported using proline catalysis. Among these, the asymmetric Michael addition is considered as one of the best early stage exploratory reactions for the evaluation of newly designed catalysts.[3] The Michael products with all-carbon quaternary stereogenic centers were found to be prominent scaffolds serving as versatile templates for the construction of various bioactive compounds.[4,5] The generation of all-carbon quaternary stereogenic centers is considered to be a challenging task in asymmetric synthesis.[5] Though, a large number of organocatalysts were known to be highly efficient for Michael addition of unmodified carbonyls to nitroolefins, only some of them were found to be effective for Michael reaction between α,α-disubstituted aldehydes and nitroolefins.[6] Recently, we have reported on the Michael addition of α,α-disubstituted aldehydes and nitroolefins using pyrrolidine–pyrazole as the organocatalyst.[7] Therefore, further investigation into new catalytic methods for this relatively underexplored transformation is highly desirable. In continuation of our interest on organocatalysis,[8] we herein demonstrate the application of pyrrolidine–oxyimides **1** and **2** (Fig. 1) for the asymmetric Michael reactions of α,α-disubstituted aldehydes to nitroolefins. Pyrrolidine–oxyimides **1** and **2** were recently designed and successfully employed as organocatalysts for the Michael reaction of ketones to nitroolefins. Having been encouraged by this study and considering the consistency of catalytic mechanism, wherein the pyrrolidine backbone functions as an activation site and the oxyimide appendage acts as a steric controller and has additional hydrogen bonding sites for activation of nitroolefins. We therefore started our investigations by testing whether oxyimide catalysts **1** and **2** would also catalyze asymmetric Michael reactions of α,α-disubstituted aldehydes to nitroolefins; our results are reported herein.

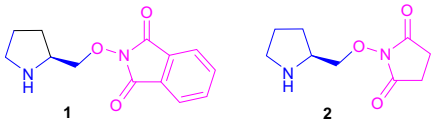

Figure 1. Pyrrolidine–oxyimides.

2. Results and discussion

Initially, a model reaction was chosen between isobutyraldehyde **3a** and nitrostyrene **4a** to test the applicability and efficacy of **1** and **2** for enantioselective Michael additions of α,α-disubstituted aldehydes to nitroolefins (Scheme 1). Screening experiments were conducted for the selection of optimal reaction parameters such as solvent, additive, catalyst loading, and temperature. The solvent screening experiments were conducted by performing the reactions simultaneously in various solvents using 10 mol %

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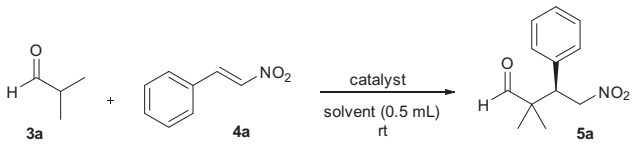


Scheme 1. Michael addition of isobutyraldehyde to nitrostyrene.

Table 1
Screening of solvents and catalyst[a]

Entry	Solvent	Catalyst (10 mol%)	Time (h)	Yield[b] (%)	ee[c](%)
1	Neat	**1**	36	73	71
2	Neat	**2**	36	60	67
3	H_2O	**1**	36	55	63
4	H_2O	**2**	36	40	59
5	Toluene	**1**	36	60	68
6	Toluene	**2**	36	52	69
7	Hexane	**1**	36	65	70
8	Hexane	**2**	36	60	66
9	DMF	**1**	36	70	43
10	DMF	**2**	36	65	37
11	THF	**1**	36	65	54
12	THF	**2**	36	58	52
13	MeOH	**1**	36	70	61
14	MeOH	**2**	36	65	57
15	CH_3CN	**1**	36	50	53
16	CH_3CN	**2**	36	45	56
17	Dioxan	**1**	36	64	61
18	Dioxan	**2**	36	59	53

[a] Reaction conditions: isobutyraldehyde (4 mmol), nitrostyrene (1 mmol).
[b] Isolated yields.
[c] Determined by chiral HPLC.

of catalysts **1** or **2** at room temperature and the results are summarized in Table 1. As evident from the study, both catalysts **1** and **2** have good compatibility for Michael reactions regardless of the type of solvent used and afforded the Michael adduct, γ-nitrocarbonyl compound **5a** in good yield and enantioselectivity (Table 1, entries 1–18). However, the reaction performed under neat conditions using catalyst **1** was found to be more effective in terms of yield and enantioselectivity and thus was selected for further optimization studies (Table 1, entry 1).

After solvent selection studies, we conducted screening experiments to test the role of an acid additive on the catalytic performance of **1**. It is well documented that the presence of an acid additive can enhance the catalytic efficiency by accelerating enamine formation thereby improving the overall productivity. As a result, reactions were conducted using various acid additives under neat conditions, employing 10 mol % of catalyst **1** at room temperature; the results are summarized in Table 2. *p*-Nitrobenzoic acid was found to show the best improvement in terms of the catalytic performance of **1** and turned out to be the most suitable additive for this transformation (Table 2, entries 14–16).

Having established the solvent and additive parameters, we next conducted experiments to screen the effect of reaction temperature and catalyst concentration on the catalytic cycle. As shown in Table 3, the catalytic performance of **1** was optimum for the reaction conducted at 0 °C with 15 mol % of **1** (Table 3, entry 5), while the other conditions were found to have no substantial progress in terms of product yield or selectivity, and instead suffered with long reaction times (Table 3, entries 1–4 and 6–9).

Having established the optimal reaction conditions, we next explored the substrate generality of this new catalytic system by conducting the Michael reaction with different substrate combinations. As shown in Tables 4 and 5, Michael reactions of

Table 2
Screening of additives[a]

Entry	Additive	(mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	TFA	5	36	61	66
2	TFA	10	36	65	72
3	CSA	5	36	53	59
4	CSA	10	36	59	67
5	C_6H_5OH	5	36	60	65
6	C_6H_5OH	10	36	61	74
7	HCOOH	5	36	65	62
8	HCOOH	10	36	69	70
9	CH_3COOH	5	36	68	66
10	CH_3COOH	10	36	73	73
11	C_6H_5COOH	2	36	62	69
12	C_6H_5COOH	5	36	71	74
13	C_6H_5COOH	20	36	76	78
14	*p*-NO_2-C_6H_4COOH	2	36	65	71
15	*p*-NO_2-C_6H_4COOH	5	36	73	77
16	*p*-NO_2-C_6H_4COOH	10	36	80	81

[a] Reaction conditions: isobutyraldehyde (4 mmol), nitrostyrene (1 mmol), catalyst **1** (10 mol%), neat, rt.
[b] Isolated yields.
[c] Determined by chiral HPLC.

Table 3
Effect of temperature and catalyst concentration[a]

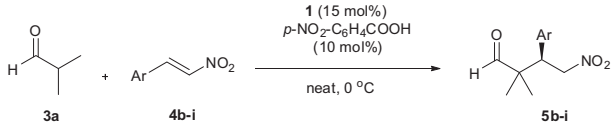
Entry	Temp. (°C)	**1** (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	RT	10	36	80	81
2	0	10	48	84	85
3	−20	10	72	61	87
4	RT	15	36	83	83
5	0	15	48	87	89
6	−20	15	72	67	90
7	RT	20	36	84	84
8	0	20	48	88	89
9	−20	20	72	69	92

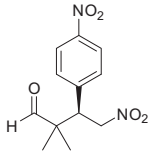
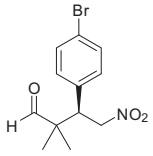
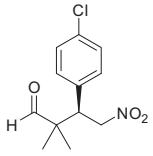
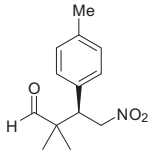
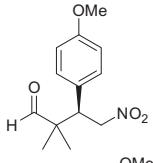
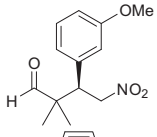
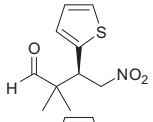
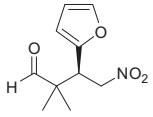
[a] Reaction conditions: isobutyraldehyde (4 mmol), nitrostyrene (1 mmol), *p*-NO_2-C_6H_4COOH (10 mol%), neat.
[b] Isolated yields.
[c] Determined by chiral HPLC.

isobutyraldehyde **3a** (Table 4, entries 1–8) and cyclopentanecarboxaldehyde **3b** (Table 5, entries 1–8) with nitroolefins **4b–i** were smoothly conducted under the optimized reaction conditions and the corresponding Michael products **5b–i** and **6a–h** were obtained in good yields and with high enantioselectivities irrespective of the nature of the substitution pattern in the nitroolefins. However, nitroolefins with electron donating substitutions were found to be slightly inferior in overall productivity compared to electron withdrawing counterparts (Table 4, entries 4–6 and Table 5, entries 2, 3 respectively). Overall, the substrate scope observed for the conjugate addition of α,α-disubstituted aldehydes to nitroolefins employing pyrrolidine–oxyimide **1** catalyst, is in good agreement with those reported and provides an access to a variety of γ-nitrocarbonyl compounds with an all-carbon quaternary center in high enantioselectivities.

The observed stereochemical outcome of this transformation could be rationalized by considering the possible transition state[9,10] model (Fig. 2). The catalytic system operates by an enamine mechanism, wherein the pyrrolidine ring activates the aldehyde toward enamine formation and the phthalimide template serves as an efficient steric controller and also provides H-bonding stabilization. As depicted in Figure 2, the overall arrangement might result in a pocket like compact transition state, and the nucleophilic enamine attacks the nitroolefin from the *Si* face leading to the formation of the desired products with high selectivities.

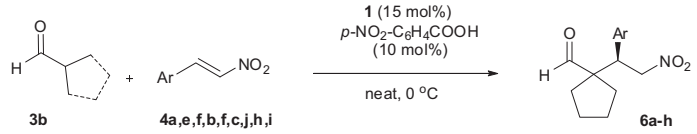
Table 4
Enantioselective Michael addition of isobutyraldehyde to nitroolefins[a]

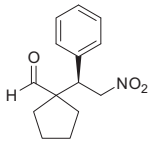
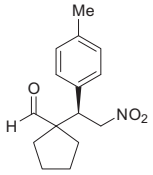
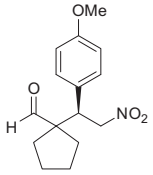
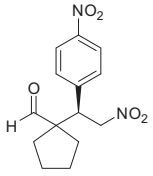
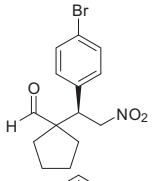
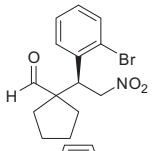
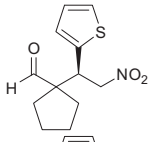
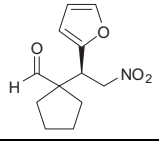


Entry	Product		Time (h)	Yield[b] (%)	ee[c] (%)
1		**5b**	48	91	92
2		**5c**	48	87	90
3		**5d**	48	89	91
4		**5e**	48	81	83
5		**5f**	48	77	81
6		**5g**	48	85	88
7		**5h**	48	90	86
8		**5i**	48	88	83

[a] Reaction conditions: isobutyraldehyde (4 mmol), nitroolefin (1 mmol).
[b] Isolated yields.
[c] Determined by chiral HPLC.

Table 5
Enantioselective Michael addition of cyclopentanecarboxyaldehyde to nitroolefins[a]



Entry	Product		Time (h)	Yield[b] (%)	ee[c] (%)
1		**6a**	48	87	90
2		**6b**	48	84	78
3		**6c**	48	80	75
4		**6d**	48	93	92
5		**6e**	48	90	90
6		**6f**	48	91	91
7		**6g**	48	85	86
8		**6h**	48	87	84

[a] Reaction conditions: cyclopentanecarboxaldehyde (4 mmol), nitroolefin (1 mmol).
[b] Isolated yields.
[c] Determined by chiral HPLC.

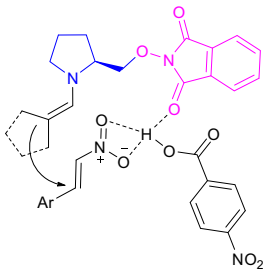


Figure 2. Proposed transition state.

3. Conclusions

In conclusion, the application of pyrrolidine–oxyimides **1** and **2** as organocatalysts for enantioselective Michael additions of α,α-disubstituted aldehydes to nitroolefins has been demonstrated. The catalytic cycle was found to be effective in terms of yield and enantioselectivities, by employing 15 mol % of **1** and 10 mol % of *p*-nitrobenzoic acid under neat reaction conditions. Further investigations to extend the scope of this new catalytic system are currently underway in our laboratory.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL. Chiral HPLC analysis was carried out on chiral pak OD-H, IC or IA columns using a mixture of isopropanol and hexanes as the eluent.

4.1.1. General procedure for the Michael addition of α,α-disubstituted aldehydes to nitroolefins

To a mixture of catalyst **1** (15 mol %), and α,α-disubstituted aldehyde (4 mmol) was added *p*-NO_2-C_6H_4COOH (10 mol %) and stirred for 20 min at 0 °C. Nitroolefin (1 mmol) was added to the resulting mixture and stirred for the appropriate time (Tables 4 and 5) at 0 °C. After completion of the reaction (monitored by TLC), the mixture was purified by silica-gel column chromatography to afford the desired product. Relative and absolute configurations of the products were determined by comparison of ^{1}H NMR, ^{13}C NMR, and specific rotation values with those reported in the literature.[6]

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References

1. (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005; (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010; (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992; (d) Sakthivel, K.; Notz, W.; Buli, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267; (e) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423–2425; (f) Tokoroyama, T. *Eur. J. Org. Chem.* **2010**, 2009–2016; (g) Dondoni, A.; Massi, A. *Angew. Chem.* **2008**, *120*, 4716–4739. Angew. Chem., Int. Ed. **2008**, *47*, 4638–4660; (h) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632; (i) Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42–53; (j) Aleman, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774–793; (k) Scheffler, U.; Mahrwald, R. *Chem. Eur. J.* **2013**, *19*, 14346–14396.
2. (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171; (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; (c) Bertelsen, S.; Jorgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (e) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092; (f) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.
3. For recent reviews on asymmetric Michael additions see: (a) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171–196; (b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894; (c) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580–591; (d) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933–972; (e) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716; (f) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123–3135; (g) Krkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470; (h) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812; (i) Almasi, D.; Alonso, D. A.; Gomez-Bengoa, E.; Negel, Y.; Najera, C. *Eur. J. Org. Chem.* **2007**, 2328–2343; (j) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058–11076; (k) Almasi, D.; Alonso, D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.
4. (a) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688–1690; (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597; (c) Corey, E. J.; Perez, A. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401; (d) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066.
5. (a) Bella, M.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 5672–5673; (b) Rigby, C. L.; Dixon, D. J. *Chem. Commun.* **2008**, 3798–3800; (c) Zhang, Z. H.; Dong, X. Q.; Chen, D.; Wang, C. J. *Chem. Eur. J.* **2008**, *14*, 8780–8783; (d) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949.
6. (a) Zhang, X. J.; Liu, S. P.; Li, X. M.; Yan, M.; Chan, A. S. C. *Chem. Commun.* **2009**, 833–835; (b) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem.* **2006**, *118*, 6514–6518. Angew. Chem., Int. Ed. **2006**, *45*, 6366–6370; (c) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321–4332; (d) Wang, W.; Wang, J.; Li, H. *Angew. Chem.* **2005**, *2005*, 1393–1395. Angew. Chem., Int. Ed. **2005**, *44*, 1369–1371; (e) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2527–2530; (f) Sato, A.; Yoshida, M.; Hara, S. *Chem. Commun.* **2008**, 6242–6244; (g) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599–602; (h) Chang, C.; Li, S. H.; Reddy, R. J.; Chen, K. *Adv. Synth. Catal.* **2009**, *351*, 1273–1278; (i) Chen, J. R.; Cao, Y. J.; Zou, Y. Q.; Tan, F.; Fu, L.; Zhu, X. Y.; Xiao, W. J. *Org. Biomol. Chem.* **2010**, *8*, 1275–1279; (j) He, T.; Gu, Q.; Wu, X. Y. *Tetrahedron* **2010**, *66*, 3195–3198; (k) Chen, J. R.; Zou, Y. Q.; Fu, L.; Ren, F.; Tan, F.; Xiao, W. J. *Tetrahedron* **2010**, *66*, 5367–5372; (l) Nugent, T. C.; Bibi, A.; Sadiq, A.; Shoaib, M.; Umar, M. N.; Tehrani, F. N. *Org. Biomol. Chem.* **2012**, *10*, 9287–9294; (m) Avila, A.; Chinchilla, R.; Fiser, B.; Gomez-Bengoa, E.; Najera, C. *Tetrahedron: Asymmetry* **2014**, *25*, 462–467; (n) Junpeng, H.; Qiankun, C.; Bukuo, N. *Tetrahedron Lett.* **2014**, *55*, 3030–3032.
7. (a) Kumar, T. P.; Haribabu, K. *Tetrahedron: Asymmetry* **2014**, *25*, 1129–1132.
8. (a) Chandrasekhar, S.; Kumar, T. P.; Haribabu, K.; Rajireddy, Ch. *Tetrahedron: Asymmetry* **2010**, *21*, 2372–2375; (b) Chandrasekhar, S.; Kumar, T. P.; Haribabu, K.; Rajireddy, Ch.; Kumar, C. R. *Tetrahedron: Asymmetry* **2011**, *22*, 697–702; (c) Kumar, T. P.; Sattar, M. A.; Sarma, V. U. M. *Tetrahedron: Asymmetry* **2013**, *24*, 1615–1619; (d) Kumar, T. P.; Vavle, N. C.; Patro, V.; Haribabu, K. *Tetrahedron: Asymmetry* **2014**, *25*, 457–461; (e) Kumar, T. P.; Balaji, S. V. *Tetrahedron: Asymmetry* **2014**, *25*, 473–477; (f) Chandrasekhar, S.; Kumar, T. P.; Kumar, C. P.; Haribabu, K.; Jagadeesh, B.; Lakshmi, J. K.; Mainkar, P. S. *RSC Adv.* **2014**, *4*, 30325–30331; (g) Kumar, T. P. *Tetrahedron: Asymmetry* **2014**, *25*, 1286–1291; (h) Naresh, T.; Kumar, T. P.; Haribabu, K.; Chandrasekhar, S. *Tetrahedron: Asymmetry* **2014**, *25*, 1340–1345; (i) Kumar, T. P.; Radhika, L.; Haribabu, K.; Kumar, N. V. *Tetrahedron: Asymmetry* **2014**, *25*, 1555–1560; (j) Kumar, T. P.; Shekhar, R. C.; Sunder, K. S.; Rajesh, V. *Tetrahedron: Asymmetry* **2015**, *26*, 543–547.
9. (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691–1693; (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.
10. (a) Seebach, D.; Golinski, J. *Helv. Chem. Acta* **1981**, *64*, 1413–1423; (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Synthesis* **2004**, 1509–1521; (c) Ting, Y. F.; Chang, C.; Reddy, R. J.; Magar, D. R.; Chen, K. *Chem. Eur. J.* **2010**, *16*, 7030–7038.