Journal of Organometallic Chemistry 929 (2020) 121572

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Homogeneous palladium-catalyzed enantioselective hydrogenation of 5-methylenhydantoin for the synthesis of L-Valine

Safa Hayouni[a], Christophe Michon[a,b,*], Didier Morvan[c], Virginie Bellière-Baca[c], Francine Agbossou-Niedercorn[a,*]

[a] Univ. Lille, CNRS, Centrale Lille, Univ. Artois, UMR 8181 - UCCS - Unité de Catalyse et Chimie du Solide F-59000 Lille, France
[b] Université de Strasbourg, Université de Haute-Alsace, Ecole Européenne de Chimie, Polymères et Matériaux, CNRS, LIMA, UMR 7042 25 rue Becquerel, F-67087 Strasbourg, France
[c] Adisseo France SAS, Antony Parc 2, 10 Place du Général de Gaulle, 92160 Antony, France

ARTICLE INFO

Article history:
Received 4 September 2020
Revised 28 September 2020
Accepted 7 October 2020
Available online 9 October 2020

Keywords:
Homogeneous catalysis
Palladium
Phosphine
Asymmetric hydrogenation
Hydantoin
L-Valine

ABSTRACT

In this article, we present the development of a synthetic methodology based on homogeneous catalysis for the preparation of enantioenriched L-Valine aminoacid. The enantioselective hydrogenation of 5-methylenhydantoin has been developed through broad screenings of chiral ligands, metal precursors and reaction conditions including scale-up experiments and recyclability studies. A palladium catalyzed asymmetric hydrogenation of 5-methylenhydantoin afforded the corresponding hydrogenated product in a 70% enantiomeric excess using a substrate/catalyst ratio of 500/1. A partial racemization was observed upon hydrolysis and recovery of L-Valine.

1. Introduction

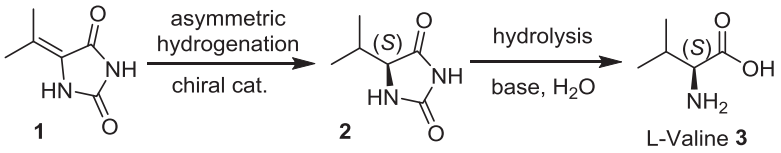
Chiral amino acids are key molecules in the pharmaceutical, food, cosmetic and agricultural industries [1] Due to increasing costs and sustainability issues, the feedstuff industry has gradually developed reduced protein diets for animals. Such strategy has led to a growing demand of L-Valine which is implied in several vital functions in animals [2]. Indeed, the use of L-Valine in reduced protein diets has been shown to increase the feed conversion and therefore the animal body weight while reducing water consumption and nitrogen waste excretions. Among hydantoins, which are saturated heterocycles comprising 2 lactam functions, 5-substituted hydantoins can be found in a wide range of natural and synthetic chemicals of biological and pharmaceutical interests. More particularly, the simple and low cost 5-substituted hydantoins have been useful intermediates in the synthesis of aminoacids [3]. Though the asymmetric hydrogenation of 5-ylidenhydantoins allows a direct access to enantioenriched aminoacids, it has scarcely been studied [4]. In this article , we present the development of a synthetic methodology based on homogeneous catalysis for the preparation of enantioenriched L-Valine **3** based on a catalyzed asymmetric hydrogenation of 5-methylenhydantoin **1** [5] into **2** [6] and a subsequent hydrolysis (Scheme 1).

2. Results and discussion

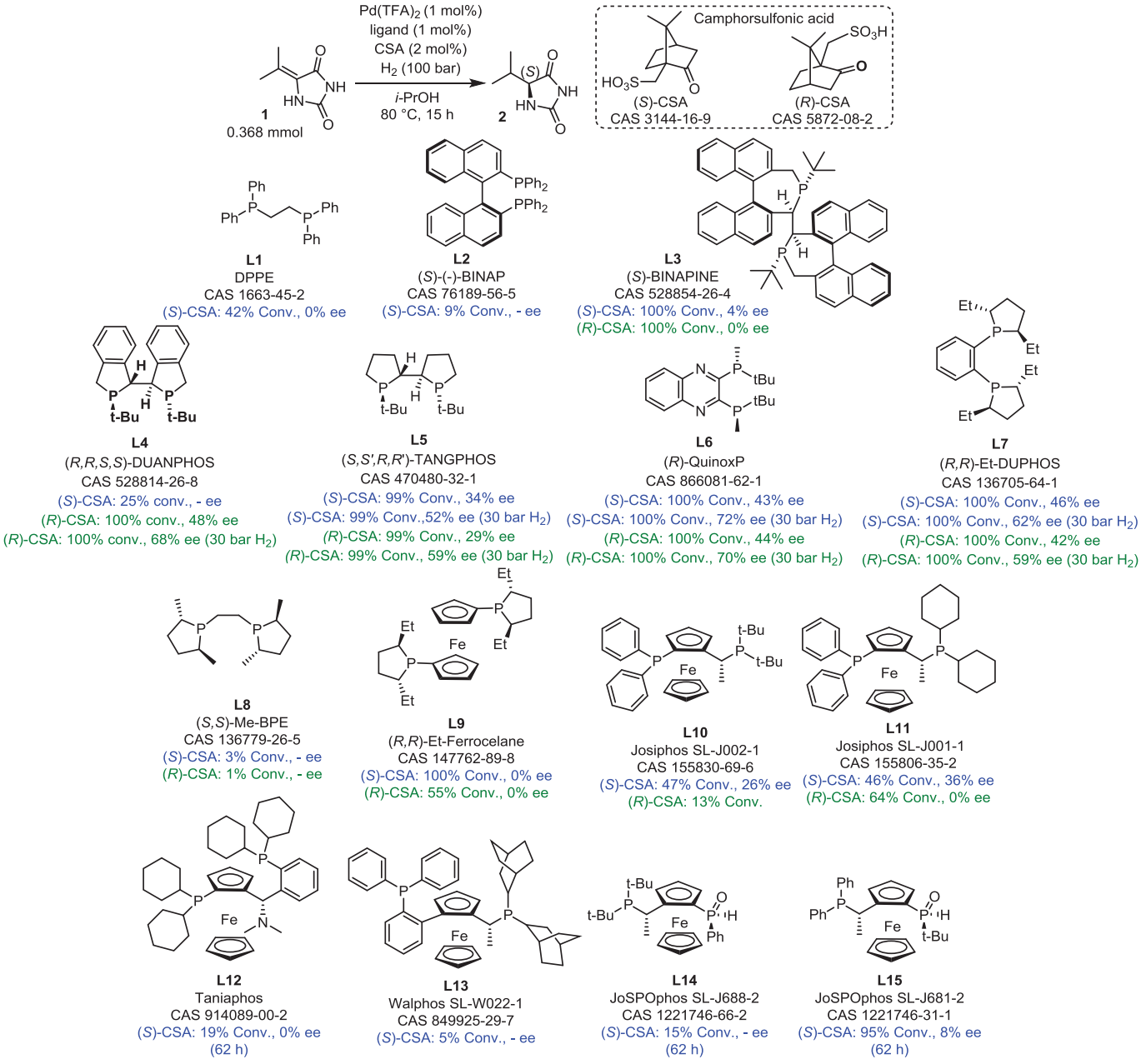
Due to solubility issues (Table S1), the asymmetric hydrogenation of 5-methylenehydantoin **1** was studied in CH_3OH, *i*-PrOH and 1,4-dioxane. At first, we screened various privileged catalysts based on iridium, cobalt and nickel but did not observe any significant conversion and enantioselectivity (Scheme S1). Afterwards, we tried rhodium based catalysts combining $[Rh(COD)_2]BF_4$ precursor and specific ligands like BIBOP [7], UREAphos and METAMORPhos bifunctional phosphoramidites [8] or Zhaophos [9–11], a ferrocene based diphosphine, bearing appended thiourea groups able to interact with one of the lactam function of **1**. Though the hydrogenations proceeded in low to quantitative conversions, there was none or low enantioselectivities (0–13% ee) (Scheme S2 and Table S2). According several reports of Zhang et al. on the asymmetric hydrogenation of 3-substituted maleinimides [9], maleic anhydrides [10] and β-substituted α,β-unsaturated lactams [11], the failure of such supramolecular bifunctional approach was somehow surprising but tetrasubstituted alkenes like hydantoin **1** are known to be challenging substrates [7,12]. In addition, substrate **1** is a

* Corresponding authors.
E-mail addresses: cmichon@unistra.fr (C. Michon), francine.niedercorn@univ-lille.fr (F. Agbossou-Niedercorn).

https://doi.org/10.1016/j.jorganchem.2020.121572
0022-328X/



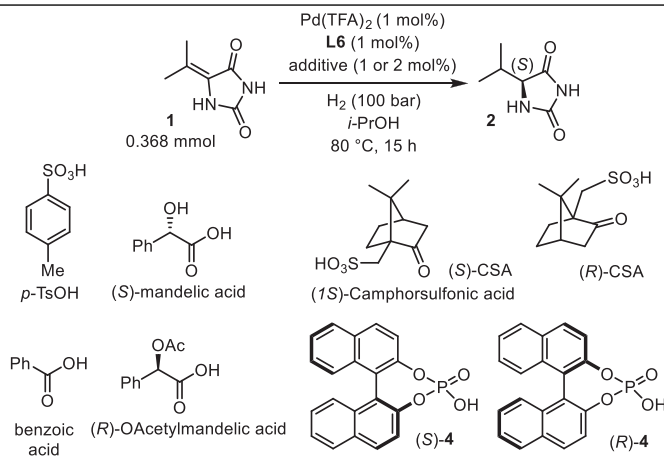
Scheme 1. Enantioselective synthesis of L-Valine **3** through asymmetric hydrogenation of hydantoin **1** and hydrolysis of **2**.



Scheme 2. Catalyst screening for the asymmetric hydrogenation of 5-methylenhydantoin **1**.

planar molecule and the two methyl substituents are not introducing great steric effects. By comparison, catalysts based on palladium proved to be more active and selective according to the screening of a selection of 15 diphosphine ligands **L1-L15** (Scheme 2). Whether the racemic **L1** confirmed the chirality from the ligand controlled the stereoselectivity of the hydrogenation, ligands **L4-L7** allowed the asymmetric hydrogenation of 5-methylenehydantoin **1** in high conversions and average enantioselectivities at a hydrogen pressure of 100 bar. When the latter was decreased to 30 bar, a significant increase of enantiomeric excesses was observed. It was worth to note **L4-L7** were all C_2-symmetric diphosphines and comprised chiral phosphorous atoms bearing bulky electron donor alkyl substituents. The latter are likely to have a significant contribution to the enantioselective process thanks to weak non-covalent attractive interactions [13] between the substrate **1** and catalyst's chiral ligand while the palladium center would coordinate the alkene moiety [4b] and activate hydrogen. By affording hydrogenated product **2** in high conversion

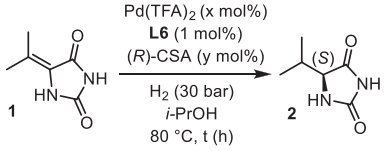
Table 1
Acid additive screening for the asymmetric hydrogenation of 5-methylenhydantoin **1**.



Entry	Additive (mol%)	Conv. (%)[a]	Ee (%)[b]
1	*p*TsOH (2)	97	27
2	Benzoic acid (2)	3	–
3	(*R*)-(−)-O-Acetylmandelic acid (2)	39	0
4	(*S*)-(+)-Mandelic acid (2)	61	0
5	(*S*)-(+)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate **4** (2)	49	50
6	(*R*)-(−)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate **4** (2)	55	31
7	(*S*)-CSA (2)	100	42
8	(*R*)-CSA (2)	100	44
9	(*R*)-CSA (1)	100	61 (70[c])
10	(*R*)-CSA (0.5)	100	38

[a] Determined by GC
[b] Determined by HPLC on a DAICEL CSP CHIRALPAK ID.
[c] at 30 bar of H_2.

Table 2
Effect of the substrate/catalyst and additive/catalyst ratios on the asymmetric hydrogenation of 5-methylenhydantoin **1**.



Entry	substrate/catalyst	additive /catalyst	solvent (mL)	time (h)	conv. (%)[a]	Ee (%)[b]
1	500	1	10	48	18	–
2	500	5	6	38	9	–
3	500	10	7	38	2	–
4	500	20	7	38	1	–
5	500	2	6	120	75	70
6	200	1	6	62	6	–
7	200	2	4	62	100	62

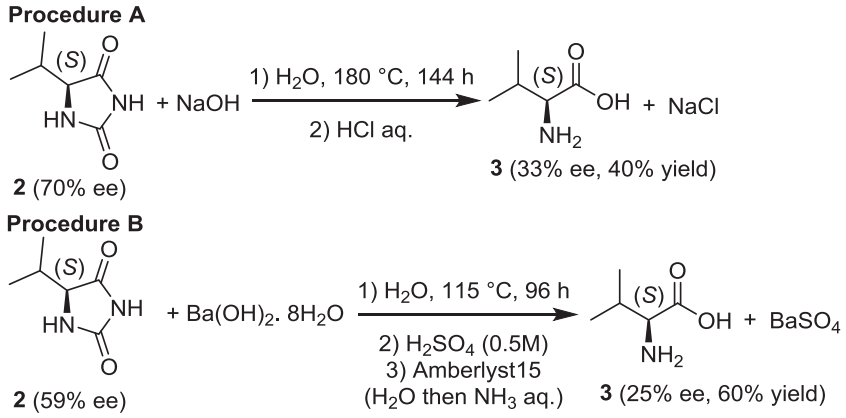
[a] Determined by GC
[b] Determined by HPLC on a DAICEL CSP CHIRALPAK ID.

and good ee, the ligand **L6** based on a quinoxaline backbone was selected for further developments.

Among the several acid additives which were subsequently screened (Table 1, entries 1–8), the (*S*)-(+)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate **4** afforded product **2** in a 49% conversion and 50% ee (entry 5). However, the (*R*)-camphor sulfonic acid (CSA) proved to be the best acid additive when a single equivalent of (*R*)-CSA was used as respect to the $Pd(TFA)_2$ precursor (entries 8–10). Indeed, the hydrogenated product was obtained in a full conversion and with an enantioselectivity of 70% ee at 30 bar of hydrogen (entry 9). It was worth to note the configuration of product **2** was always (*S*), independently of the additive used.

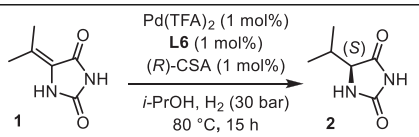
The asymmetric hydrogenation of 5-methylenhydantoin **1** implying the palladium catalyst based on ligand **L6** was next optimized by adjusting the reaction conditions. Regarding the solvent, the use of *i*-PrOH afforded the best conversions and enantioselectivities by comparison to CH_3OH, 1,4-dioxane or mixtures of *i*-PrOH and CH_3OH or trifluoroethanol (TFE). We noticed strict anhydrous conditions were required in order to get a high asymmetric induction (Table S3). The preferred reaction temperature was found at 80 °C and the hydrogen pressure could be set to 30 bar (Tables S4 and S5).

By using these optimized reaction conditions, we studied the effect of the substrate/catalyst and additive/catalyst ratios on the asymmetric hydrogenation of 5-methylenhydantoin **1** (Table 2, entries 1–7). We demonstrated the asymmetric hydrogenation of **1** proceeded well on a 1.84 mmol scale with a catalyst loading decreased to 0.2 mol% by reaching a substrate/catalyst ratio of 500/1 and an additive/catalyst ratio of 2 (entry 5). Indeed, the use of higher or lower additive/catalyst ratios was not favorable



Scheme 3. Recovery of L-Valine **3** by hydrolysis of hydantoin **2**.

Table 3
Catalyst recycling.



Cycle	Conv. (%)[a]	Ee (%)[b]	TON[c]
1[d]	100	70	100
2[e]	82	65	82
3[e]	57	64	57
4[e]	27	64	27

[a] Determined by GC
[b] Determined by HPLC
[c] Turnover number = mol of product/mol of catalyst.
[d] 3.68 10^{-4} mol of **1**, 1mol% $Pd(TFA)_2$, 1 mol% **L6**, 1 mol% (*R*)-CSA, 4 mL *i*-PrOH, 15 h
[e] After cooling, degazing and sampling, a solution of **1** (3.68 10^{-4} mol) and (*R*)-CSA (2 mol%) in *i*-PrOH (2 mL) was added in the autoclave under a nitrogen flow. The autoclave was then pressurized to 30 bar H_2 and the reaction was started by heating and stirring.

(entries 1–4,6) and the enantioselectivity was lower with a substrate/catalyst ratio of 200 (entry 7). No racemization of hydrogenated product **2** was observed while using long reaction times.

The catalyst recycling was first studied through attempts to separate the catalyst from the product by centrifugation but this resulted in poorly active catalytic species. However, we found that, once a reaction was finished, the cautious and direct addition of a new *i*-PrOH solution of reactant **1** into the autoclave allowed a possible recycling (Table 3). Moreover, the addition of a subsequent catalytic amount of (*R*)-CSA (1 mol%) was necessary at the beginning of each cycle in order to allow the catalytic reaction to proceed more effectively. However, a gradual decrease of the conversions in **2** and therefore of the catalyst activity (TON) was noticed.

The hydrolysis of chiral hydantoin **2** was first performed using NaOH in water at 180 °C (Scheme 3, procedure A) [14]. A full conversion of hydantoin **2** in L-Valine **3** was only observed after 144 h of reaction. Afterwards, an acidification with HCl followed by a purification by distillation under vacuum were required in order to separate the product from NaCl by-product and recover L-Valine **3** in a moderate yield. HPLC analyses showed such hydrolysis resulted in a partial racemization of the substrate, L-Valine **3** being isolated with a 33% ee starting from hydantoin **2** with an enantiopurity of 70% ee. Therefore, the hydrolysis of hydantoin **2** was performed following a different procedure using $Ba(OH)_2$ in water at 115 °C (Scheme 3, procedure B). Indeed, the hydrolysis of enantiopure 5-difluoromethyl-5-methyl-hydantoin [15] and 5-phenyl-5-(trifluoromethyl)hydantoin [16] were previously performed without any racemization. In our case, we noticed 96 h of reaction were required in order to reach a full conversion of hydantoin **2** in the L-Valine product **3**. The latter was recovered in a fair yield after acidification with H_2SO_4, filtration of the $BaSO_4$ and subsequent flash chromatography on an acidic resin like Amberlyst 15. However, a partial racemization was again observed by HPLC analyses, L-Valine **3** being isolated with a 25% ee starting from hydantoin **2** with an enantiopurity of 59% ee. Furthermore, we noticed the purity of reagent **2**, e.g. a material purified by flash chromatography or sublimation, had no influence on the observed racemization. By comparison to the previous hydrolysis of enantiopure 5-difluoromethyl-5-methyl-hydantoin [15] and 5-phenyl-5-(trifluoromethyl)hydantoin [16], such a racemization may be explained by the substitution pattern of the asymmetric carbon, hydantoin **2** comprising a tertiary stereocenter and compounds of reference [15,16] having quaternary asymmetric carbons. Therefore, the NaOH or $Ba(OH)_2$ base used for the hydrolysis may deprotonate the tertiary stereocenter of hydantoin **2** and allow a racemization. Interestingly, it was previously noticed that other derivatives like tetrahydroisoquinoline hydantoins [17] or 3,5-disubstituted thiohydantoins [17] gradually racemize in aqueous solutions at acid, basic or neutral pH. Nevertheless, according several reports [18], a hydrolysis of hydantoin **2** through the use of enzymatic methods like the "Hydantoinase Process" is likely to afford L-Valine **3** without racemization.

3. Conclusion

We developed a synthetic methodology for the preparation of enantioenriched L-Valine **3** based on a catalyzed asymmetric hydrogenation of 5-methylenhydantoin **1** and a subsequent hydrolysis. Selected palladium homogeneous catalysts based on chiral diphosphine ligands were the single effective species allowing the hydrogenation of 5-methylenhydantoin in high yields and good enantioselectivities. Though L-Valine was obtained through hydrolysis of the hydrogenated product, a significant racemization was observed upon hydrolysis. Overall, these results are encouraging considering the asymmetric hydrogenation of tetrasubstituted alkenes like 5-methylenhydantoin **1** is challenging. From an industrial perspective, two main goals remain to fulfill in order to produce L-Valine in bulk quantities at a low cost below 10 €/kg. First, a highly active and enantioselective catalytic hydrogenation, i.e. with high turnover numbers and enantiomeric excesses, is desired. Second, the hydrogenated product **2** need to be rapidly hydrolyzed using enzymatic methods to avoid racemization of L-Valine **3**. Finally, further applications in flow chemistry [19] may be appreciated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research was first funded by ADISSEO France SAS. The CNRS, the Chevreul Institute (FR 2638), the Ministère de l'Enseignement Supérieur et de la Recherche, the Région Hauts-de-France and the FEDER are acknowledged for supporting and funding partially this work. Mrs C. Delabre (UCCS) is thanked for GC and GC–MS analyses and some HPLC separations.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2020.121572.

References

[1] a) C.T. Walsh, R.V. O'Brien, C. Khosla, Angew. Chem. Int. Ed. 52 (2013) 7098–7124; b) K. Lang, J.W. Chin, Chem. Rev. 114 (2014) 4764–4806; c) M.A. Blaskovich, J. Med. Chem. 59 (2016) 10807–10836.
[2] EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed). Scientific Opinion on the safety and efficacy of L-valine produced by Escherichia coli NITE SD 00066 for all animal species, EFSA J. 13 (2015) 3965–3978.
[3] a) M. Meusel, M. Gütschow, Org. Prep. Proced. Int. 36 (2004) 391–443; b) J.M. Fraile, G. Lafuente, J.A. Mayoral, A. Pallares, Tetrahedron 67 (2011) 8639–8647.
[4] a) Z. Zhang, N.A. Butt, W. Zhang, Chem. Rev. 116 (2016) 14769–14827; b) B.-D. Ma, S.-H. Du, Y. Wang, X.-M. Ou, M.-Z. Huang, L.-X. Wang, X.-G. Wang, Tetrahedron 28 (2017) 47–53.
[5] N.C. Mathur, S.K. Wong, H. Shechter, Tetrahedron Lett. 44 (2003) 5141–5144.
[6] a) B.F. Erlanger, H. Sachs, E. Brand, J. Am. Chem. Soc. 76 (1954) 1806–1810; b) L. Konnert, B. Reneaud, R.M. de Figueiredo, J.-M. Campagne, F. Lamaty, J. Martinez, E. Colacino, J. Org. Chem. 79 (2014) 10132–10142; c) I. Nicolas, O. Jeannin, D. Pichon, M. Fourmigué, Cryst. Eng. Comm. 18 (2016) 9325–9333.
[7] Z. Zhang, J. Wang, J. Li, F. Yang, G. Liu, W. Tang, W. He, J.J. Fu, Y.H. Shen, A. Li, W.D. Zhang, J. Am. Chem. Soc. 139 (2017) 5558–5567.
[8] a) J. Meeuwissen, M. Kuil, A.M. van der Burg, A.J. Sandee, J.N.H. Reek, Chem. Eur. J. 15 (2009) 10272–10279; b) F.W. Patureau, M. Kuil, A.J. Sandee, J.N.H. Reek, Angew. Chem. Intern. Ed. 47 (2008) 3180–3183.
[9] Z. Han, P. Li, Z. Zhang, C. Chen, Q. Wang, X.-Q. Dong, X. Zhang, ACS Catal. 6 (2016) 6214–6218.
[10] Z. Han, R. Wang, G. Gu, X.-Q. Dong, X. Zhang, Chem. Commun. 53 (2017) 4226–4229.
[11] Q. Lang, G. Gu, Y. Cheng, Q. Yin, X. Zhang, ACS Catal. 8 (2018) 4824–4828.
[12] S. Kraft, K. Ryan, R.B. Kargbo, J. Am. Chem. Soc. 139 (2017) 11630–11641.
[13] a) I.D. Gridnev, Chem. Cat. Chem. 8 (2016) 3463–3465; b) J. Zhang, J. Jia, X. Zeng, Y. Wang, Z. Zhang, I.D. Gridnev, W. Zhang, Angew. Chem. Int. Ed. 58 (2019) 11505–11512; c) J. Chen, I.D. Gridnev, iScience 23 (2020) 100960–100972.
[14] E. Ndzié, P. Cardinael, A.-R. Schoofs, G. Coquerel, Tetrahedron 8 (1997) 2913–2920.
[15] F. Bravo, S. Capelli, S.V. Meille, P. Seresini, A. Volonterio, M. Zanda, Tetrahedron 7 (1996) 2321–2332.
[16] T. Martin, C. Massif, N. Wermester, J. Linol, S. Tisse, P. Cardinael, G. Coquerel, J.-P. Bouillon, Tetrahedron 22 (2011) 12–21.
[17] Y. Chen, L. Sub, Y. Xinying, P. Wenyan, H. Fang, Tetrahedron 71 (2015) 9234–9239.
[18] a) J.M. Clemente-Jiménez, S. Martínez-Rodríguez, F. Rodríguez-Vico, F.J.L. Heras-Vázquez, Recent Pat. Biotechnol. 2 (2008) 35–46; b) M. O'Neill, B. Hauer, N. Schneider, N.J. Turner, ACS Catal. 1 (2011) 1014–1016; c) N.M. Weckenmann, B.J. Nachtsheim, Eur. J. Org. Chem. 2015 (2015) 6624–6630; d) M.J. Rodríguez-Alonso, F. Rodríguez-Vico, F.J.L. Heras-Vázquez, M.J. Clemente-Jiménez, Catalysts 7 (2017) 192.
[19] a) E.J. O'Neal, C.H. Lee, J. Brathwaite, K.F. Jensen, ACS Catal. 5 (2015) 2615–2622; b) D. Geier, P. Schmitz, J. Walkowiak, W. Leitner, G. Francio, ACS Catal. 8 (2018) 3297–3303; c) T. Touge, M. Kuwana, K. Komatsuki, S. Tanaka, K. Matsumu, N. Sayo, Y. Kashibuchi, T. Saito, Org. Process Res. Dev. 23 (2019) 452–461.