COMMUNICATION

Efficient Synthesis of Chiral γ-Aminobutyric Esters via direct Rhodium-Catalysed Enantioselective Hydroaminomethylation of acrylates

Received 00th January 20xx,
Accepted 00th January 20xx

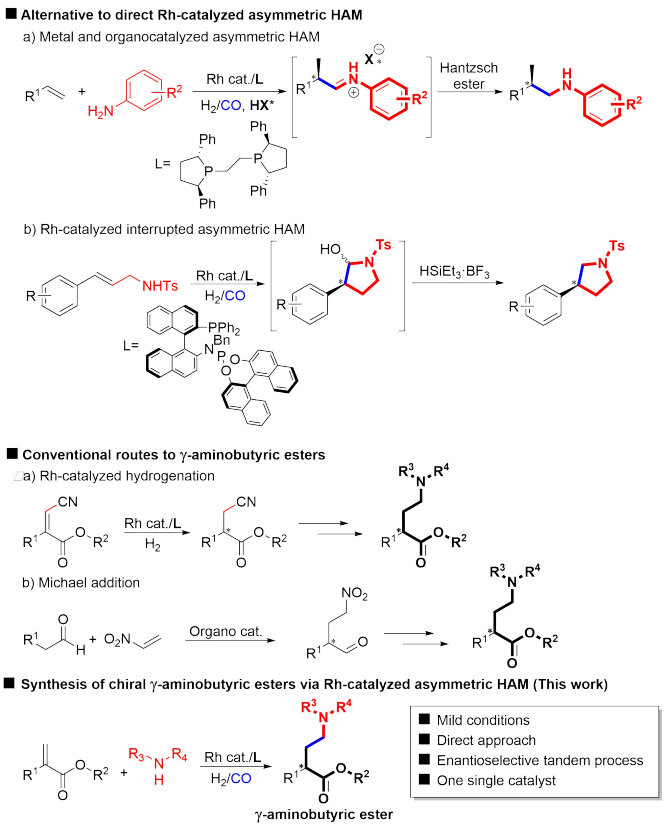
DOI: 10.1039/x0xx00000x

Anton Cunillera,[a] Miriam Díaz de los Bernardos,[b] Martine Urrutigoïty,[c] Carmen Claver,[a,b] Aurora Ruiz,[a] and Cyril Godard*[a]

The successful rhodium catalysed asymmetric intermolecular hydroaminomethylation (HAM) of alkenes using a single catalyst bearing the (*R,R*)-QuinoxP* ligand is reported. The HAM of α-alkyl acrylates revealed an efficient tool for the regio- and enantioselective synthesis of γ-amino esters with ee's up to 86%. HPNMR experiments provided insights into the reaction mechanism.

The efficient and selective synthesis of amines using readily available and abundant precursors such as alkenes is a long-standing goal of chemical research, since they are useful building blocks for the synthesis of pharmaceutical, peptides, alkaloids and agrochemicals.[1]

The rhodium catalysed HAM of alkenes is an efficient tandem reaction for the production of nitrogen containing molecules[2] in one pot.[3] Furthermore, its utility as a synthetic tool for the synthesis of pharmaceuticals and pharmacological entities has been demonstrated.[4] However, no asymmetric version of the HAM using a single catalyst was reported to date[5] and there are only reports using alternative strategies for this reaction. Xiao's and Han's groups developed a combination of metal and organo-catalysed processes in which the rhodium catalyst is in charge of the hydroformylation, and the reduction is carried out using a chiral Brønsted acid and Hantzsch esters (Scheme 1).[6] Recently, Zhang and co-workers reported the asymmetric interrupted intramolecular hydroaminomethylation of 1,2-disubstituted olefins.[7] In this approach the rhodium catalyst is in charge of the asymmetric hydroformylation (AHF). However, an external silane was used as reducing agents to afford the chiral amine (Scheme 1). Among amine containing compounds, amino acids are the most crucial molecules in human life, since



Scheme 1. Current strategies for asymmetric HAM and synthesis γ-aminobutyric esters

they have relevant biological activity, and also act as precursors for the synthesis of hormones and low-molecular weight nitrogenous substances of biological importance.[8] In particular, γ-amino acids act as major inhibitory transmitters in the mammalian central nervous system[9] and drugs containing γ-amino acids are currently commercialized by pharmaceutical agents.[10] Furthermore, α-substituted-γ-amino acid derivatives have been applied in the treatment of several diseases and disorders.[11]

In this context, the development of efficient systems for the synthesis of γ-amino acid and derivatives has been of interest in recent years.[12] Currently, the metal catalysed asymmetric hydrogenation of cyano-substituted acrylates is the most common strategy to access enantiomerically pure α-alkyl-γ-aminobutyric acids (GABA).[13] The use of either organocatalysed

[a] *Departament de Química Física i Inorgànica, Universitat Rovira I Virgili, C/ Marcel·lí Domingo, s/n, 43007, Tarragona, Spain.*
[b] *Centre Tecnològic de Química de Catalunya-Eurecat, C/ Marcel·lí Domingo, s/n, 43007, Tarragona, Spain.*
[c] *Laboratoire de Chimie de Coordination, LCC, Université de Toulouse, CNRS, 4 allee Emile Monso, 31030 Toulouse Cedex 4, France.*

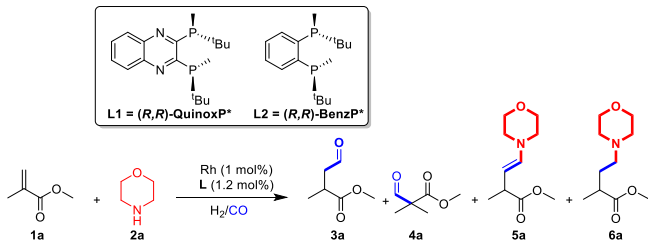
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

or enzyme-catalysed Michael addition was also reported to access this scaffold.[14] However, these systems require high synthetic efforts to access the substrates, or extra synthetic steps to provide the GABA motif (Scheme 1). Therefore, a system that can directly provide chiral γ-amino acid moieties from readily available reagents would be of high interest.

We envisioned the direct synthesis of chiral α-substituted-γ-amino esters via rhodium catalysed asymmetric HAM of acrylates (Scheme 1). Through this approach, the AHF should provide the linear aldehyde, and the subsequent amine condensation and Rh-catalysed hydrogenation steps should not affect the chirality induced in the first step. For this purpose, the commercial (*R,R)*-QuinoxP* **L1** and (*R,R*)-BenzP* **L2** ligands were selected since these ligands were reported to provide high enantioselectivity in the AHF of α-acrylates.[15]

First, an optimization of reaction conditions was performed using methyl methacrylate **1a** and morpholine **2a** as model substrates, and (*R,R)*-QuinoxP* **L1** as ligand (Table 1).

Table 1. Optimization of reaction conditions[a]



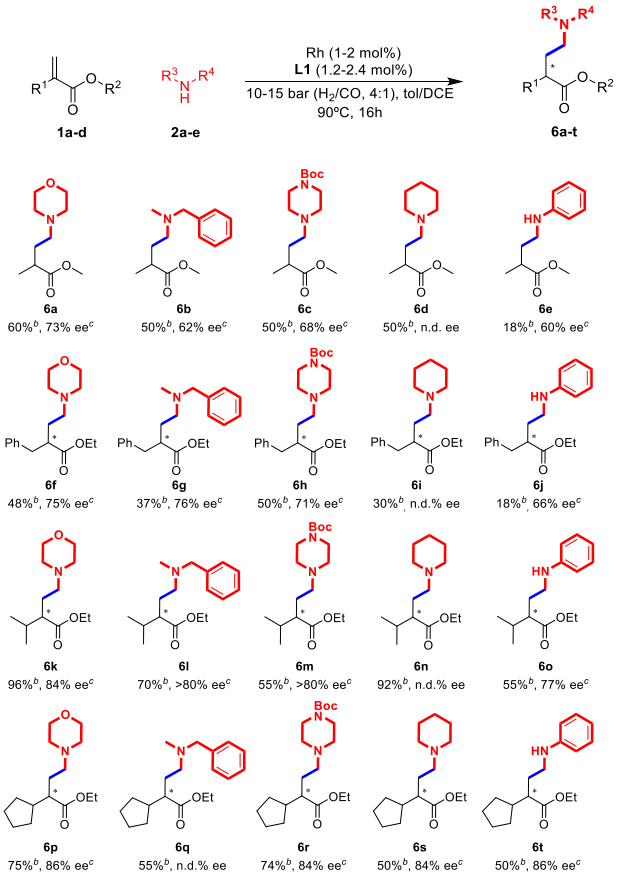
Entry	3a	4a	5a	6a	ee (%)
1	5	9	45	-	-
2[b]	2	52	28	-	-
3[c]	12	8	20	-	-
4[d]	20	11	4	38 [30]	72
5[e]	-	6	-	63 [60]	73
6[f]	-	5	-	30 [20]	60
7[g]	-	4	-	28 [24]	70

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), [Rh(acac)(CO)$_2$] (1 mol%), **L1** (1.2 mol %), P = 10 bar (H$_2$/CO, 4:1), toluene (0.4 mL), T = 90 °C, t = 16 h. Conversion and yield determined by ^{1}H NMR using naphthalene as internal standard, values in brackets refer to isolated yields, residual mass corresponds to alkene hydrogenation. ee of **6a** determined by chiral HPLC. [b]P = 10 bar (H$_2$/CO, 1:1). [c]P = 20 bar (H$_2$/CO, 4:1). [d]tol/DCE (1:1, 0.4 ml). [e] [Rh(COD)$_2$]BF$_4$ (1 mol%), tol/DCE (1:1, 0.4 mL). [f][Rh(COD)$_2$]BF$_4$ (1 mol%), tol/MeOH (1:1, 0.4 mL). [g][Rh(COD)$_2$]BF$_4$ (1 mol%), tol/DCE (1:1, 0.4 mL) **L2** (1.2 mol%).

When the reaction was performed at 90 °C under 10 bar of syngas (H$_2$/CO, 4:1) using 1mol% of catalyst during 16h, incomplete reaction was observed (entry 1, Table 1). The enamine **5a** was the major product while the linear aldehyde **3a** and branched aldehyde **4a** were detected in low yields and the amino ester **6a** was not detected. Increasing the CO partial pressure or total pressure only provided higher regioselectivity to the branched aldehyde product **4a** and increased the hydrogenation of the alkene (entries 2 and 3, Table 1). In contrast, when a mixture of toluene/1,2-dichloroethane (tol/DCE) was used as solvent (entry 4) the amino ester **6a** was afforded in 38% yield and 72% enantioselectivity. However, the linear aldehyde **3a** and the enamine **5a** were still detected in the crude. Interestingly, when the cationic rhodium precursor [Rh(COD)$_2$]BF$_4$ (COD = 1,5-cyclooctadiene) was used, the amino ester **6a** was afforded in 63% yield and 73% ee (entry 5). When DCE was replaced by MeOH, lower yield (30%) and ee (60%) were obtained (entry 6). The presence of relatively acidic proton from MeOH might favor the alkene hydrogenation. When the ligand (*R,R*)-BenzP* **L2** was tested (entry 7), the amino ester **6a** was obtained in only 28% yield and the alkene hydrogenation product was mainly formed.

Encouraged by these results, the preparation of a series of chiral γ-aminobutyric esters **6** was performed using the acrylates **1a-d** in the presence of amines **2a-e** as nucleophiles (Scheme 2).

Scheme 2. Rh-catalysed enantioselective HAM of α-alkyl-acrylates[a]



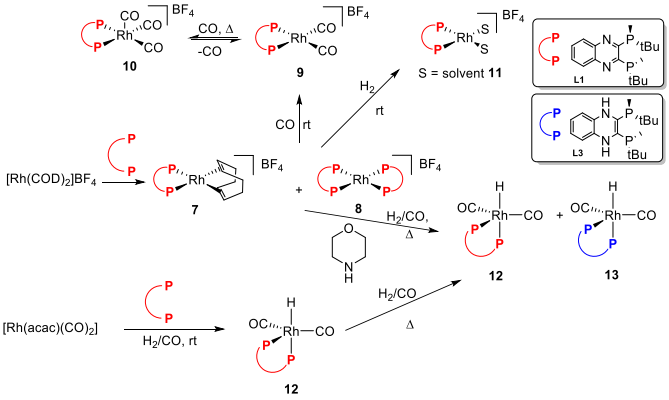
[a]*Reaction conditions as* in entry5, Table 1. For **6e, j, o, t** Rh = [Rh(acac)(CO)$_2$] (2 mol%) and **L1** (2.4 mol%); for **6k-n** P = 15 bar (H$_2$/CO, 4:1); for **6p-s**, Rh (1.5 mol%), **L1** (1.8 mol%). [b]Isolated yields obtained from two independent runs. [c]ee determined by chiral HPLC or ^{1}H NMR using Eu(hcf)$_3$. n.d = not determined.

Methylmethacrylate **1a** efficiently underwent HAM in the presence of various amines to afford the corresponding γ-aminobutyric esters **6a-e** in good yield and enantioselectivity. Interestingly, protecting groups were well tolerated and for instance, N-methylbenzyl amine provided secondary amino ester **6b** with 50% yield and 62% ee and no deprotection was observed. Furthermore, Boc protecting group remained untouched during the preparation of the product **6c**. Surprisingly, in the case of aniline, no conversion was observed under optimized conditions. After a brief screening of

conditions, the use of [Rh(acac)(CO)$_2$] in tol/DCE revealed the best combination using this amine to afford **6e** in 18% yield and 60% ee (See SIV, Table S1 in ESI). The use of the ethylbenzylacrylate **1b** provided the amino esters **6f-j** in moderate yield, but with ee up to 76%. When the isopropyl and cyclopentyl acrylate **1c** and **1d** were tested as substrates, high regioselectivity and enantioselectivity (up to 86%) were obtained. In the case of amino esters **6d, i, n** and **q** it was not possible to measure the ee.[16] These results constitute the first example of successful asymmetric intermolecular HAM of alkenes in which the rhodium catalyst is in charge of the asymmetric hydroformylation and the hydrogenation step. The variations in ee observed when the amine nucleophile was varied could be attributed to the coordination of the amine to the rhodium centre, which somehow could affect the catalyst reactivity. Moreover, when primary alkylamines were used as nucleophiles with a high degree of hydrogenation was observed. However, when phenyl-substituted acrylates were tested, only hydrogenation of these substrates was observed, indicating the scope limitations of our system. Investigations with other acrylates are currently on going in our lab.

High-Pressure (HP) NMR experiments constitute a powerful tool to get insights into catalytic reaction mechanisms.[17] In particular, crucial reaction intermediates were identified in the Rh-catalysed hydrogenation and hydroformylation of alkenes using this technique. In view of the unprecedented results achieved in the Rh-catalysed asymmetric HAM, a series of HP-NMR experiments were conducted under catalytic conditions to shed light on the species present during the course of the reaction. The results are summarized in Scheme 3. First, the cationic precursor [Rh(COD)$_2$]BF$_4$ was mixed with (*R,R*)-QuinoxP* **L1** in a mixture of tol/DCE (1:1) to afford the species [Rh(COD)**L1**]BF$_4$ **7** and [Rh(**L1**)$_2$]BF$_4$ **8**. These complexes were isolated and fully characterized (See SVII in ESI). When the mixture of cationic species was submitted to CO pressure at room temperature, the dicarbonyl species [Rh(CO)$_2$**L1**]BF$_4$ **9** was formed while upon warming at 90 °C, the tricarbonyl species [Rh(CO)$_3$**L1**]BF$_4$ **10** was produced (see SVII in ESI).[18] Under hydrogen pressure at room temperature the formation of the cationic species [Rh(solvent)$_2$**L1**]BF$_4$ **11** was evidenced but no hydrides were detected by ^{1}H NMR.[19] Upon warming at 90 °C, a black precipitated formed, indicating decomposition of this species. Interestingly, under syngas pressure (10 bar H$_2$/CO, 4:1) at 90 °C, the signals corresponding to the tricarbonyl species **10** were again observed but the expected [Rh(H)(CO)$_2$(**P-P**)] complex, common resting state in HF,[17] was not detected. However, when the experiment was repeated in the presence of morpholine, two rhodium hydride species were detected by ^{1}H and ^{31}P NMR spectroscopy. These species were identified as [Rh(H)(CO)$_2$**L1**] **12** and [Rh(H)(CO)$_2$**L3**] **13** containing the partially reduced QuinoxP ligand **L3** (Scheme 3), (See SVIII-D in ESI). A series of experiments were carried out in order to investigate the formation of these hydride species. Starting from the neutral precursor [Rh(acac)(CO)$_2$] in the presence of **L1** under syngas pressure at RT, the selective formation of species **12** was achieved. However, upon warming to 90 °C, the species **13** was again detected, indicating that its formation arises from the reduction of the ligand in species **12** (See SVIII-E in ESI).

In view of the results obtained with aniline in catalysis, an additional experiment was performed. The cationic rhodium species **7** and **8** were submitted to syngas pressure at 90 °C in the presence of aniline instead of morpholine. In this case, signals corresponding to the rhodium tricarbonyl species **10** were observed by ^{31}P NMR spectroscopy (Scheme 3), but no rhodium hydride species were detected. In previous reports, Kalck *et al.* proposed that a strong base might be required to promote the heterolytic cleavage of hydrogen and allow the formation of rhodium hydrides.[18] The results described in this study would thus indicate that aniline is not sufficiently basic to promote this process and would explain why the neutral precursor [Rh(acac)(CO)$_2$] was required (Scheme 2).



Scheme 3. Reactivity studies via HP-NMR spectroscopy

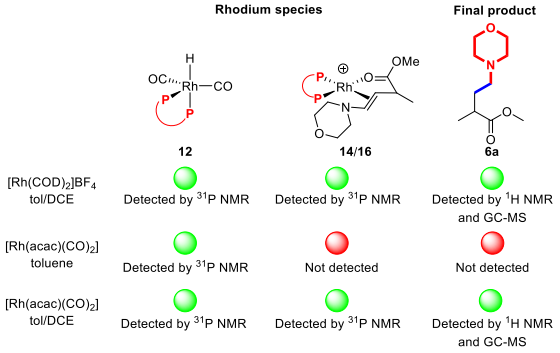
Finally, the monitoring of the HAM reaction was completed under catalytic conditions to investigate the differences observed in catalysis (see conditions in entries 1, 4 - 5, Table 1). Initially, the reaction was monitored under optimized reaction conditions (entry 5, Table 1). The signals corresponding to the enamine **5a** and the reaction product **6a** were initially detected by ^{1}H NMR spectroscopy. However, under these conditions, the linear aldehyde **3a** was not detected, indicating a rapid reaction with the amine to form the enamine **5a**. The presence of these products was confirmed by GC-MS analysis. ^{31}P signals corresponding to cationic species **7** and **8** and the hydride complex **12** were initially detected. Nevertheless, the resonances corresponding to the latter species were not detected at longer reaction times (See Figure S22 in ESI). In addition, two new signals were detected as doublets of doublets and tentatively attributed to the cationic species [Rh(**L1**)(**5a**)]BF$_4$ **14** (Figure 1) based on previous reports on Rh-catalysed hydrogenation of enamides.[20] The detection of **14**, together with that of the enamine **5a**, suggests that the hydrogenation of **5a** was slow in comparison with the hydroformylation and condensation steps.

Next, the neutral precursor [Rh(acac)(CO)$_2$] was used with toluene as solvent, conditions in which the catalytic reaction revealed incomplete (entry 1, Table 1). In this case, the final aminoester **6a** was not detected and the enamine **5a** was the main product, in agreement with the catalytic results. Moreover, the signals corresponding to the rhodium species **14**

were not observed. Indeed, only signals corresponding neutral rhodium hydride **12** species and [Rh(acac)(**L1**)] **15** were observed by ^{31}P NMR spectroscopy (Figure 1).

To investigate the role of the solvent, [Rh(acac)(CO)$_2$] was maintained as precursor but the mixture tol/DCE was used as solvent (entry 4 vs. entry 1, Table 1). In this case, two doublets of doublets at 38.1 ppm ($J_{Rh,P}$ = 123 Hz, $J_{P,P}$ = 41 Hz) and 59.8 ppm ($J_{Rh,P}$ = 154 Hz, $J_{P,P}$ = 41 Hz) were detected by ^{31}P NMR. Due to the similarity with those arising from the cationic complex [Rh(**L1**)(**5a**)][BF$_4$] **14**, these resonances were attributed to the related species [Rh(**L1**)(**5a**)][acac] **16** containing acetylacetonate as counter-ion (See Figure S24 in ESI). In this experiment, the signal corresponding to **6a** was again detected. These results thus provide evidence that both neutral and cationic species coexist during the HAM reaction and highlight the role of the solvent to solubilize cationic species. When the final product **6a** was formed, the absence of signals corresponding to the linear aldehyde suggests that the alkene hydroformylation and aldehyde condensation steps are very rapid while the hydrogenation of the enamine is slow. It is worth mention that rhodium hydride **13** containing the partially reduced ligand was not detected during the HP-NMR monitoring experiments. The role this species in catalysis is still not clear and is currently under investigation.

Fig. 1: Species detected during the HAM reaction via HP-NMR.



Conclusions

In summary, the first successful direct Rh-catalysed intermolecular asymmetric HAM of acrylates for the efficient synthesis of chiral γ-aminobutyric esters is reported. A series of chiral γ-aminobutyric esters has been obtained in poor to excellent yields, reaching high enantioselectivities. In contrast with previous reports, neither external reducing agent nor co-catalyst was required. HP-NMR study showed that the coexistence of neutral and cationic species is required to achieve the HAM reaction. Moreover, a new rhodium hydride containing a partially reduced ligand has been identified by NMR spectroscopy. Expansion of the scope of alkene substrates and testing of bulkier P-stereogenic ligands are currently on going in our lab to improve the enantioselectivity.

Acknowledgements

The authors are grateful to the Ministerio de Economia y Competividad and the Fondo Europeo de Desarrollo Regional FEDER (CTQ2016-75016-R, AEI/FEDER,UE) for funding and PhD grant (BES-2014-069199) to AC. We also thankf the Chromatography and X-Ray diffraction units of ICIQ for the support provided and Prof. Sergio Castillón for insightful discussions.

Conflicts of interest

There are no conflicts to declare.

References

1 J.W. Blunt, B.R. Copp, R.A. Keyzers, M.H.G. Munro, M.R. Prinsep, *Nat. Prod. Rep.* 2012, **29**, 144.
2 a) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B.E. Kitsos-Rzychon, C.L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev*. 1999, **99**, 3329. b) C. Chen, X-Q. Dong, X. Zhang, *Org. Chem. Front.* 2016, **3**, 1359. c) P. Kalck, M. Urrutigoïty, *Chem. Rev.* 2018, **118**, 3833.
3 a) A. Seayad, M. Ahmed, H. Klein, R. Jackstell, T. Gross, M. Beller, *Science*, 2002, **297**, 1676. b) S. Hanna, J. C. Holder, J. F. Hartwig, *Angew. Chem. Int. Ed.* 2019, **58**, 3368.
4 a) J.R. Briggs, J. Klosin, G. T. Whiteker *Org. Lett.* 2005, **7**, 4795. b) T.O. Vieira, H. Alper, *Org. Lett.* 2008, **10**, 485. c) S. Li, K. Huang, J. Zhang, W. Wu, X. Zhang, *Org. Lett.* 2013, **15**, 1036. d) G.T. Whiteker, *Top. Catal.* 2010, **53**, 1025.
5 D. Crozet, C.E. Kefalidis, M. Urrutigoïty, L. Maron, P. Kalck, *ACS Catal.* 2014, **4**, 435.
6 a) B. Villa-Marcos, J. Xiao, *Chin. J. Catal.* 2015, **36**, 106. b) J. Meng, X-H. Li, Z-Y. Han, *Org. Lett* 2017, **19**, 1076.
7 a) C. Chen, S. Jin, Z. Zhang, B. Wei, H. Wang, K. Zhang, H. Lv, X-Q. Dong, X. Zhang, *J. Am. Chem. Soc.* 2016, **138**, 9017. b) C. Chen, S. Jin, Z. Zhang, B. Wei, H. Wang, K. Zhang, H. Lv, X-Q. Dong, X. Zhang, *J. Am. Chem. Soc.* 2017, **139**, 4230.
8 a) I. Wagner, H, Musso, *Angew. Chem. Int. Ed.* 1983, **22**, 816. b) G. Wu, *Amino Acids*, 2009, **37**, 1.
9 a) K.M. Brown, K.K. Roy, G.H. Hockerman, R.J. Do-erksen, D.A. Colby, *Med. Chem.* 2015, **58**, 6336. b) H. Abdel-Halim, J. R. Hanrahan, D.E. Hibbs, G.A.R. Johnston, M. Chebib, *Chem. Biol. Drug Des.* 2008, **71**, 306.
10 a) B.A. Lauria-Homer, R.B. Phol. *Expert Opin. Investig. Drugs*, 2003, **12,** 663. b) I. Lapin, *CNS Drugs Reviews*, 2001, **7**, 471. c) M. Tomic, U. Pecikoza, A. Micov, S. Vuckovic, R. Stepanovic-Petrovic, *Pharmacol. Ther.* 2018, **192**, 42.
11 a) K. Kumar, S. Sharma, P. Kumar, R. Deshmukh, *Pharmacol., Bio-chem. Behav.* 2013, **110**, 174. b) R.J. Tyacke, A. Lingford-Hughes, L. J. Reed, D. J. Nutt, *Adv. Pharmacol.* 2010, **58**, 373.
12 a) M. Ordóñez, C. Cativiela, *Tetrahedron: Asymmetry*, 2007, 3. b) M. Ordóñez, C. Cativiela, I. Romero-Estudillo, *Tetrahedron Asymmetry*, 2016, 999.
13 D. Kong, M. Li, R. Wang, G. Zi, G. Hou, *Org. Biomol. Chem.* 2016, **14**, 1216.
14 a) Y. Chi, L. Guo, N.A. Kopf, S.H. Gellman, *J. Am. Chem. Soc.* 2008, **130**, 5608. b) L. Biewenga, T. Saravanan, A. Kunzendorf, J-Y. van der Meer, T. Pijning, P.G. Tepper, R. van Merkerk, S. J. Charnock, A-M. W. H. Thunnissen, G. J. Poelarends, *ACS Catal.* 2019, **9**, 1503.
15 X. Wang, S.L. Buchwald, *J. Am. Chem. Soc.* 2011, **133**, 19080.
16 The conditions for the separation of enantiomers for the amino esters **6d,i,n** and **q** could not be determined, nor those for the corresponding amino alcohols.
17 P.C.J. Kamer, J.N.H. Reek, P.W.N.M. van Leeuwen Rhodium catalysed Hydroformylation in Mechanisms in Homogeneous Catalysis. A Spectroscopic Approach; B. Heaton Eds.; Wiley-VCH, Weinheim, 2006; pp 231.
18 D. Crozet, A. Gual, D. McKay, C. Dinoi, C. Godard, M. Urrutigoïty, J-C. Daran, L. Maron, C. Claver, P. Kalck, *Chem. Eur. J.* 2012, **18**, 7128.
19 G.J. Kubas, *Chem. Rev.* 2007, **107**, 4152.
20 I. D. Gridnev, T. Imamoto, *ACS Catal.* 2015, **5**, 2911 and references therein.