COMMUNICATIONS DOI: 10.1002/adsc.201900642

Synthesis of $\beta^{2,2}$-Amino Esters via Rh-Catalysed Regioselective Hydroaminomethylation

Anton Cunillera,[a] Aurora Ruiz,[a] and Cyril Godard[a,*]

[a] Department de Química Física i Inorgànica, Universitat Rovira i Virgili, C/Marcel·lí Domingo, n1, 43007, Tarragona, Spain
E-mail: cyril.godard@urv.cat

Manuscript received: May 23, 2019; Revised manuscript received: June 17, 2019;
Version of record online: July 23, 2019

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201900642

Abstract: The synthesis of $\beta^{2,2}$-amino esters was successfully achieved via Rh-catalysed regioselective hydroaminomethylation of methyl methacrylate with secondary amines using the neutral precursor $[Rh(acac)(CO)_2]$. In this process, the presence of molecular sieves revealed crucial in order to access the final amino ester. For the synthesis of products containing aniline derivatives, the use of the cationic precursor $[Rh(COD)_2]BF_4$ and ^{Me}CgPPh phosphine as ligand was necessary in a mixture of toluene/DCE as solvent. Effects of the steric and electronic properties of the amines were observed during this study. Interestingly, poisoning effect of CO in the hydrogenation of the imine intermediate was observed when benzyl amine was used.

Keywords: Hydroaminomethylation; β-amino acids; tandem; hydroformylation; hydrogenation

β-amino acids are incorporated into secondary metabolites in bacteria, plants, fungi and cyanobacteria, and have potential biological and physical activities.[1] Moreover, they are precursors for the synthesis of β-lactams, which constitute an important class of antibiotics.[2] Over the last years, significant efforts have been devoted to the synthesis of these building blocks as pharmaceutical intermediates and peptidomedics.[3] Most of these strategies are based on the hydrogenation of unsaturated compounds[4], Mannich reaction[5], or conjugated additions[6]. However, either high catalyst loadings or the use of reagents that are not readily available is required. $\beta^{2,2}$-amino acids, which containing a quaternary carbon centre in α-position of the carbonyl, such as HY-2901 and H1/5-HT2A antagonist are potential sleeping disorder drugs for the insomnia treatment (Figure 1).[7] Due to the interest for these target molecules, various strategies have been reported for their synthesis such as Mannich reaction and C–H amination.[8] However, these processes require multi-step synthetic routes or the presence of directing groups in the structure of the substrate.

The hydroaminomethylation (HAM) of alkenes is a powerful tool to access nitrogen containing molecules from readily available reagents.[9] However, to the best of our knowledge, there are no reports to the date on the synthesis of β-amino acids or derivatives via HAM reaction.

The synthesis of $\beta^{2,2}$-amino acid derivatives via tandem HAM reaction requires the formation of quaternary carbon centre in the hydroformylation step (Scheme 1), which is disfavoured according to Keuleman's rule.[10]

However, Clarke and co-workers reported the regioselective hydroformylation of α-substituted acrylates using ^{Me}CgPPh **L1** ligand (Scheme 1, top reaction).[11] The branched aldehyde was afforded in excellent yield with a wide variety of acrylates. In this report, the synthesis of $\beta^{2,2}$-amino ester was performed in two steps using two distinct catalysts: one Rh catalyst for the hydroformylation step and an Ir species for the hydrogenation of the imine (Scheme 1). Similarly, the same group reported the hydroaminovi-

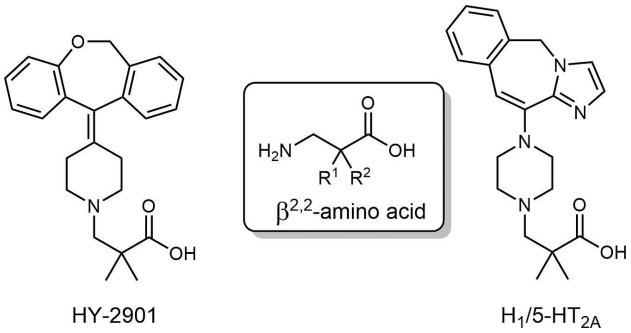
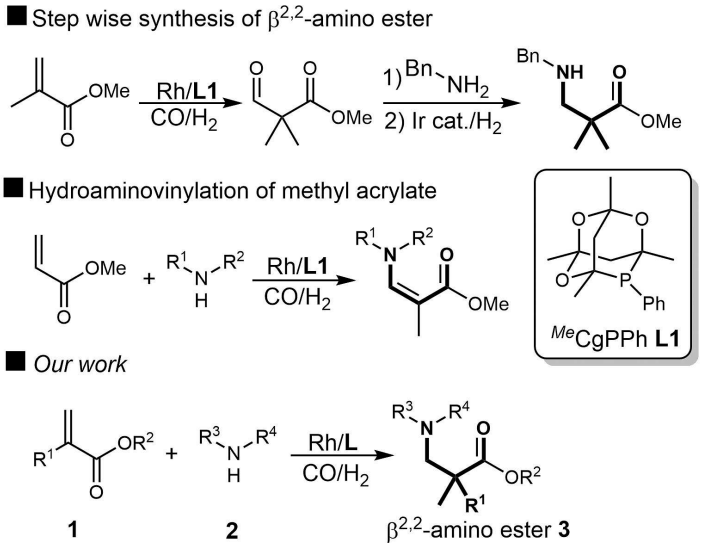


Figure 1. Examples of biologically active $\beta^{2,2}$-amino acids.

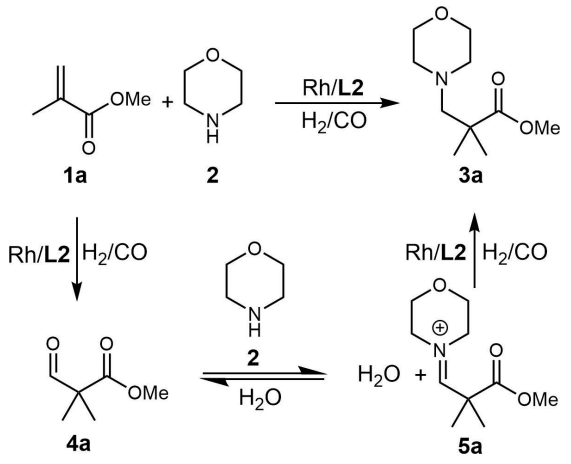


Scheme 1. Attempted HAM of acrylates in the synthesis of β-amino esters and our work.

nylation of methyl acrylate and obtained the corresponding enamine (Scheme 1).[12] However, it was observed that depending on the amine, the hydroamination product was the major one.

In view of these precedents, we envisioned the regioselective hydroaminomethylation of α-substituted acrylates **1** with amines **2** as an efficient method to access $\beta^{2,2}$-amino esters **3** (Scheme 1).

First a screening of ligands was performed using methyl methacrylate **1a** and morpholine as model substrates (See Table S1 in SI). The highest regioselectivity towards the branched aldehyde **4a** was obtained using methyldiphenylphosphine **L2** (Scheme 2). Nonetheless, no traces of the amino ester product **3a** were detected in these reactions and the aldehyde was the main product.



Scheme 2. Process for the synthesis of $\beta^{2,2}$-amino ester **3a**.

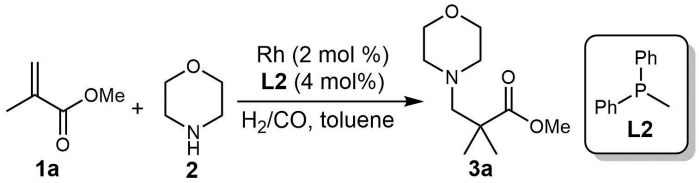
We hypothesized that the presence of water formed as a by-product could explain this result. Indeed, if the hydroformylation takes place at internal position of the alkene, the branched aldehyde **4a** is generated (Scheme 2). Next, condensation of the morpholine produces the iminium cation **5a**, which is expected to be highly reactive, and could react with water and reform the branched aldehyde **4a**.

The reaction was therefore run in the presence of 4 Å molecular sieves (MS) (entry 1, Table 1) and under these conditions, the amino ester product **3a** was obtained, although in moderate yield. This result confirmed the importance of removing the water from the reaction mixture. The use of an excess of morpholine decreased the yield of **3a** (entry 3, Table 1).

When the temperature was decreased to 70 °C and the amount of MS increased (entry 4, Table 1), the yield increased up to 42%. Increasing the time up to 72 h also favoured the formation of **3a** (62% isolated yield) (entry 5, Table 1). Moreover, when the temperature was reduced to 50 °C the amino ester **3a** was isolated in 79% yield (entry 6, Table 1).

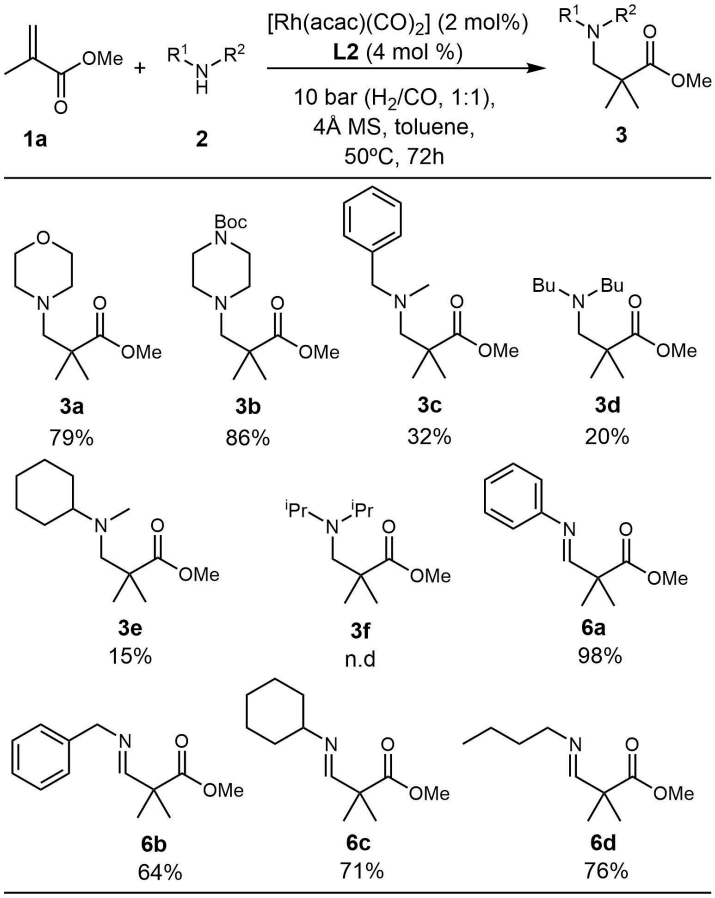
Motivated by these result (entry 6, Table 1), a series of $\beta^{2,2}$-amino esters **3** was synthesised using methyl methacrylate **1a** as model substrate (Scheme 3). The steric hindrance revealed an important factor since cyclic secondary amines such as morpholine and 1-Boc-piperazine, provided the amino esters **3a–b** in high yield (up to 86%) while non-cyclic secondary amines produced amino esters **3c–e** in moderate to low yields. In the case of diisopropylamine, the corresponding amino ester **3f** was not detected. Interestingly, when primary amines such as aniline, benzylamine, cyclohexylamine, and butylamine, were applied under these conditions, the corresponding imino esters **6a–d** were isolated in good to excellent yields

Table 1. Optimisation of reaction conditions.



Entry[a]	MS(mg)	T(°C)	t(h)	C(%)[b]	3a[b]
1	–	90	20	>99	-
2	50	90	20	>99	36
3[c]	50	90	20	>99	21
4	100	70	20	>99	42
5	100	70	72	>99	67[62]
6	100	50	72	>99	82[79]

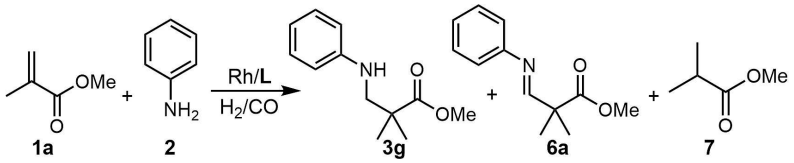
[a] Reaction conditions: **1 a** (0.5 mmol), morpholine (0.5 mmol), Rh = [Rh(acac)$(CO)_2$] (2 mol%), toluene (0.4 mL), P = 10 bar (CO/H2, 1:1).
[b] % Conversion and yield determined by GC-MS analysis using naphthalene as external standard. Values between brackets refer to isolated yield.
[c] morpholine (0.75 mmol), linear enamine and amino ester detected by GC.



Scheme 3. Rh-catalysed HAM of methyl methacrylate **1 a** with secondary and primary amines.

(Scheme 3), but the corresponding amino esters were not formed. These results can be related with previous reports describing the reduction of the unsaturated nitrogen intermediate as the limiting step of the reaction. [10,12] In conclusion, β[2,2]-amino ester **3 a–e** have been synthesised in low to high yield via Rh-

Table 2. Optimisation of reaction conditions for Rh-catalysed HAM of **1a** with aniline.



Entry[a]	L	C(%)[b]	3 g[b]	4a[b]	6a[b]	7[b]
1	**L2**	>99	–	–	>99	–
2[c]	**L1**	>99	–	60	40	–
3[d]	**L2**	>99	25	–	–	75
4[e]	**L1**	>99	31	29	34	6
5[f]	**L1**	>99	67	4	11	17
6[g]	**L1**	>99	90	–	–	10
7[h]	**L1**	>99	94[87]	–	–	6

[a] Reaction conditions: **1a** (0.5 mmol), aniline (0.5 mmol), Rh = [Rh(acac)$(CO)_2$] (2 mol%), **L2** (4 mol%), toluene (0.4 mL), P = 10 bar (CO/H_2, 1:1).
[b] % Conversion and yield determined by ^{1}H NMR analysis using naphthalene as internal standard. Values between brackets refer to isolated yield.
[c] Rh = [Rh(acac)$(CO)_2$] (2 mol%), **L1** (4 mol%).
[d] Rh = [Rh$(COD)_2$]BF_4 (2 mol%), **L2** (4 mol%), tol/DCE (1:1, 0.4 mL).
[e] Rh = [Rh$(COD)_2$]BF_4 (2 mol%), **L1** (4 mol%), tol/DCE (1:1, 0.4 mL).
[f] Rh = [Rh$(COD)_2$]BF_4 (2 mol%), **L1** (4 mol%), T = 70 °C, tol/DCE (1:1, 0.4 mL).
[g] Rh = [Rh$(COD)_2$]BF_4 (2 mol%), **L1** (4 mol%), T = 70 °C, P = 30 bar (CO/H_2, 1:1), tol/DCE (1:1, 0.4 mL).
[h] Rh = [Rh$(COD)_2$]BF_4 (1 mol%), **L1** (2 mol%), T = 70 °C, P = 30 bar (CO/H_2, 1:1), tol/DCE (1:1, 0.4 mL).

catalysed HAM of methyl methacrylate **1a** with various secondary amines **2** using **L2** as ligands (Scheme 3). The reaction conditions were appropriate to reduce the iminium **5** obtained with secondary amines, but not to reduce the imino ester **6**.

At this point, an optimisation of the reaction conditions using methyl methacrylate **1a** and aniline as model substrates was performed (Table 2). Both **L1** and **L2** were tested under the optimised conditions for secondary amines, and in both cases, the amine product **3g** was not obtained (entries 1 and 2, Table 2).

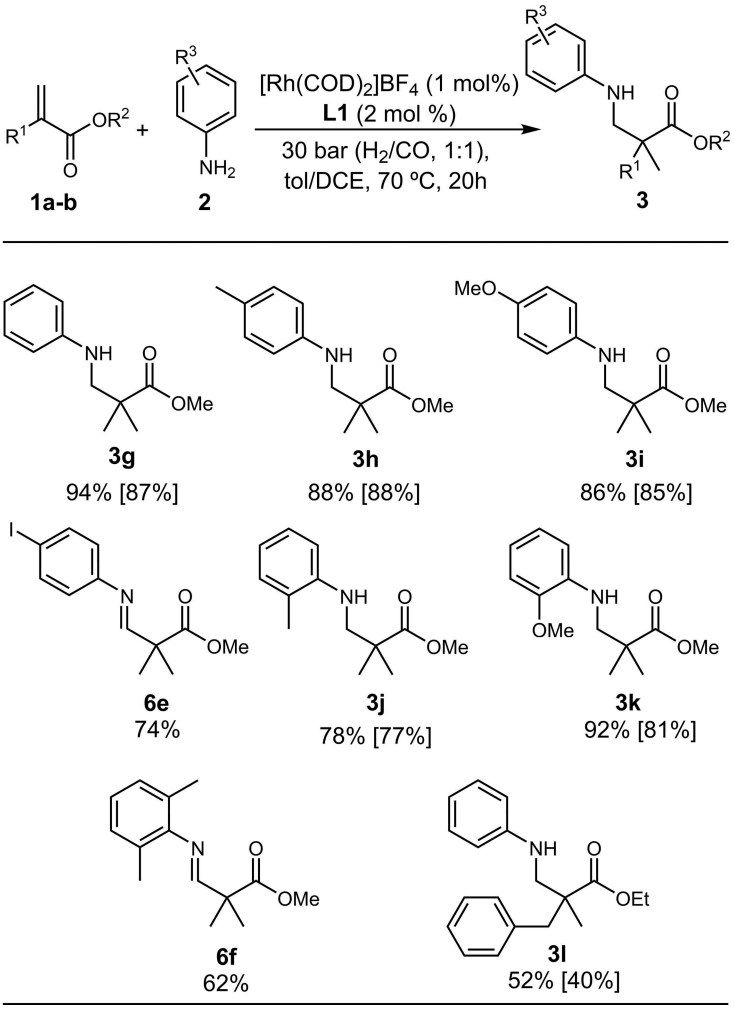
Interestingly, the use of the cationic precursor [Rh$(COD)_2$]BF_4 in a mixture of toluene/1,2-dichloroethane (tol/DCE) resulted in the formation of amino ester **3g** in moderate yield (entries 3 and 4, Table 2). In the case of **L2**, high selectivity towards alkene hydrogenation product **7** was observed (entry 3, Table 2), while with **L1**, the alkene hydrogenation was substantially reduced, but both the branched aldehyde **4a** and the imine **6a** were still detected (entry 4, Table 2). Increasing the temperature to 70 °C afforded **3g** in 67% yield (entry 5, Table 2). Under higher total syngas pressure (up to 30 bar), the formation of amino ester **3g** was achieved in excellent yield (entry 6, Table 2). When the catalyst loading was 1 mol%, the high selectivity towards **3g** was maintained (entry 7, Table 2). Thus, the use of a cationic precursor in a mixture of tol/DCE revealed crucial to complete the HAM reaction when using aniline.

In order to expand the scope of $\beta^{2,2}$-amino esters **3**, various aniline derivatives **2** and acrylates **1** were tested (Scheme 4). First, the electronic effect was studied using *para*-substituted anilines. No significant effect was observed when *para*-substituted anilines bearing electron-donating methyl and methoxy group, respectively, were used. In both cases, the corresponding amino esters **3h** and **3i** were afforded in high yields (up to 88%).

In contrast, when the aniline derivative bearing electron-withdrawing iodide group in *para*-position was tested, the imine **6e** was the main reaction product. Using *ortho*-substituted anilines bearing methyl and methoxy groups, the amino esters **3j** and **3k** were afforded in high isolated yield (up to 81%). However, when the steric hindrance was further increased using 2,6-dimethyl aniline, the imine **6f** was obtained. A possible explanation for this result is that the coordination of this imine to the Rh catalyst is disfavoured, and consequently, the hydrogenation cannot take place.

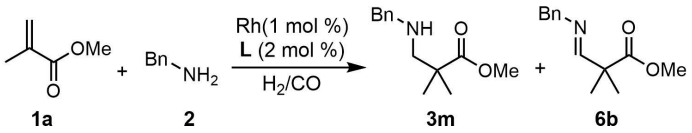
Interestingly, when the ethyl benzylacrylate **1b** was used as substrate and aniline as nucleophile, the corresponding amino ester **3l** was afforded in 40% isolated yield.

The results described thus demonstrated that under appropriate conditions, $\beta^{2,2}$-amino esters **3** can be obtained by HAM reaction, either using secondary amines or aniline derivatives.



Scheme 4. Rh-catalysed HAM of acrylates **1 a–b** with aniline derivatives **2**. Values between brackets refer to isolated yields.

Table 3. Optimisation of reaction conditions for Rh-catalysed HAM of **1 a** with benzyl amine.

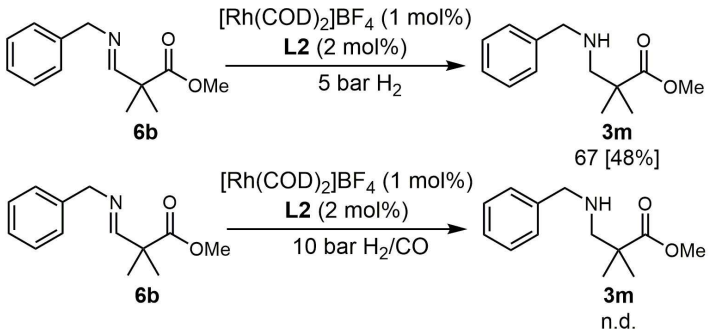


Entry[a]	L	C(%)[b]	3 m[b]	4a[b]	6b[b]	7[b]
1	L1	>99	–	–	85	15
2	L2	>99	–	–	>99	–
3[c]	L2	95	–	6	82	7

[a] Reaction conditions: **1 a** (0.5 mmol), benzyl amine (0.5 mmol), Rh = $[Rh(COD)_2]BF_4$ (1 mol%), **L** (2 mol%), tol/DCE (1:1, 0.4 mL), P = 10 bar (H_2/CO, 1:1), 50 °C.
[b] Conversion and yields determined by ^{1}H NMR using naphthalene as internal standard.
[c] HBF_4 (2 mol%).

Nevertheless, when the HAM of methyl methacrylate **1 a** with benzyl amine was attempted (Table 3) either using **L1** or **L2** in the presence of cationic [Rh $(COD)_2$]BF4 in tol/DCE, the imine **6 b** was mainly produced (entry 1 and 2, Table 3).

Kalck and co-workers proposed the existence of an equilibrium between neutral species involved in the HF reaction, and cationic species, which are expected to hydrogenate the imine.[13] In this equilibrium, a dihydride intermediate is generated from the neutral



Scheme 5. Rh-catalysed hydrogenation of **6b**.

rhodium hydride species in the presence of a protic source. Moreover, Beller and co-workers reported that the use of tetrafluoroboric acid facilitated the formation of amines in the HAM of vinylarenes.[14] For this reason, the addition of tetrafluoroboric acid was tested in the reaction (entry 3, Table 3). However, under these conditions, the addition of an acid did not promote the hydrogenation of imine **6b**.

At this point, two control experiments were conducted (Scheme 5). First, the imine **6b** was treated with hydrogen in the presence of **L2** and $[Rh(COD)_2]BF_4$ in tol/DCE, and interestingly, the amino ester **3m** was obtained in good yield. It was then concluded that the system is capable of reducing the imine. Finally, the imine **6b** was treated under syngas mixture, and this time no amino ester **3m** was detected (Scheme 5). These results therefore indicated that carbon monoxide was poisoning the hydrogenation step in the HAM reaction with benzyl amine. The same result was obtained using other primary amines such as butyl amine or cyclohexyl amine. This could indicate that under syngas pressure, coordination of CO competes with that of the imine intermediates when primary amines are used, thus inhibiting their hydrogenation.

In conclusion, a series of $\beta^{2,2}$-amino esters **3** was successfully synthesised through the regioselective Rh-catalysed HAM of methyl methacrylate with secondary amines and aniline derivatives. For the secondary amines, the use of molecular sieves resulted crucial to remove the water from the media. For the aniline derivatives, the use of a cationic rhodium precursor in tol/DCE was required to afford the amino ester **3**. Both electronic and steric properties of the amine reagents were highly important to obtain the corresponding amine. In this case, ethyl benzylacrylate was successfully applied to access amino ester containing benzyl substituent. For other primary amines, such as benzyl amine, carbon monoxide acted as a poison under the tested conditions and the hydrogenation step could not be completed, resulting in the formation of the corresponding imines. The synthesis of the biologically active $\beta^{2,2}$-amino acids HY-2901 and H1/5-HT2 A using this methodology is currently on going in our lab and will be reported in the near future.

Experimental Section

The Rh-catalysed HAM reaction was set up in a CAT24 autoclave from HEL Inc. and was stirred with a teflon-coated magnetic stirring bar.

General Procedure for the Synthesis of $\beta^{2,2}$-Amino Esters Using Secondary Amines

A 2 mL glassware reactor tube was charged with methyl methacrylate **1a** (0.5 mmol), secondary amine **2** (0.5 mmol), 100 mg of 4 Å MS, ligand **L2** (3.7 µL, 0.02 mmol), dicarbonyl (acetylacetonato)rhodium(I) (2.6 mg, 0.01 mmol) in toluene (0.4 mL). The reaction tube was placed in the reactor which was pressurised with 10 bar of H_2/CO (1:1), heated at 50 °C and left stirring at 800 rpm. The reaction was stopped after 72 h by cooling the reactor in an ice bath for 20 min followed by venting the system. The mixture was purified by chromatographic column with Al_2O_3 to afford the resulting $\beta^{2,2}$-amino esters **3**.

General Procedure for the Synthesis of $\beta^{2,2}$-Amino Esters Using Aniline and Derivatives

A 2 mL glassware reactor tube was charged with α-alkyl acrylate **1** (0.5 mmol), aniline derivative **2** (0.5 mmol), bis(1,5-cyclooctadiene)rhodium (I) tetrafluoroborate (2 mg, 0.005 mmol) in DCE (0.2 mL), and ligand **L1** (2.9 mg, 0.01 mmol) in toluene (0.2 mL). The reaction tube was placed in the reactor which was pressurised with 30 bars of H_2/CO (1:1), heated at 70 °C and left stirring at 800 rpm. The reaction was stopped after 20 h by cooling the reactor in an ice bath for 20 min followed by venting the system. The mixture was purified by chromatographic column with SiO_2 to afford the resulting $\beta^{2,2}$-amino esters **3**.

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.

References

[1] Enantioselective Synthesis of Beta-Amino Acids, *2nd ed* (Eds: E. Juaristi, V. A. Sholoshonok), Wiley-VCH, New Jersey, 2005.

[2] P. A. Magriotis, *Angew. Chem. Int. Ed.* **2001**, *40*, 4377–4379; *Angew. Chem.* **2001**, *113*, 4507–4509.

[3] a) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, B. L. Feringa, *Chem. Soc. Rev.* **2010**, *39*, 1656–1691. b) C. Bruneau, J–L. Renaud, T. Jerphagnon, *Coord. Chem. Rev.* **2008**, *252*, 532–544. c) M. Yoshihiko, Y. Akira JP Patent 4813342B2, **2008**.

[4] a) J–H. Xie, S–F. Zhu, Q–L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760. b) Q. Dai, W. Yang, X. Zhang, *Org. Lett.* **2005**, *7*, 5343–5345. c) G. Hou, W. Li, M. Ma, X. Zhang, X. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12844–12846.

[5] A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102–112.

[6] S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069–1094.

[7] a) A. Palomer, M. Príncep, A. Guglietta, *Annu. Rep. Med. Chem.* **2007**, *42*, 63–80. b) D. M. Edgar, D. G. Hangauer, J. F. White, M. Solomon, WO Patent 2005058880, **2005**. c) K. Kawamura, H. Sone, C. Uchida, WO Patent 2006090279, **2006**.

[8] a) A. Romanens, G. Bélanger, *Org. Lett.* **2015**, *17*, 322–325. b) J. He, T. Shigenari, T. J.-Q. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 6545–6549; *Angew. Chem.* **2015**, *127*, 6645–6649. c) Q. Gou, Y–W. Yang, Z.-N. Liu, J. Qin, *Chem. Eur. J.* **2016**, *22*, 16057–16061. d) M. Shang, J. Z. Chan, M. Cao, Y. Chang, Q. Wang, B. Cook, S. Torker, M. Wasa, *J. Am. Chem. Soc.* **2018**, *140*, 10593–10601.

[9] For reviews on hydroaminomethylation, see: a) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. M. Schmidt, *Chem. Rev.* **1999**, *99*, 3329–3365. b) P. Eilbracht, A. M. Schmidt in *Transition Metals for Organic Synthesis, Vol. 1* (Eds.: M. Beller, C. Bolm) Wiley-VCH: Weinheim, **2004**, pp 57–85. c) D. Crozet, M. Urrutigoïty, P. Kalck, *ChemCatChem*, **2011**, *3*, 1102–1118. d) C. Chen, X.-Q. Dong, X. Zhang, *Org. Chem. Front.* **2016**, *3*, 1359–1370. e) P. Kalck, M. Urrutigoïty, *Chem. Rev.* **2018**,*118*, 3833–3861.

[10] A. I. Keulemans, A. Kwantes, T. van Bavel, *Rec. Trav. Chim. Pays Bas.* **1948**, *67*, 298–308.

[11] a) M. L. Clarke, *Tetrahedron Lett.* **2004**, *45*, 4043–4035; b) M. L. Clarke, G. J. Roff, *Chem. Eur. J.* **2006**, *12*, 7978–7986.

[12] M. L. Clarke, G. J. Roff, *Green Chem.* **2007**, *9*, 792–796.

[13] 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*, 7128–7140.

[14] L. Routaboul, C. Buch, H. Klein, R. Jackstell, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 7401–7405.

