CHEMISTRY
AN ASIAN JOURNAL
www.chemasianj.org

Accepted Article

Title: Enantioselective Sequential-Flow Synthesis of Baclofen Precursor via Asymmetric 1,4-Addition and Chemoselective Hydrogenation on Platinum/Carbon/Calcium Phosphate Composites

Authors: Haruro Ishitani, Yuichi Furiya, and Shu Kobayashi

To be cited as: *Chem. Asian J.* 10.1002/asia.202000065

Link to VoR: http://dx.doi.org/10.1002/asia.202000065

A Journal of
ACES Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

10.1002/asia.202000065

WILEY-VCH

Enantioselective Sequential-Flow Synthesis of Baclofen Precursor via Asymmetric 1,4-Addition and Chemoselective Hydrogenation on Platinum/Carbon/Calcium Phosphate Composites

Haruro Ishitani,*[a] Yuichi Furiya,[b] and Shu Kobayashi*[a, b]

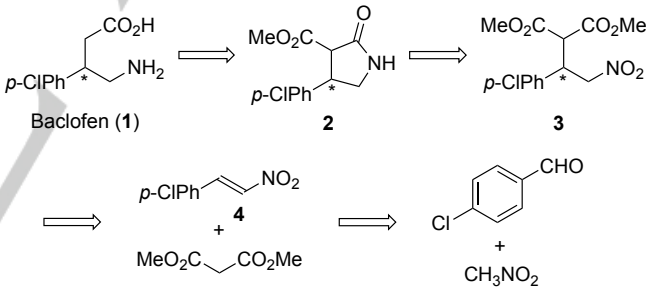
Dedication ((optional))

Abstract: Continuous-flow synthesis of baclofen precursor (**2**) was achieved using achiral and chiral heterogeneous catalysts in high yield with high enantioselectivity. The key steps are chiral calcium-catalyzed asymmetric 1,4-addition of a malonate to a nitroalkene and chemoselective reduction of a nitro compound to the corresponding amino compound by using molecular hydrogen. A dimethylpolysilane (DMPS)-modified platinum catalyst supported on activated carbon (AC) and calcium phosphate (CP) has been developed that has remarkable activity for the selective hydrogenation of nitro compounds.

Continuous-flow synthesis of active pharmaceutical ingredients (APIs) has attracted much attention because the approach has several advantages over conventional batch synthesis in terms of environmental compatibility, efficiency, and safety.[1] Moreover, in a practical sense, continuous production of APIs can offer benefits such as saving time, space, and energy, allowing production sites to be easily moved, decreasing the risk of human error, and enabling on-demand synthesis; ultimately, the approach can be expected to lead to high-quality production and low-cost synthesis.[2]

Baclofen (**1**) is one of the most important gamma-aminobutyric acid (GABA) receptor agonists, and it is used as a medication for the treatment of muscle spasticity and multiple sclerosis.[3] Recently, attention has also focused on therapy for alcohol dependence.[4] Commercialized baclofen is usually an (*R*)/(*S*)-mixture; however, differences in the biological activity of the enantiomers have been discussed recently.[5] While enantioselective synthesis of baclofen in batch has been reported, no continuous synthesis has been achieved. Here, we describe enantioselective continuous-flow synthesis of a baclofen precursor by using asymmetric 1,4-addition and chemoselective hydrogenation as key steps. A novel Pt catalyst consisting of dimethylpolysilane (DMPS), activated carbon (AC), and calcium phosphate (CP) has been developed for the synthesis.

A retrosynthetic analysis of the continuous enantioselective synthesis of baclofen (**1**) is shown in Scheme 1. Chiral induction could be conducted by asymmetric 1,4-addition of malonate to nitroalkene **4** to afford the optically active compound **3**, and a polymer-supported chiral calcium catalyst would be promising for this asymmetric reaction.[6] Another key step is the chemoselective reduction and cyclization of **3**, providing lactam **2**. Among the various methods available for transformations of nitro groups into amino groups, catalytic hydrogenation with molecular hydrogen as a reductant is one of the best and most promising ways to achieve green and sustainable chemical processes, because the by-product is only water.[7-9] In the current case, however, anticipated issues included low reactivity of the aliphatic nitro compound and selectivity between the nitro group and the *p*-chlorophenyl group of **3**.



Scheme 1. Retrosynthetic plan for baclofen (**1**).

In the context of our previous investigations on continuous-flow hydrogenation of aliphatic nitro compounds, a DMPS-modified palladium on bone charcoal (BC) catalyst was found to be a sustainable, powerful catalyst to give the corresponding amines in good yields and high space–time yields (STYs).[10-12] BC is a component of animal biomass and is produced by charring cow bones. A problem is that its composition is dependent on the method of production. In addition, a BC supply crisis occurred due to mad cow disease. We then decided to reinvestigate the hydrogenation of aliphatic nitro compounds by using polysilane-supported precious-metal catalysts, and to assess the use of a number of supports that can be chemical surrogates of bone char.

Bone char mainly consists of calcium phosphate (CP), calcium carbonate, and carbon. Therefore, we started this investigation by searching for an appropriate combination of CP and activated carbon (AC) as a catalyst support. A procedure for the preparation of catalysts for our purpose (DMPS-Pd/AC-CP)

[a] *Dr. H. Ishitani, Prof. Dr. S. Kobayashi*
Green & Sustainable Chemistry Cooperation Laboratory, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)
E-mail: hishitani@chem.s.u-tokyo.ac.jp
E-mail: skobayashi@chem.s.u-tokyo.ac.jp
[b] *Dr. Y. Furiya, Prof. Dr. S. Kobayashi*
Department of Chemistry, School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

is shown in Scheme S1. AC was used as the first support and $Pd(OAc)_2$ was used as a palladium source. The palladium species dissolved in tetrahydrofuran was reduced with $NaBH_4$ and the reduced Pd was deposited onto the first support. After this treatment, the other two components, CP and DMPS, were added successively. We set the amount of $Pd(OAc)_2$ as 0.1 mmol and changed the amounts of AC and CP systematically. The DMPS concentration in the whole mass of the support was set to 10 wt%. Given that it is well known that the state of metal dispersion on the support strongly influences the properties of the catalyst, the catalyst support used in this study consisted of two different types of materials that are expected to give different effects on metal species. A series of catalysts were tested in the sequential hydrogenation–cyclization reactions of **3a** to afford **2a**, a precursor in the synthesis of rolipram,[10d] under batch conditions (Scheme 2 and Figure 1). The highest values of 96% conversion and 91% yield were attained by using a catalyst in which the composition of the support was AC:CP:DMPS = 67.5:22.5:10.0 and the target Pd loading was 0.10 mmol/g.

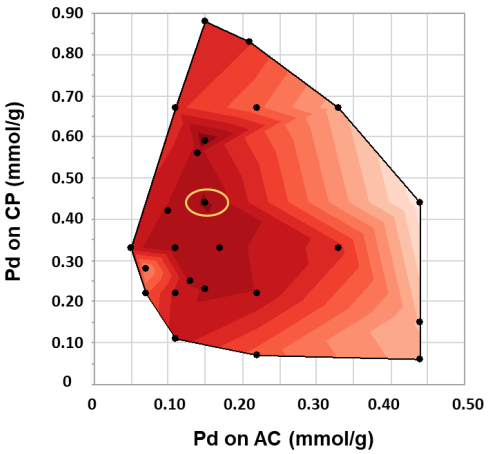
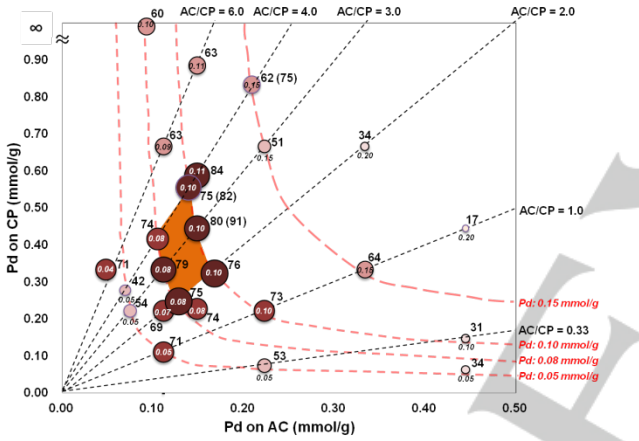
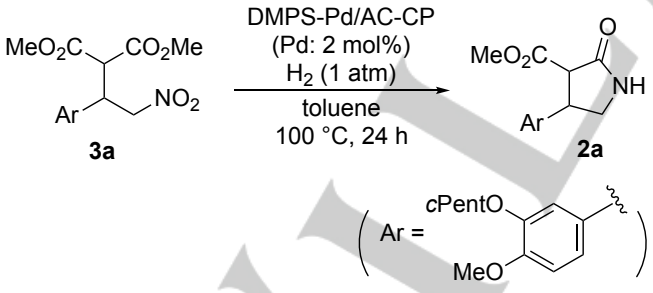


Figure 1. Effect of Pd concentration with AC and CP supports. (a) Top: Yield is represented by size and color of the circle. The corresponding number is the yield for each catalyst. (b) Bottom: Yield is represented by the contour lines. Dots indicate the catalysts tested; fields in dark red indicate high-performance catalysts. The best catalyst is indicted with a yellow ellipse.

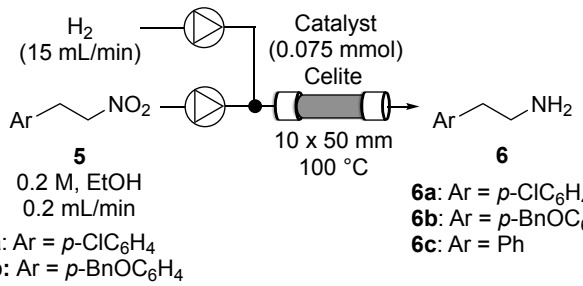




Scheme 2. Sequential hydrogenation–lactamization reaction.

We then applied DMPS-Pd/AC-CP for the chemoselective hydrogenation. 2-(*p*-Chlorophenyl)nitroethane (**5a**) was chosen as a model and the hydrogenation was conducted under the continuous-flow conditions shown in Table 1. Both chloro and nitro groups of **5a** were fully reduced using DMPS-Pd/AC-CP (entry 1). Another heterogeneous Pd catalyst (Pd/C) was tested; however, lower activity was observed (entry 2). We then decided to prepare DMPS-Pt/AC-CP as a new platinum catalyst. The latter platinum catalyst, with a composition of AC:CP:DMPS = 67.5:22.5:10.0 and a target Pt loading of 0.10 mmol/g, was prepared as described for the preparation of Pd catalysts, except now, CP was used as the first added support and AC was used as the second added support. Evaluation of the novel platinum catalyst was performed under continuous-flow hydrogenation of **5a** and **5b** (bearing a reducible benzyloxy group). The DMPS-Pt/AC-CP catalyst successfully converted both these nitro substrates into the corresponding phenethylamine derivatives **6a** and **6b**, in high yields without loss of either the Cl or the BnO group (entries 3 and 7). Pt/C and Pt/Al_2O_3 showed lower activity and selectivity (entries 4 and 5). Notably, the corresponding Pd catalyst gave nonselective hydrogenation product (entry 6). These results indicate that the novel platinum catalyst is more efficient than the palladium catalyst for several substrates that require site-selective activation for hydrogenation, due to the mild catalytic ability of platinum.

Table 1. Site-selective hydrogenation using a flow system.



Entry	Ar (**5**)	Catalyst	Yield (%)
1	*p*-ClC_6H_4 (**5a**)	DMPS-Pd/AC-CP	0[a]
2	**5a**	Pd/C	0[b]
3	**5a**	DMPS-Pt/AC-CP	92
4	**5a**	Pt/C	30
5	**5a**	Pt/Al_2O_3	0
6	*p*-$BnOC_6H_4$ (**5b**)	DMPS-Pd/AC-CP	0[c]
7	**5b**	DMPS-Pt/AC-CP	91

[a] Compound **6c** was obtained in 65% yield. [b] Compound **6c** was obtained in 25% yield. [c] 4-(2-Aminoethyl)phenol was obtained in 85% yield as a single product.

With this selective catalyst in hand, we conducted continuous-flow synthesis of baclofen precursor **2** (Figure 2). A solution of *p*-chlorobenzaldehyde and nitromethane in toluene was flowed into the first column reactor, containing amine-functionalized silica gel and MS 4A to afford nitroalkene **4**.[9] The resulting solution was then combined with a toluene solution of dimethyl malonate including a small amount of triethylamine and flowed into chiral column reactors containing a polymer-supported PyBOX-$CaCl_2$ catalyst.[6] This sequential-flow enantioselective conversion proceeded to give intermediate **3** with high enantioselectivity (92% ee). The ongoing processes could be monitored to check the progress of the reaction by switching the valves set at the end of the first and the second reactor. The flow chemoselective hydrogenation–cyclization of **3** was conducted sequentially in the third column reactor, containing DMPS-Pt/AC-CP. The overall yield of **2** based on nitromethane during the 69-hour operation was 93–96% with 92% ee (1.75 g/day). The target (*S*)-baclofen **1** was obtained by following the reported methods.[13]

In summary, we achieved continuous-flow synthesis of baclofen precursor **2** in high yield with high enantioselectivity. Three columns with achiral and chiral heterogeneous catalysts were connected and materials were flowed into the columns sequentially. It is noted that such sequential-flow synthesis[14] does not require any isolation or separation of intermediates, by-products, co-products, unreactive/excess materials, etc., during the synthesis. The key steps are chiral heterogeneous calcium-catalyzed asymmetric 1,4-addition of a malonate to a nitroalkene and chemoselective reduction of a nitro compound to an amino compound using molecular hydrogen with a heterogeneous catalyst. For the latter reduction, we developed a DMPS-modified platinum catalyst supported on AC and CP that has remarkable activity for the selective hydrogenation.

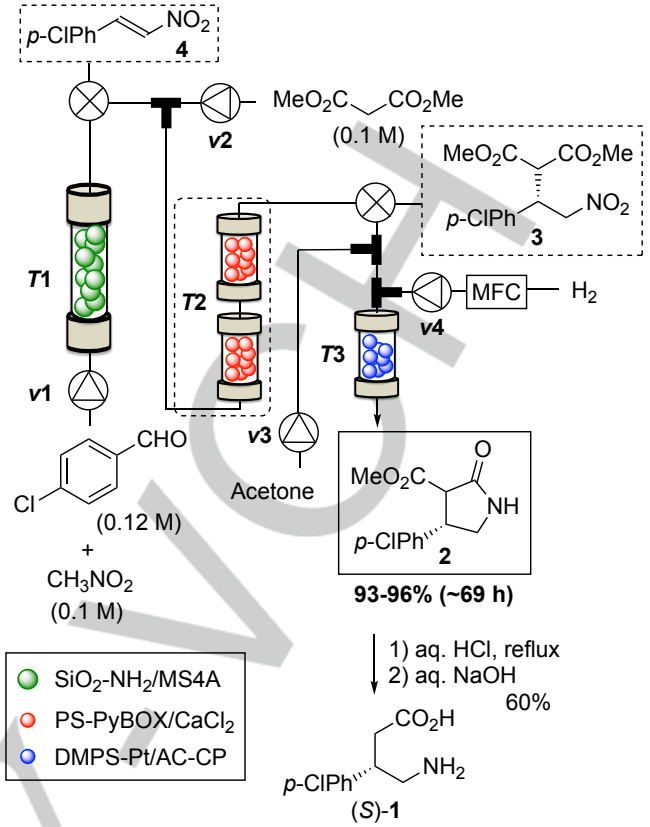


Figure 2. Sequential flow synthesis of baclofen precursor **2**. Note: Toluene was used as a solvent. v1 = 0.05 mL/min, v2 = 0.05 mL/min, the malonate solution contained 0.016 M Et3N, v3 = 0.033 mL/min, v4 = 3.0 mL/min. T1 = 75 °C, T2 = 0 °C, T3 = 100 °C.

Experimental procedures

Continuous-flow synthesis of baclofen

Flow setups

For nitroalkene synthesis (Flow 1): An SUS (ϕ 10 mm × 300 mm) column with column ends protected with filters was used as Column I. A mixture of amine-functionalized silica gel (Chromatorex DM1020 of Fuji Silysia, 0.73 mmol/g of amine concentration, 7.0 g) and molecular sieves 4A (powdered, Aldrich, 14.0 g) was introduced into the column.

Asymmetric 1,4-addition reaction (Flow 2): Two glass columns (ϕ 10 mm × 100 mm) were used. Celite® (1.40 g), calcium chloride (Wako Pure Chemical, 0.37 g), and polymer-supported (*S*,*S*)-Ph_2Pybox (0.77 mmol/g, 0.83 g) were charged into the columns (Column II-1, II-2). A pre-column (glass column, ϕ 5 mm × 50 mm) filled with Celite® (0.35 g) equipped with two-way column-head unit was inserted between Columns I and II.

Hydrogenation (Flow 3): An SUS (ϕ 10 mm × 200 mm) column was used. A mixture of Celite® (1.9 g) and DMPSi-Pt/AC-CP (Pt: 0.10 mmol/g, 7.5 g) was charged into the column (Column III). To mix well the elution from Flow 2 and co-solvent, acetone, a pre-column (glass, ϕ 5 mm × 50 mm) equipped with two-way column-end unit was filled with dried Celite® (0.35 g) and inserted between Columns II-2 and III.

Sequential flow reaction (Figure 2): A solution of 4-chlorobenzaldehyde and nitromethane was introduced into Column I at 0.05 mL/min. After confirming the progress of the reaction, the resulting solution (nitroalkene **4** in toluene) and a 0.1 M solution of malonate in toluene were both introduced into the pre-column at 0.05 mL/min. The

mixed solution was introduced into Columns II at a total flow rate of 0.10 mL/min. During the reactions, Column I was heated at 75 °C and Columns II-1 and II-2 were cooled at 0 °C. The resulting solution from Column II-2 and acetone were introduced into the pre-column at flow rates of 0.10 mL/min and 0.033 mL/min, respectively. The mixed solution (total flow rate 0.133 mL/min) and gaseous hydrogen (3.0 mL/min) were introduced into Column III on the top of the column. During the reactions, Column III was heated at 100 °C. After stabilization, several fractions were collected to check the progress of the reaction. To analyze composition, the collected solution was evaporated under vacuum and then purified by preparative TLC (ethyl acetate) to determine the yield. The enantioselectivity of the obtained product was determined by chiral HPLC analysis.

Acknowledgments

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), the Global COE Program, the University of Tokyo, the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan, the Japan Science and Technology Agency (JST), and the Japan Agency for Medical Research and Development (AMED).

Keywords: Sequential flow reaction • Heterogeneous catalyst • Hydrogenation • Trickle-bed reactor • Baclofen

[1] S. Kobayashi, *Chem. Asian J.* **2016**, *11,* 425-436.

[2] For example, a) S. V. Ley, I. R. Baxendale, *Nature Rev. Drug Discov.* **2002**, *1*, 573–586. B) P. Van Arnum, *Pharm. Technol.* **2013**, *37*, 78–82.

[3] a) S. Dzitoyeva, N. Dimitrijevic, H. Manev, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 5485-5490; b) M. Mezler, T. Muller, K. Raming, *Eur. J. Neurosci.* **2001**, *13*, 477-486; c) G. Costantino, A. Macchiarulo, A. E. Guadix, R. Pellicciari, *J. Med. Chem.* **2001**, *44*, 1827-1832.

[4] M. Pierce, A. Sutterland, E. M. Beraha, K. Morley, W. van den Brink, *Eur. Neuropsychopharm.* **2018**, *28,* 795-806.

[5] a) G. H. Fromm, T. Shibuya, M. Nakata, C. F. Terrence, *Neuropharmacology* **1990**, *29*, 249-254; b) Y. Hong, J. L. Henry, *Eur. J. Pharmacol.* **1991**, *196*, 267-275; c) C. R. Kasten, S. N. Blasingame, S. L. Boehm II, *Alcohol* **2015**, *49*, 37-46; d) J. L. Silverman, M. C. Pride, J. E. Hayes, K. R. Puhger, H. M. Butler-Struben, S. Baker, J. N. Crawley, *Neuropsychopharmacology* **2015**, *40*, 2228-2329; e) I. Lorrai, P. Maccioni, G. L. Gessa, G. Colombo, *Front. Psychiatry* **2016**, *7*, 68.

[6] T. Tsubogo, Y. Yamashita, S. Kobayashi, *Chem. Eur. J.* **2012**, *18*, 13624-13628.

[7] a) N. Ono, in *The Nitro Group in Organic Synthesis* (Ed.: H. Feuer), Wiley-VCH, New York, **2001**, pp. 159-181; b) H. U. Blaser, U. Siegrist, H. Steiner, M. Studer, in *Fine Chemicals through Heterogeneous Catalysis* (Eds: R. A. Sheldon, H. van Bekkum), Wiley-VCH, Weinheim, **2001**, pp. 389; c) V. L. Khilnani, B. Chandalia, *Org. Process Res. Dev.* **2001**, *5*, 257-262; d) L. Henry, *Compt. Rend.* **1895**, *120*, 1265-1268.

[8] a) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675-680; b) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583-4592; c) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *345*, 17-57; d) T. Tsubogo, T. Ishiwata, S. Kobayashi, *Angew. Chem. Int. Ed.* **2013**, *52*, 6590-6604; e) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849-8869; f) S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425-426.

[9] a) H. Ishitani, Y. Saito, T. Tsubogo, S. Kobayashi, *Org. Lett.* **2016**, *18*, 1346-1349; b) H. Ishitani, Y. Furiya, S. Kobayashi, *Bioorg. Med. Chem.* **2017**, *25*, 6229-6232.

[10] a) S. Kobayashi, M. Okumura, Y. Akatsuka, H. Miyamura, M. Ueno, H. Oyamada, *ChemCatChem* **2015**, *7*, 4025-4029; b) H. Oyamada, T. Naito, S. Miyamoto, R. Akiyama, H. Haigo, S. Kobayashi, *Org. Biomol. Chem.* **2008**, *6*, 61-65; c) H. Oyamada, R. Akiyama, H. Haigo, T. Naito, S. Kobayashi, *Chem. Commun.* **2006**, 4297-4299; d) T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329-332.

[11] Y. Saito, H. Ishitani, S. Kobayashi, *Asian J. Org. Chem.* **2016**, *5,* 1124-1127.

[12] a) K. K. Yeong, A. Gavriilidis, R. Zapf, V. Hessel, *Catal. Today* **2003**, *81*, 641-651; b) K. K. Yeong, A. Gavriilidis, R. Zapf, V. Hessel, *Chem. Eng. Sci.* **2004**, *59*, 3491-3494; c) M. T. Kreutzer, F. Kapteijn, J. A. Moulijn, *Catal. Today* **2005**, *105*, 421-428; d) R. Jones, L. Godorhazy, D. Szalay, J. Gerencser, G. Dorman, L. Urge, F. Darvas, *QSAR Comb. Sci.* **2005**, *24*, 722-727; e) S. McGovern, G. Harish, C. S. Pai, W. Mansfield, J. A. Taylor, S. Pau, R. S. Besser, *Chem. Eng. J.* **2008**, *135S*, S229-S236; f) S. McGovern, G. Harish, C. S. Pai, W. Mansfield, J. A. Taylor, S. Pau, R. S. Besser, *J. Chem. Technol. Biotechnol.* **2009**, *84*, 382-390; g) M. D. H. Bhuiyan, A. B. Mahon, P. Jensen, J. K. Clegg, A. C. Try, *Eur. J. Org. Chem.* **2009**, 687-698; h) M. Ueno, Y. Morii, K. Uramoto, H. Oyamada, Y. Mori, S. Kobayashi, *J. Flow. Chem.* **2014**, *4*, 160-163; i) J. Chen, K. Przyuski, R. Roemmele, R. P. Bakale, *Org. Process Res. Dev.* **2014**, *18*, 1427-1433; j) A. L. Nuzhdin, B. L. Moroz, G. A. Bukhtiyarova, S. I. Reshetnikov, P. A. Pyrjaev, P. V. Aleksandrov, V. I. Bukhtiyarov, *ChemPlusChem* **2015**, *80*, 1741-1749; k) P. Loos, H. Alex, J. Hassfeld, K. Lovis, J. Platzek, N. Steinfeldt, S. Hübner, *Org. Process Res. Dev.* **2016**, *20*, 452-464; l) A. K. Rathi, M. B. Gawande, V. Ranc, J. Pechousek, M. Petr, K. Cepe, R. S. Varma, R. Zboril, *Catal. Sci. Technol.* **2016**, *6*, 152-160.

[13] For example; a) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119-125; b) Q. Lang, G. Gu, Y. Chen, Q. Yin, X. Zhang, *ACS Catal.* **2018**, *8,* 4824-4828.

[14] K. Masuda, T. Ichitsuka, N. Koumura, K. Sato, S. Kobayashi, *Tetrahedron* **2018**, *74*, 1705–1730.

10.1002/asia.202000065

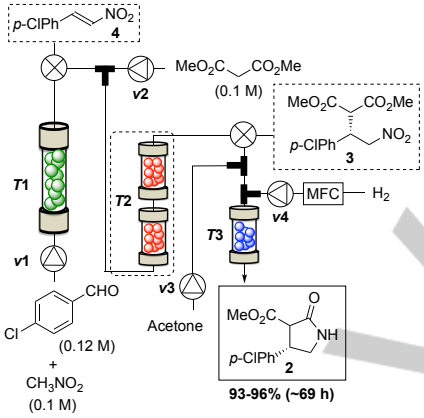
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Continuous-flow synthesis of baclofen precursor (**2**) was achieved using achiral and chiral heterogeneous catalysts in high yield with high enantioselectivity. A dimethylpolysilane (DMPS)-modified platinum catalyst supported on activated carbon (AC) and calcium phosphate (CP) has been developed for the chemoselective hydrogenation of nitro compounds.



Haruro Ishitani,[a] Yuichi Furiya,[b] and Shu Kobayashi*[a, b]*

Page No. – Page No.

Enantioselective Sequential-Flow Synthesis of Baclofen Precursor via Asymmetric 1,4-Addition and Chemoselective Hydrogenation on Platinum/Carbon/Calcium Phosphate Composites

Layout 2:

COMMUNICATION

((Insert TOC Graphic here))

*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Text for Table of Contents