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Facile synthesis of supported Ru–Triphos catalysts for continuous flow application in selective nitrile reduction†

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The selective catalytic hydrogenation of nitriles represents an important but challenging transformation for many homogeneous and heterogeneous catalysts. Herein, we report the efficient and modular solid-phase synthesis of immobilized Triphos-type ligands in very high yields, involving only minimal work-up procedures. The corresponding supported ruthenium–Triphos catalysts are tested in the hydrogenation of various nitriles. Under mild conditions and without the requirement of additives, the tunable supported catalyst library provides selective access to both primary amines and secondary imines. Moreover, the first application of a Triphos-type catalyst in a continuous flow process is presented demonstrating high catalyst life-time over at least 195 hours without significant activity loss.

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Introduction

Amines represent essential platform chemicals pivotal for industrial synthesis of both bulk and fine chemicals as well as for pharmaceuticals.^{1–3} Common methods towards the catalytic production of primary amines include amination of alcohols,⁴ reductive amination,⁵ and reduction of nitro compounds^{6–9} and amides.^{10,11} Atom-economical hydrogenation of nitriles using inexpensive molecular hydrogen can offer an alternative route to primary amines. While conventional but less benign procedures often use stoichiometric amounts of metal hydrides, heterogeneous catalysts are widely applied in manufacture of bulk chemicals, *e.g.* reduction of adiponitrile to hexamethylenediamine in the production of nylon-66.¹² Heterogeneous catalysts are commonly based on noble (Pd) or base metals (RANEY®-Ni, Co and iron), which often suffer from reduced selectivity combined with low functional group tolerance.^{13–16} Base metals usually require harsh conditions and the use of additives, such as ammonia and mineral acids, to suppress side reactions.^{13,17} Milder reaction conditions can be applied when utilizing supported Pd catalysts, however, these are still reliant on acidic conditions to produce the terminal amines selectively.^{18–20} On the other hand, there has been a growing interest to develop highly selective homogeneous catalysts for applications in nitrile reduction under very mild conditions. Most

transition-metal complexes are based on precious metals featuring well-defined ligand structures,^{17,21,22} but more recently also base metals^{23,24} have been employed. Tripodal phosphorus-based ligands, such as Triphos (Fig. 1, I), remain less studied in nitrile reduction despite their successful application in hydrogenations of challenging carboxylic acids derivatives.^{25–29} Initial attempts by Suarez and Fontal using a Ru–Triphos system in pure benzonitrile led to an unselective mixture of amines.³⁰ Beller and co-workers reported on the tripodal phosphorus ligand II employed in Ru-catalyzed nitrile hydrogenation achieving high selectivities for a range of aliphatic and aromatic monoamines under mild and additive-free conditions,³¹ whereas no activity in this reaction was observed for a cobalt–Triphos catalyst.³²

Moreover, the intrinsic separation issue of homogeneous catalysts remains a limiting factor for many applications.³⁵ To

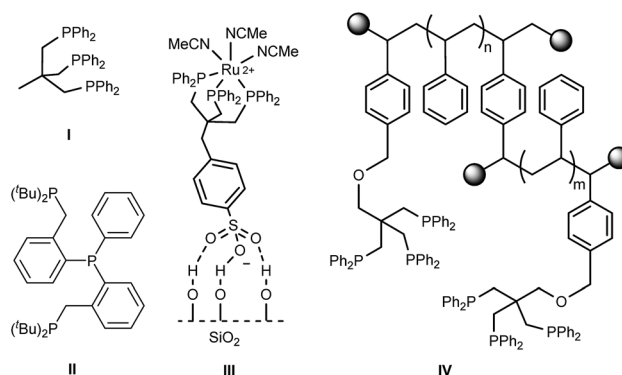


Fig. 1 Tripodal ligands I and II³¹ and examples of immobilized Triphos on silica (III)³³ and polystyrene (IV).³⁴

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overcome this problem a tremendous research effort has been devoted to heterogenization of molecular catalysts.^{35–41} Thus, the ideal catalyst would combine the best of both worlds, *i.e.* high activity, selectivity and tunability of homogeneous catalysis and the ease of separation and recycling of heterogeneous catalysts. The enhanced stability of supported tridentate ligand-based catalysts compared to mono- and bidentate analogues can prevent metal leaching from the support. Approaches towards immobilization of modified Triphos ligands on dendrimers,⁴² in ionic liquids⁴³ and in aqueous biphasic systems^{44–46} have been explored. Furthermore, SiO₂ grafted Ru-Triphos (Fig. 1, **III**) has been applied in the reduction of benzonitrile to the corresponding secondary imine.³³ Immobilization of Triphos onto polymeric supports was accomplished by a following post-modification⁴⁷ as well as a bottom-up approach (Fig. 1, **IV**).³⁴ However, all of the above mentioned strategies are cases where a single modified ligand is tethered to a support. Often these synthetic alterations require multiple steps and can lead to low yields due to troublesome purifications or functional group incompatibility which in turn hampers the creation of ligand diversity on the support.⁴⁸ Moreover, tuning ligand properties by modifying the phosphorus donor moieties remains challenging. Opposed to the uncomplicated synthesis of C_{3v} symmetrical arylphosphine tripods,⁴⁹ unsymmetrical, mixed phosphorus donor ligands rely on less straightforward synthetic protocols.^{50–52} Different leaving groups bound to the tripodal backbone to facilitate selective phosphine substitution as well as additional borane protection and removal steps are often necessary. In case of a C₁ symmetric Triphos analogue modified with one di(*p*-tolyl)phosphine and two PPh₂ groups an overall yield of 21% starting from 3-methyl-3-oxetanemethanol was obtained.⁵² This in turn calls for a more efficient modular approach. Solid-phase synthesis (SPS) provides a promising alternative offering the combinatorial synthesis of libraries of tripodal ligands on a support in high yields requiring only minimal workup procedures.^{53–55} Moreover, SPS has proven to be an invaluable tool for automated parallel synthesis of ligand libraries in terms of application in high throughput experimentation.^{56–58} Since covalently bound to the support, recycling of the corresponding heterogenized catalysts can be vastly facilitated making them suitable candidates for application in continuous flow catalysis. Continuous processes allow exploring the long-term catalyst performance but also offer environmentally benign and safe processing, facile optimization for scale-up and high process reliability for multiphasic hydrogenation reactions, which in general are a prerequisite for economical process development.^{59–61} Herein, we report a modular SPS protocol towards recyclable Ru-Triphos complexes and their application in highly selective nitrile reduction. Furthermore, the first application of Triphos-based ligands under continuous flow processing is presented.

Results and discussion

Solid-phase synthesis of supported Triphos ligands

The SPS of supported tripodal phosphorus ligands was adapted from literature procedures in solution-phase.^{51,62} The secondary

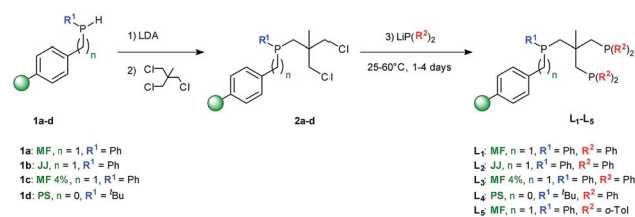
phosphines **1a–d** immobilized on Merrifield resin cross-linked with 1% and 4% divinylbenzene (DVB, MF), JandaJel™ resin (JJ) and polystyrene (PS) were prepared as we reported previously.^{63,64} Deprotonation of **1a–d** by using an excess of lithium diisopropylamide (LDA) yielded the corresponding supported lithium phosphides (Scheme 1, step 1).

In the gel-phase ³¹P NMR spectrum, phenyl substituted lithiated phosphines (**Li·1a–c**) exhibit signals at $\delta = -40$ ppm (see Fig. 2 for a representative example), while for ^tBu bearing lithium phosphide **Li·1d** supported on PS a shift of around $\Delta\delta = 7$ ppm is observed. Next, **Li·1a–d** were reacted at room temperature with a slight excess of 1,1,1-tris(chloromethyl) ethane readily proceeding to the supported phosphine dimethylenechloride intermediates **2a–d** (Scheme 1, step 2). Quantitative conversion was confirmed by ³¹P NMR by the appearance of a single peak at around $\delta = -30$ ppm in cases of **2a–c** and $\delta = -11.4$ ppm for **2d** respectively. High purity of representative compound **2a** was confirmed by determination of the P and Cl loading by elemental analysis. Subsequently, intermediates **2a–d** were treated with a secondary lithium phosphide to obtain the desired supported Triphos ligands **L₁–L₅**. By using an excess of LiPPh₂ (for **L₁–L₄**) or LiP(*o*-Tol)₂ (for **L₅**) at 60 °C, full conversions to the corresponding ligands were achieved leading to a library of 5 supported Triphos-type ligands (Scheme 1, step 3).

The Triphos analogue **L₁** supported on MF exhibits two single peaks ($\delta = -25.4$ and -28.1 ppm) in the ³¹P NMR spectrum, occurring in a 2 : 1 ratio (Fig. 2). For JJ-supported ligand **L₂** as well as **L₃** immobilized on the MF 4% DVB, nearly identical spectra were obtained. In case of PS supported **L₄**, two peaks were observed for the PPh₂ groups ($\delta = -25.0$ and -25.8 ppm) which are present in an approximate ratio of 1 : 1 : 1 with the ^tBu moiety ($\delta = -8.8$ ppm). This could be attributed to the presence of the bulky ^tBu group leading to sterically hindered rotation which allows for the detection of the two inequivalent diastereotopic phosphorus nuclei on the NMR time scale. Similarly, **L₅** shows a signal for the PPh group ($\delta = -28.3$ ppm) together with two signals for the diastereotopic P(*o*-Tol)₂ moieties ($\delta = -51.9$ and -52.0 ppm). The supported tripodal ligands **L₁–L₅** were further characterized using FTIR and Raman spectroscopy and the exact phosphorus loading was determined by elemental analysis (see ESI†).

Solid-phase synthesis of supported ruthenium complexes

The corresponding immobilized Ru-Triphos complexes **C₁–C₅** were synthesized by treatment of **L₁–L₅** with [RuHCl(PPh₃)₃CO] in toluene at 80 °C (Scheme 2).



Scheme 1 SPS approach towards supported Triphos ligands **L₁–L₅**.

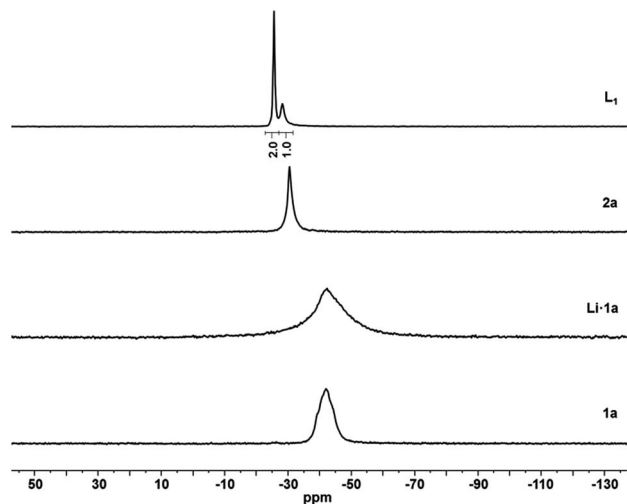


Fig. 2 ^{31}P NMR (THF) monitoring of the representative SPS of supported Triphos-ligand L_1 .

The quantitative disappearance of the free ligand peaks was monitored by ^{31}P NMR until full complexation was achieved. C_1 shows three new broad signals appearing in an approximate 1 : 1 : 1 ratio (Fig. 3). While two sharper single resonances are observed at $\delta = 15.3$ and 1.2 ppm for the remote PPh_2 moieties, the broader signal of the phosphorus atom bound to the polymeric support exhibits a splitting ($\delta = 49.8$ and 41.8 ppm) which could be attributed to the presence of isomeric Ru-complexes as observed in non-symmetrical homogeneous systems.⁵² The gel-phase ^{31}P NMR of JandaJelTM-supported complex C_2 shows an analogous spectrum compared to C_1 (Fig. S13, see ESI[†]). In this case however, much sharper signals are observed as a consequence of enhanced solution-like behavior of the JJ resin. Coupling constants cannot be assigned due to peak broadening which is commonly observed for molecular complexes heterogenized on solid supports.^{34,63,65,66} However, the chemical shifts of C_1 are in line with those obtained for its solution-phase counterpart **3** ($\delta = 48.9$, 12.2 and -0.4 ppm, Fig. 4a). **3** solely differs in a Ph group attached to the phosphorus atom instead of a benzyl group belonging to the MF support. Moreover, the supported complexes were characterized by solid-state ^{31}P , ^1H and ^{13}C MAS NMR. In the case of C_1 , the ^{31}P MAS NMR spectrum exhibits two signals appearing in a 1 : 2 ratio (Fig. 4c). The presence of a CO ligand and Ru–H was confirmed by FTIR and Raman spectroscopy (see ESI[†]). For CO and Ru–H, bands are observed at 1975 – 1968 cm^{-1} and 1925 – 1920 cm^{-1} , respectively.

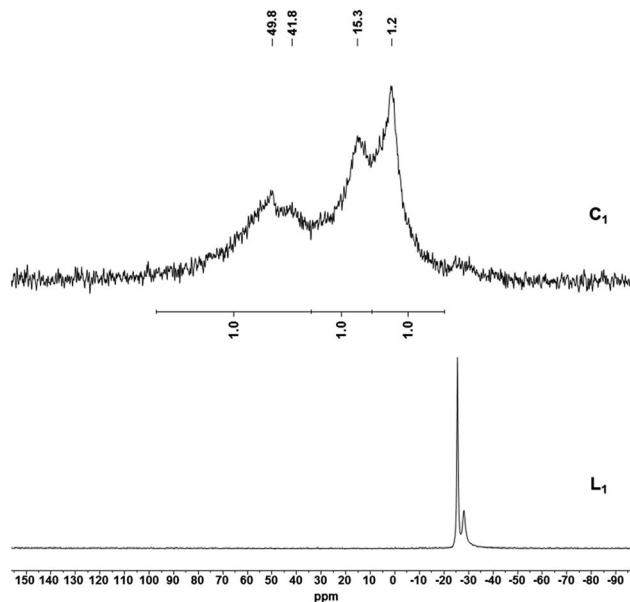
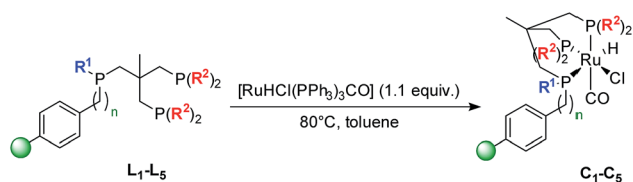


Fig. 3 ^{31}P NMR (THF) monitoring of the representative SPS of supported Ru–Triphos complex C_1 .

Application in Ru-catalyzed nitrile reduction

Subsequently, the supported Ru–Triphos library was screened in the hydrogenation of nitriles to primary mono- and diamines. Prior to catalyst screening, benzonitrile (S_1) and C_1 were used to determine optimized reaction conditions. 1,4-Dioxane was chosen as solvent providing sufficient polymer swelling properties opposed to $i\text{PrOH}$, which was found to be the ideal solvent in homogeneous Ru–Triphos catalyzed nitrile



Scheme 2 Synthesis of supported complexes C_1 – C_5 .

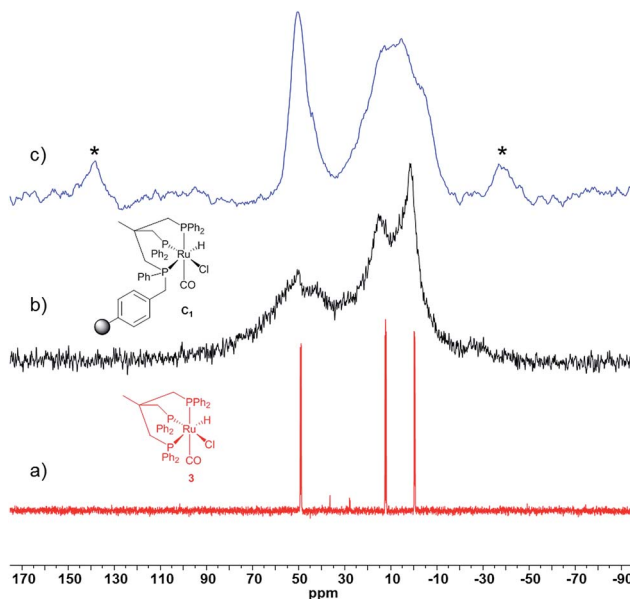


Fig. 4 (a) ^{31}P NMR spectrum of solution-phase analogue **3**, (b) gel-phase ^{31}P NMR spectrum of supported complex C_1 and (c) solid-state ^{31}P MAS NMR spectrum of C_1 . Rotational sidebands are denoted by asterisks (*).

reduction.³¹ After 18 h at 10 bar H₂ pressure and 100 °C, **S**₁ was readily converted with excellent selectivity towards the desired benzylamine (**A**) using 1.0 mol% of **C**₁ (Table 1, entry 1). A similar performance was obtained when reducing the temperature to 80 °C (Table 1, entry 2) whereas 0.5 mol% gave 47% conversion with 97% selectivity to **A** (Table 1, entry 3). Further optimization conditions are listed in Table S1.† For selectivity enhancement towards the primary amine, both homogeneous and heterogeneous catalysts often require the use of base additives.^{13,18–20,67,68} Remarkably, mild and additive-free conditions can be applied for this highly selective heterogeneous Ru–Triphos system similar to the homogeneous system of Beller and co-workers.³¹ When screening the whole supported catalyst library at 100 °C and 1.0 mol% catalyst loading, JJ-supported **C**₂ and PS-bound **C**₄ performed analogously compared to **C**₁ (Table 1, entries 4 and 6). Notably, **C**₃ immobilized on MF 4% DVB, which is lacking solvent dependent swelling properties opposed to **C**₁, gave 62% conversion and 97% selectivity (Table 1, entry 5) which could be driven to full conversion after 50 h.

Unexpectedly, **C**₅ bearing more bulky P(*o*-Tol)₂ groups resulted in 86% conversion with 92% selectivity towards the secondary imine **B** (Table 1, entry 7) which could be increased to >99% selectivity at 56% conversion after 8 hours (Table S1,† entry 10). In case of the solution-phase combination of [Ru(cod)(methallyl)₂] (cod = cyclooctadiene) and **II**, no activity was observed when using 1,4-dioxane as a solvent.³¹ When applying homogeneous catalyst **3** under the same conditions as for its supported counterparts, an unselective mixture of **A** (30%), **B** (68%) and **C** (2%) was obtained (Table 1, entry 8). The superior selectivity of the developed heterogeneous catalyst can be attributed to the high local catalyst to substrate concentration within the confined space of a resin bead suppressing non-catalytic side-reactions. Moreover, the SiO₂ supported system **III**

(Fig. 1) gave 88% selectivity towards **B** instead of **A** (Table 1, entry 9).³³ This showcases both the competitively high selectivity towards primary amines and the facile tunability of the resin-bound Triphos using SPS. Next, **C**₁ was employed to determine the substrate scope. Electron-withdrawing *para*-bromo (**S**₂) and *para*-fluoro-benzonitrile (**S**₃) were converted selectively whereas NO₂-substituted **S**₄ led to no activity accompanied by the formation of ruthenium black as observed in homogeneous deaminative nitrile hydrogenation to primary alcohols (Fig. 5).⁶⁹ This may be attributed to phosphine oxidation followed by deposition of the metal. More electron-donating *para*-methoxy groups (**S**₅) resulted in 79% conversion and 97% selectivity. Methyl substituents in *ortho*-position (**S**₆) proved to be more challenging with only 45% conversion but with excellent selectivity. At 120 °C, **S**₇ bearing an *ortho*-methoxy group was fully converted with 79% selectivity. Finally, the 1,3-disubstituted benzonitrile **S**₈ was quantitatively converted into the corresponding diamine after 24 h at 100 °C and 30 bar of H₂. Aliphatic cyclohexanecarbonitrile (**S**₉) gave 46% conversion with high selectivity at 120 °C. Heptanenitrile (**S**₁₀) was fully converted with 87% selectivity to heptylamine. Mainly partial hydrogenation of adiponitrile (**S**₁₁) was observed with 92% selectivity to ω-aminocapronitrile which can serve as a precursor for the synthesis of nylon-6.⁷⁰ Benzylic nitriles were selectively hydrogenated with excellent to moderate conversions (99% for **S**₁₂ and 72% for **S**₁₃).

Finally, the recyclability of the resin-bound catalyst **C**₁ was examined. However, under batch conditions, a loss in activity was observed after the fourth run due to mechanical abrasion of the support (Table S2†). Hence, the novel supported catalyst was employed in continuous flow hydrogenation to determine the long-term catalyst performance. The system was initially studied under various flow rates, temperatures and pressures reaching up to 84% selectivity towards the primary amine **A** with

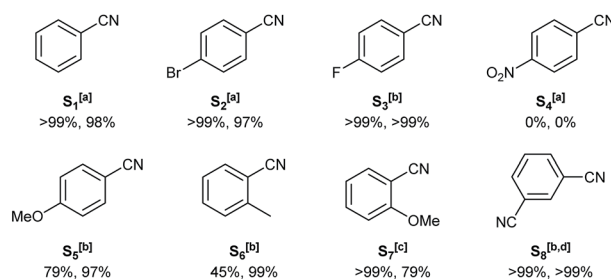
Table 1 Ru-catalyzed hydrogenation of **S**₁ using supported catalysts **C**₁–**C**₅^a

$\text{Ph}-\text{C}\equiv\text{N} \xrightarrow[\text{10 bar H}_2, 18 \text{ h, 1,4-dioxane}]{\text{C}_1\text{-C}_5 (0.5\text{--}1.0 \text{ mol}\%)} \text{Ph}-\text{CH}_2\text{NH}_2 + \text{Ph}-\text{CH}=\text{N}-\text{CH}_2\text{Ph} + \text{Ph}-\text{CH}_2\text{NH}-\text{CH}_2\text{Ph}$						
Entry	Catalyst [mol%]	<i>T</i> [°C]	Conv. ^b [%]	Selectivity ^b [%]		
				A	B	C
1	C ₁ (1.0)	100	>99	99	1	<1
2	C ₁ (1.0)	80	>99	98	1	<1
3	C ₁ (0.5)	80	48	97	3	<1
4	C ₂ (1.0)	100	>99	99	1	<1
5	C ₃ (1.0)	100	62	97	3	<1
6	C ₄ (1.0)	100	>99	99	1	<1
7	C ₅ (1.0)	100	86	5	92	2
8	3 (1.0)	100	>99	30	68	2
9 ^c	III (0.2)	100	95	3	88	5

^a Conditions: substrate (0.5 mmol), dioxane (1.0 mL), H₂ (10 bar), 18 h.

^b Conversion and selectivity determined by GC using dodecane as internal standard. ^c Data taken from ref. 33; conditions: substrate (2.15 mmol), *n*-octane (30 mL), H₂ (30 bar), 12 h.

Aromatic



Aliphatic

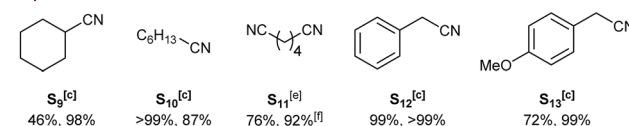


Fig. 5 Substrate scope using supported catalyst **C**₁ (conversion and selectivity to mono- or diamine indicated below structures). ^aReaction conditions: substrate (0.5 mmol), [Ru] (1.0 mol%), dioxane (1.0 mL), 80 °C, H₂ (10 bar), 18 h. ^b100 °C. ^c120 °C. ^dH₂ (30 bar). 24 h. ^e100 °C, H₂ (30 bar), 24 h. ^fSelectivity towards ω-aminocapronitrile.



full conversion at 150 °C (Table S3, Fig. S2†). While the secondary imine **B** was observed as the sole by-product, increasing amounts of secondary amine **C** formed when exceeding a process temperature of 120 °C.

Next, constant conditions of 100 °C and 20 bar pressure at a flow rate of 0.1 mL min⁻¹ were chosen to provide moderate conversion and selectivity to enable monitoring of actual catalyst stability during the flow experiment. An initial incubation time followed by an increase in activity and selectivity were observed attaining a steady conversion (75%) and selectivity towards **A** (60%) after 100 h (Fig. 6). This could be attributed to the slow formation of the potentially active Ru-hydrido species analogous to the [Ru(cod)(methallyl)₂]/**II** system reported by the group of Beller.³¹ Hence, pre-activation of the supported catalyst **C**₁ with H₂ or the addition of base to the feed could possibly diminish this activation period. In addition to **A**, the product mixture contained 40% of secondary imine **B** and 0.5% of secondary amine **C** after 100 h time-on-stream (TOS). The amount of **C** remained constant throughout the experiment. The difference in selectivity compared to the batch process is a consequence of the presence of the higher concentration of the imine intermediate resulting from the low conversion level (75%) needed to monitor catalyst stability. Conversion of the imine intermediate to the primary amine is prevented once the imine has left the catalyst bed.

Replacing the feed solution after 100 h caused a flow outage for 1 h followed by an activity increase of the catalyst to nearly full conversion requiring a subsequent restabilization period. Steady conversion (86%) and selectivity towards benzylamine **A** (65%) were recovered after 171 h followed by a small drop in activity (3%) within the next 24 h. Over 195 h TOS, a remarkable catalyst life-time and a total TON of 1605 were achieved together with no Ru metal contamination observed in the product stream indicated by ICP-OES analysis.

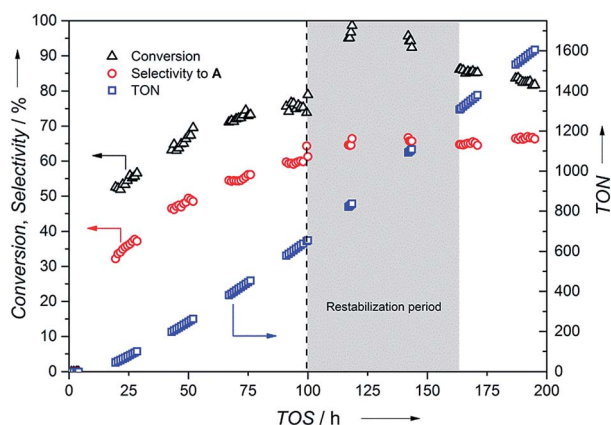


Fig. 6 Continuous flow hydrogenation of **S**₁ using **C**₁. Conditions: $n_{\text{cat}} = 0.134$ mmol, $T = 100$ °C, 20 bar, 0.25 M **S**₁ in dioxane at 0.1 mL min⁻¹, $\dot{V}(\text{H}_2) = 2.5$ mL min⁻¹. Change of substrate feed at 100 h caused malfunctioning of HPLC pump for 1 h (dashed line). Grey area indicates catalyst restabilization period. Conversion determined by GC using dodecane as internal standard. Selectivity is reported towards formation of primary amine **A**.

Conclusions

In summary, we developed an efficient and modular solid-phase synthesis protocol to access diverse supported Triphos-type ligands (**L**₁–**L**₅) and their corresponding Ru-complexes (**C**₁–**C**₅) requiring only minimal work-up steps. The solid phase approach opens the way to automated synthesis of large ligand libraries enabling a fine-tuned design of catalysts that allow transformations with high selectivity. The library was successfully applied in highly selective nitrile reduction under mild conditions in the absence of any performance enhancing additive as reported for many monophasic and heterogeneously catalyzed liquid/solid reactions. Opposed to homogeneous counterparts, the robust heterogeneous system provided highly selective access to both primary amines and secondary imines due to the modular and hence easily tunable ligand structure. Moreover, a novel Triphos-type catalyst was applied for the first time in a continuous flow process proving high catalyst stability without significant loss in performance for at least 195 hours. Screening of conditions leading to a shorter catalyst incubation time is currently ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- 1 B. R. Brown, *The organic chemistry of aliphatic nitrogen compounds*, Oxford University, New York, 1994.
- 2 S. A. Lawrence, *Amines: Synthesis, Properties and Applications*, Cambridge University Press, Cambridge, 2004.
- 3 P. Roose, K. Eller, E. Henkes, R. Rossbacher and H. Höke, in *Amines, Aliphatic: Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, 2015.
- 4 S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853–1864.
- 5 S. Gomez, J. A. Peters and T. Maschmeyer, *Adv. Synth. Catal.*, 2002, **344**, 1037–1057.
- 6 A. M. Tafesh and J. Weiguny, *Chem. Rev.*, 1996, **96**, 2035–2052.
- 7 P. Loos, H. Alex, J. Hassfeld, K. Lovis, J. Platzek, N. Steinfeldt and S. Hübner, *Org. Process Res. Dev.*, 2015, **20**, 452–464.
- 8 M. Orlandi, D. Brenna, R. Harms, S. Jost and M. Benaglia, *Org. Process Res. Dev.*, 2018, **22**, 430–445.
- 9 D. Formenti, F. Ferretti, F. K. Scharnagl and M. Beller, *Chem. Rev.*, 2019, **119**, 2611–2680.



- 10 A. A. N. Magro, G. R. Eastham and D. J. Cole-Hamilton, *Chem. Commun.*, 2007, 3154–3156.
- 11 E. Balaraman, B. Gnanaprakasam, L. J. W. Shimon and D. Milstein, *J. Am. Chem. Soc.*, 2010, **132**, 16756–16758.
- 12 B. D. Herzog and R. A. Smiley, in *Hexamethylenediamine: Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, Germany, 2012.
- 13 S. Nishimura, in *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, John Wiley & Sons, New York, 2001, ch. 7, pp. 254–285.
- 14 T. G. Dewdney, D. A. Dowden, B. D. Hawkins and M. Wyndham, Ger. Offen., DE 2429293 A1 19750320, 1975.
- 15 A. F. Elsasser, WO98/19991, 1998.
- 16 P. Kukula, M. Studer and H.-U. Blaser, *Adv. Synth. Catal.*, 2004, **346**, 1487–1493.
- 17 C. de Bellefon and P. Fouilloux, *Catal. Rev.*, 1994, **36**, 459–506.
- 18 L. Hegedűs and T. Máthé, *Appl. Catal., A*, 2005, **296**, 209–215.
- 19 Y. Saito, H. Ishitani, M. Ueno and S. Kobayashi, *ChemistryOpen*, 2017, **6**, 211–215.
- 20 M. Yoshimura, A. Komatsu, M. Niimura, Y. Takagi, T. Takahashi, S. Ueda, T. Ichikawa, Y. Kobayashi, H. Okami, T. Hattori, Y. Sawama, Y. Monguchi and H. Sajiki, *Adv. Synth. Catal.*, 2018, **360**, 1726–1732.
- 21 D. B. Bagal and B. M. Bhanage, *Adv. Synth. Catal.*, 2015, **357**, 883–900.
- 22 S. Werkmeister, K. Junge and M. Beller, *Org. Process Res. Dev.*, 2014, **18**, 289–302.
- 23 G. A. Filonenko, R. van Putten, E. J. M. Hensen and E. A. Pidko, *Chem. Soc. Rev.*, 2018, **47**, 1459–1483.
- 24 L. Alig, M. Fritz and S. Schneider, *Chem. Rev.*, 2019, **119**, 2681–2751.
- 25 T. vom Stein, M. Meuresch, D. Limper, M. Schmitz, M. Holscher, J. Coetzee, D. J. Cole-Hamilton, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2014, **136**, 13217–13225.
- 26 X. Cui, Y. Li, C. Topf, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2015, **54**, 10596–10599.
- 27 Y. Li, C. Topf, X. Cui, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2015, **54**, 5196–5200.
- 28 I. Mellone, F. Bertini, L. Gonsalvi, A. Guerriero and M. Peruzzini, *Chimia*, 2015, **69**, 331–338.
- 29 J. R. Cabrero-Antonino, E. Alberico, K. Junge, H. Junge and M. Beller, *Chem. Sci.*, 2016, **7**, 3432–3442.
- 30 T. Suarez and B. Fontal, *J. Mol. Catal.*, 1988, **45**, 335–344.
- 31 R. Adam, C. B. Bheeter, R. Jackstell and M. Beller, *ChemCatChem*, 2016, **8**, 1329–1334.
- 32 R. Adam, C. B. Bheeter, J. R. Cabrero-Antonino, K. Junge, R. Jackstell and M. Beller, *ChemSusChem*, 2017, **10**, 842–846.
- 33 C. Bianchini, V. Dal Santo, A. Meli, W. Oberhauser, R. Psaro and F. Vizza, *Organometallics*, 2000, **19**, 2433–2444.
- 34 C. Bianchini, M. Frediani and F. Vizza, *Chem. Commun.*, 2001, 479–480.
- 35 D. J. Cole-Hamilton, *Science*, 2003, **299**, 1702–1706.
- 36 N. E. Leadbeater and M. Marco, *Chem. Rev.*, 2002, **102**, 3217–3274.
- 37 D. E. Bergbreiter, *Chem. Rev.*, 2002, **102**, 3345–3384.
- 38 R. van Heerbeek, P. C. J. Kamer, P. W. N. M. van Leeuwen and J. N. H. Reek, *Chem. Rev.*, 2002, **102**, 3717–3756.
- 39 D. J. Cole-Hamilton and R. P. Tooze, in *Catalyst Separation, Recovery and Recycling: Chemistry and Process Design*, ed. D. J. Cole-Hamilton and R. P. Tooze, Springer Netherlands, Dordrecht, 2006, pp. 1–8.
- 40 P. J. C. Hausoul, C. Broicher, R. Vegliante, C. Göb and R. Palkovits, *Angew. Chem., Int. Ed.*, 2016, **55**, 5597–5601.
- 41 P. C. J. Kamer, D. Vogt and J. W. Thybaut, *Contemporary Catalysis: Science, Technology, and Applications*, The Royal Society of Chemistry, 2017.
- 42 R. A. Findeis and L. H. Gade, *Eur. J. Inorg. Chem.*, 2003, **2003**, 99–110.
- 43 L. Harmand, S. Samer, J. Andrieu, H. Cattey, M. Picquet and J.-C. Hierro, *Open Org. Chem. J.*, 2012, **6**, 1–11.
- 44 C. Bianchini, A. Meli, V. Patinec, V. Sernau and F. Vizza, *J. Am. Chem. Soc.*, 1997, **119**, 4945–4954.
- 45 I. Rojas, F. L. Linares, N. Valencia and C. Bianchini, *J. Mol. Catal. A: Chem.*, 1999, **144**, 1–6.
- 46 C. Bianchini, A. Meli and W. Oberhauser, *New J. Chem.*, 2001, **25**, 11–12.
- 47 P. Schober, G. Huttner, L. Zsolnai and A. Jacobi, *J. Organomet. Chem.*, 1998, **571**, 279–288.
- 48 R. A. Findeis and L. H. Gade, *Dalton Trans.*, 2003, 249–254.
- 49 W. Hewertson and H. R. Watson, *J. Chem. Soc.*, 1962, 1490–1494.
- 50 H. Heidel, G. Huttner and G. Helmchen, *Z. Naturforschung B*, 1993, **48**, 1681–1692.
- 51 L. Söncksen, C. Gradert, J. Krahmer, C. Näther and F. Tuczek, *Inorg. Chem.*, 2013, **52**, 6576–6589.
- 52 N. Nakagawa, E. J. Derrah, M. Schelwies, F. Rominger, O. Trapp and T. Schaub, *Dalton Trans.*, 2016, **45**, 6856–6865.
- 53 D. Obrecht and J. M. Villalgordo, in *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*, Elsevier Science Ltd., Oxford, 1998, ch. 1, pp. 1–184.
- 54 K. Burgess, *Solid-Phase Organic Synthesis*, John Wiley & Sons, Inc., New York, 2002.
- 55 M. C. Samuels, B. H. G. Swennenhuis and P. C. J. Kamer, in *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*, ed. P. C. J. Kamer and P. W. N. M. v. Leeuwen, John Wiley & Sons, Ltd, Chichester, 2012, ch. 16, pp. 463–479.
- 56 S. E. Booth, C. M. Dreef-Tromp, P. H. H. Hermkens, J. A. P. A. de Man and H. C. J. Ottenheijm, in *Combinatorial Chemistry*, ed. G. Jung, Wiley-VCH Verlag GmbH, Weinheim, 1999, ch. 2, pp. 35–76.
- 57 C. Gennari and U. Piarulli, *Chem. Rev.*, 2003, **103**, 3071–3100.
- 58 M. Renom-Carrasco and L. Lefort, *Chem. Soc. Rev.*, 2018, **47**, 5038–5060.
- 59 A. Kirschning, W. Solodenko and K. Mennecke, *Chem.-Eur. J.*, 2006, **12**, 5972–5990.
- 60 C. G. Frost and L. Mutton, *Green Chem.*, 2010, **12**, 1687–1703.
- 61 F. M. Akwi and P. Watts, *Chem. Commun.*, 2018, **54**, 13894–13928.
- 62 A. Muth, O. Walter, G. Huttner, A. Asam, L. Zsolnai and C. Emmerich, *J. Organomet. Chem.*, 1994, **468**, 149–163.



- 63 F. J. L. Heutz, M. C. Samuels and P. C. J. Kamer, *Catal. Sci. Technol.*, 2015, **5**, 3296–3301.
- 64 M. C. Samuels, F. J. L. Heutz, A. Grabulosa and P. C. J. Kamer, *Top. Catal.*, 2016, **59**, 1793–1799.
- 65 T. T. Adint and C. R. Landis, *J. Am. Chem. Soc.*, 2014, **136**, 7943–7953.
- 66 X. Wang, E. A. P. Ling, C. Guan, Q. Zhang, W. Wu, P. Liu, N. Zheng, D. Zhang, S. Lopatin, Z. Lai and K.-W. Huang, *ChemSusChem*, 2018, **11**, 3591–3598.
- 67 S. Enthaler, D. Addis, K. Junge, G. Erre and M. Beller, *Chem.–Eur. J.*, 2008, **14**, 9491–9494.
- 68 S. Enthaler, K. Junge, D. Addis, G. Erre and M. Beller, *ChemSusChem*, 2008, **1**, 1006–1010.
- 69 I. G. Molnár, P. Calleja, M. Ernst, A. S. K. Hashmi and T. Schaub, *ChemCatChem*, 2017, **9**, 4175–4178.
- 70 A. J. M. van Dijk, R. Duchateau, E. J. M. Hensen, J. Meuldijk and C. E. Koning, *Chem.–Eur. J.*, 2007, **13**, 7673–7681.

