Asymmetric Hydrogenation of Indazole-Containing Enamides Relevant to the Synthesis of Zavegepant Using Neutral and Cationic Cobalt Precatalysts

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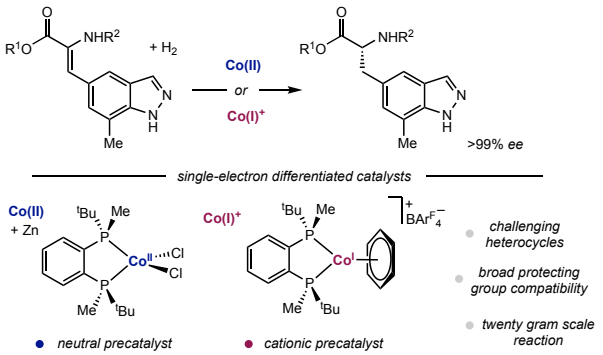
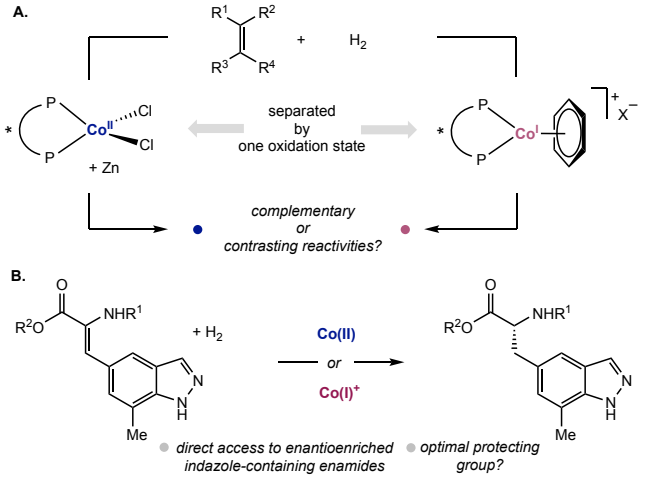


ABSTRACT: The cobalt-catalyzed asymmetric hydrogenation of indazole-containing enamides relevant to the synthesis of calcitonin gene-related peptide (CGRP) receptor antagonist, zavegepant (**1**), approved for the treatment of migraines, is described. Both neutral bis(phosphine)cobalt(II) and cationic bis(phosphine)cobalt(I) complexes served as efficient precatalysts for the enamide hydrogenation reactions, providing excellent yield and enantioselectivities (up to >99.9%) for a range of related substrates, though key reactivity differences were observed. Hydrogenation of indazole-containing enamide, methyl (*Z*)-2-acetamido-3-(7-methyl-1*H*-indazol-5-yl)acrylate, was performed on a 20 gram scale.

Transition-metal-catalyzed asymmetric hydrogenation is a widely used transformation in the synthesis of pharmaceuticals and other fine chemicals.[1–4] Most catalysts have historically relied on precious metals such as rhodium, ruthenium and iridium[5] but there is continued interest to transition to more Earth-abundant metals. In addition to their potential lower cost and increased sustainability, first-row transition metal catalysts may also offer enhanced or complimentary functional group tolerance and activity compared to their second- and third-row counterparts.[6,7] Moreover, first-row transition metals may undergo both one- and two-electron redox changes, providing new opportunities in precatalyst design, function and optimization.

Among the various Earth-abundant metal-based alkene hydrogenation catalysts, bis(phosphine) cobalt complexes have emerged as highly active, enantioselective and versatile catalysts (Scheme 1). One distinguishing feature of these complexes is the ability to access active hydrogenation catalysts from oxidation states separated by one-electron, a property largely absent with precious metals. Well-defined neutral cobalt(0),[8] (I)[8] and (II)[8,9] precatalysts have been

Scheme 1. A. Enantiopure bis(phosphine) cobalt precatalysts in two oxidation states. B. This work: Asymmetric hydrogenation of heterocycle-containing enamides.

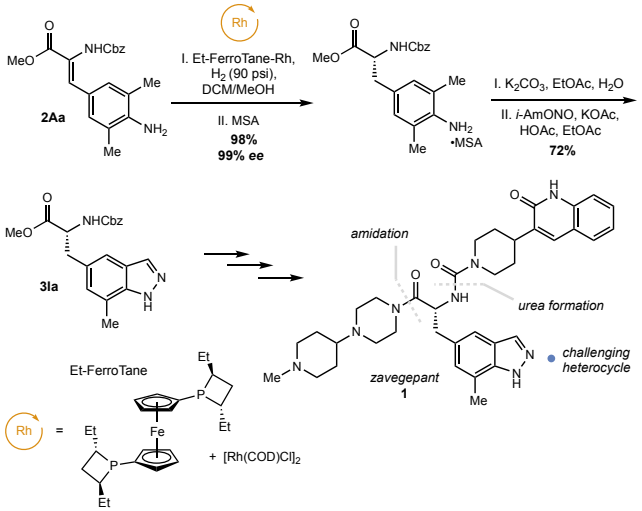


successfully applied to alkene hydrogenation reactions, including substrates with a wide variety of functional groups, hindered alkenes,

and pharmaceutical precursors.[8–17] Cationic bis(phosphine)cobalt(I), analogs of well-established rhodium(I) precursors, have been synthesized and applied to the asymmetric hydrogenation of commercially-available enamides and to the asymmetric synthesis of sitagliptin.[18,19]

One potential application of cobalt-catalyzed asymmetric hydrogenation is in the synthesis of the calcitonin gene-related peptide (CGRP) receptor antagonist, zavegepant (**1**), a molecule approved by the FDA for the treatment of migraines and related neurological disorders.[20,21] A previously reported route to this compound involves a rhodium-catalyzed asymmetric hydrogenation of aniline **2Aa** prior to cyclization by nitrosation to the enantioenriched indazole, **3Ia** (Scheme 2).[22] It was hypothesized that cobalt precatalysts may also promote the asymmetric hydrogenation of **2Aa**. However, an even more interesting and potentially impactful transformation is the direct cobalt-catalyzed asymmetric hydrogenation of a related indazole-containing enamide as it avoids the nitrosation following formation of the valuable enantioenriched material. Such a direct route is unprecedented with rhodium catalysts, as these are typically ineffective towards the asymmetric hydrogenation of related unprotected indazole-containing enamides, likely due to the complexation of the NH of the free indazole to the catalyst.[23] Therefore, methods for the direct hydrogenation of indazole-containing enamides would be transformative in broadening the applications of asymmetric hydrogenation and in streamlining the synthesis of **1**. Here we describe a cobalt-catalyzed method for the asymmetric hydrogenation of indazole-containing enamides with high yields and enantioselectivities. Notably, effective catalysis was achieved with both neutral and cationic cobalt precursors and one example was demonstrated on 20-gram scale.

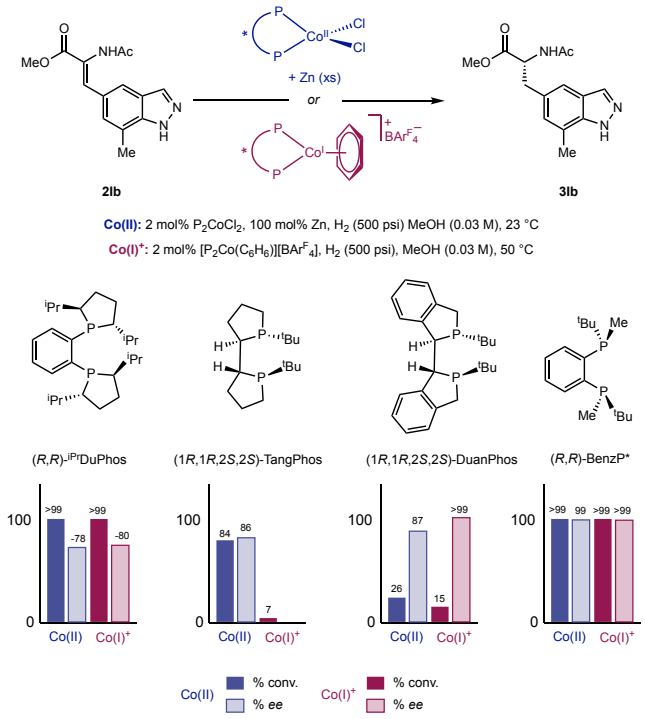
Scheme 2. Existing process for the synthesis of CGRP receptor antagonist **1** using Rh-catalyzed asymmetric hydrogenation.



The performance of cobalt precatalysts was initially evaluated for the asymmetric hydrogenation of the previously reported intermediate, aniline-containing enamide **2Aa** using 10 mol% (*R,R*)-(^{iPr}DuPhos)$CoCl_2$ with 100 mol% Zn in MeOH. These conditions were selected as this cobalt precatalysts and associated activation mode have produced high activities and enantioselectivities across a host of enamide hydrogenation reactions.[8] The catalytic hydrogenation reaction was initially conducted at 500 psi of H_2 at 23 °C and resulted in >99% conversion to **3Aa** with 56% *ee* (*S*). By comparison, the hydrogenation of the analogous indazole-containing enamide **2Ia** under identical conditions furnished the corresponding reduced product in >99% conversion to **3Ia** and 72% *ee* (*S*), demonstrating the compatibility of the cobalt-catalyst towards indazole-containing substrates. In addition, changing the identity of the *N*-protecting group from carboxybenzyl (Cbz) to acetyl (Ac) (**2Ib**) resulted in improved performance and furnished the hydrogenated product in >99% conversion to **3Ib** and 82% *ee* (*S*). Because of this promising result, **2Ib** was selected as the representative substrate for additional optimization.

Motivated by the results obtained with (*R,R*)-(^{iPr}DuPhos)$CoCl_2$ activated with zinc, additional cobalt(II) complexes bearing neutral bidentate phosphines were evaluated. Hydrogenation of **2Ib** (0.03 M in MeOH) using 2 mol% of each bis(phosphine)$CoCl_2$ complex with Zn dust (100 mol%) as an activator, in the presence of 500 psi H_2 was used to evaluate hydrogenation performance.[8] Scheme 3 presents the chiral bis(phosphines) that produced high conversion and enantioselectivity, including (*R,R*)-(^{iPr}DuPhos), (1*R*,1*R*′,2*S*,2*S*′)-(TangPhos), ((1*R*,1*R*′,2*S*,2*S*′)-(DuanPhos), and (*R,R*)-(BenzP*) (see SI for full precatalysts evaluation). Generally, C_2-symmetric ligands bearing large alkyl groups provided the highest conversions and enantioselectivities, whereas ligands bearing smaller alkyl or phenyl groups provided poorer results.

Scheme 3. Evaluation of cobalt precatalysts and phosphines for the asymmetric hydrogenation of 2Ib.[a]



[a]Conversion to product determined by NMR spectroscopy. Percent *ee* determined by chiral SFC analysis. The absolute configuration was assigned based on the crystal structure of enantiopure **3Ib**.

Notably, utilization of (*R*,*R*)-(BenzP*)$CoCl_2$ promoted the hydrogenation of **2Ib** in >99% conversion to **3Ib** and 99% *ee* (*R*).

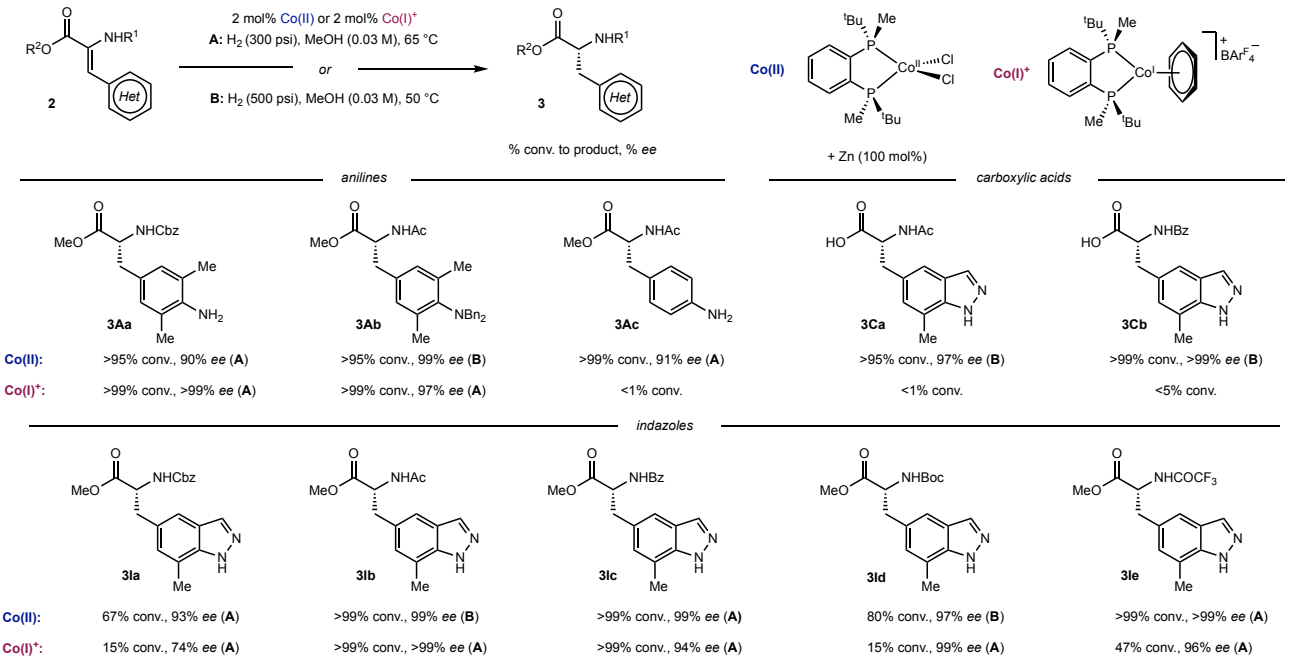
To evaluate the effect of single-electron differentiation on the performance of cobalt precatalysts, a series of cationic bis(phosphine)cobalt(I) arene complexes was also employed. Hydrogenation of **2Ib** (0.03 M in methanol) was performed in the presence of 2 mol% [bis(phosphine)Co(η^6-C_6H_6)][$BArF_4$] with 500 psi H_2 at 50 °C. Similar trends for ligand effect on activity and enantio-induction were observed as the neutral cobalt precatalysts, with sterically demanding, C_2-symmetric ligands providing the best performance. Again, (*R*,*R*)-(BenzP*) proved optimal, resulting in 99% conversion to **3Ib** with an *ee* of >99% (*R*).

Both the neutral and cationic precatalysts maintained their performance at 2 mol% catalyst loading for the hydrogenation of **2Ib** at a lower hydrogen pressure 300 psi of H_2 and 65 °C (condition **A**). These conditions are more favorable for scale up and ultimately for commercialization as they obviate the need for more specialized high-pressure hydrogenation vessels. While the cationic precatalysts maintained >99% *ee* (*R*) under these conditions, the neutral variant produced a lower enantioselectivity of 93% *ee* (*R*). Therefore, catalysis with the neutral cobalt complex was evaluated under both condition **A**, as well as at 500 psi H_2 at 23 °C (condition **B**).

The cobalt-catalyzed asymmetric hydrogenation of related substrates was also assessed, particularly with those relevant to the synthesis of **1** (Table 1). Using optimized conditions, the previously-reported aniline-containing enamide, **2Aa**, was reevaluated. Using the neutral precatalysts, the hydrogenated product was obtained in >95% conversion to **3Aa** and 90% *ee* (*R*). Use of the cationic precatalysts afforded the hydrogenated product in quantitative conversion and near perfect (>99%) enantioselectivity. These results demonstrate the versatility of cobalt-catalysis for accessing **1**through both the existing and more direct routes. The effect of additional modification of the aryl substituent on the performance of cobalt-catalyzed hydrogenation was also examined. Dibenzylation of the aniline with *N*-Ac protection (**2Ab**) furnished excellent (>99%) conversion to **3Ab** and 99% *ee* and 97% *ee*, respectively, for the neutral and cationic precatalysts. Removal of the 2,5-dimethyl groups to form the free aniline (**2Ac**) produced >99% conversion to **3Ac** and 91% *ee* with neutral precatalysts, but no conversion with the cationic precatalysts, demonstrating the reactivity changes induced by one-electron differentiation.

For the indazoles, evaluation of the role of the *N*-protecting group was also conducted, as acetamide deprotection requires acid reflux and milder conditions may be advantageous. Five *N*-protecting groups were studied with the indazole-containing class of amidoacrylates: Ac, benzoyl (Bz), Cbz, *tert*-butoxycarbonyl (Boc), and trifluoroacetyl. Introduction of an *N*-Bz protecting group, as in the case of **2Ic**, resulted in complete conversion to **3Ic** using condition **A** with enantioselectivities of 99 and 94%, for neutral and cationic cobalt precatalysts, respectively. Switching to the more sterically encumbered Boc-protected enamide **2Id**, the neutral precatalysts provided 80% conversion to **3Id** and 97% *ee* with condition **B**. In contrast, the cationic precatalysts resulted in only 15% conversion with 99% *ee*. Hydrogenation of the Cbz-protected substrate **2Ia** by the neutral precatalyst gave 67% conversion to **3Ia** and 93% *ee* (condition **A**), whereas cationic precatalysts furnished 15% conversion and 74% *ee*. Both the neutral and cationic cobalt precatalysts provided lower conversion for the Cbz- and Boc-protected substrates **2Ia** and **2Id** than the Ac- and Bz-protected substrates **2Ib** and **2Ic**. This is in line with reported activity trends for cationic rhodium-catalyzed asymmetric amidoacrylate hydrogenation, where a general rate trend of *N*-Ac≈Bz>Boc≈Cbz has been reported.[24]

Table 1. Scope of (*R*,*R*)-BenzP*Co-catalyzed hydrogenation of related enamides.[a]



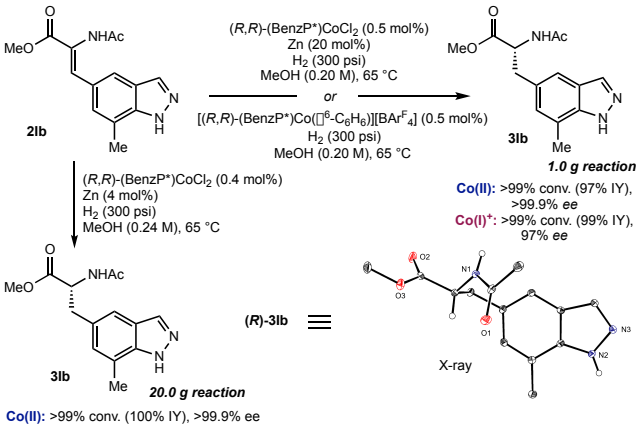
[a]Conversion to product determined by NMR spectroscopic analysis. Percent *ee* determined by chiral SFC analysis. The absolute configuration was assigned based on the crystal structure of enantiopure **3Ib**.

The potential electronic effect of *N*-protecting group on the catalytic turnover was probed by evaluating the hydrogenation performance of the trifluoroacetyl-protected substrate **2Ie**, which is sterically similar to Ac-protected substrate **2Ib**, but less electron donating. Whereas the neutral precatalysts maintained activity with **2Ie** (>99% conversion, >99% *ee*), a significant decrease in conversion was observed with the cationic precatalysts (47% conversion to product, 99% *ee*). In contrast, asymmetric hydrogenation of prochiral enamides bearing *N*-$COCF_3$ protecting groups with rhodium(I) catalysts has been shown to both decrease the conversion and erode the optical purity of the hydrogenated product.[25]

In addition to varying the *N*-protecting group, other modifications to the indazole substrate were made to probe reactivity differences between the cationic cobalt(I) and neutral cobalt(II) precatalysts. Of interest was the hydrogenation of the α,β-unsaturated carboxylic acid variants, whose activities have recently been reported with neutral cobalt(0/II) catalysts but have yet to be explored with the analogous cations. As expected from previous reports, the neutral precatalysts maintained high activity and selectivity when the methyl-ester was replaced with the carboxylic acid. Hydrogenation of *N*-Ac protected carboxylic acid **2Ca** by neutral precatalysts with condition **B** furnished >95% conversion to **3Ca** and 97% *ee*. Similarly, hydrogenation of the *N*-Bz protected carboxylic acid **2Cb** with neutral precatalysts under identical conditions produced >99% conversion to **3Cb** and >99% *ee*. By contrast, cationic precatalysts gave trace conversion with both of these substrates, demonstrating a significant reactivity change upon single-electron differentiation.

Due to its high conversion and selectivity with both the neutral and cationic precatalysts, as well as its direct synthetic route, the *N*-Ac substrate **2Ib** was chosen as the target for gram-scale hydrogenations. Hydrogenation of 1 gram of **2Ib** (3.63 mmol) by (*R*,*R*)-(BenzP*)$CoCl_2$ (0.008 g, 0.5 mol%) with Zn reductant (0.047 g, 20 mol%) in MeOH (18 mL, 0.20 M) under 300 psi H_2 at 65 °C for 48 hours furnished the hydrogenated product in >99% conversion (97% isolated yield, 0.979 g, 3.56 mmol) and >99% *ee* (Scheme 4). Similarly, hydrogenation of **2Ib** (1.00 g, 3.63 mmol) by [(*R*,*R*)-(BenzP*)$Co(C_6H_6)$][BAr^F_4] (0.023 g, 0.5 mol%) under identical conditions provided the hydrogenated product in >99% conversion (99% isolated yield, 1.00 g, 3.65 mmol) and 97% *ee*. Single crystals suitable for X-ray diffraction were obtained from a concentrated solution of chloroform, confirming the absolute configuration of the product. The hydrogenation of **2Ib** with (*R*,*R*)-(BenzP*)$CoCl_2$ (0.121 g, 0.400 mol%) was also performed on a 20-gram scale (73.23 mmol) with Zn (0.191 g, 4.00 mol%) in MeOH (300 mL, 0.24 M) under 300 psi H_2 at 65 °C to afford **3Ib** in >97% isolated yield and enantiopurity. The deprotection of **3Ib** to the free amine methyl ester was performed in quantitative yield by refluxing the hydrogenated product (2.5 g, 9.0 mmol) in 200 mL of HCl/EtOH (pH = 1) for 6 hours.

Scheme 4. Multigram-scale hydrogenations of 2Ib with neutral and cationic cobalt precatalysts.[a]



[a]Conversion to product determined by NMR spectroscopy. IY = isolated yield. Percent *ee* determined by chiral SFC analysis. The absolute configuration was assigned based on the crystal structure of enantiopure **3Ib**.

In conclusion, a highly-enantioselective hydrogenation of traditionally challenging indazole-containing substrates has been demonstrated with both neutral and bis(phosphine) cobalt(II) and cationic cobalt(I) precatalysts. Among the bidentate phosphines evaluated, (*R*,*R*)-(BenzP*) was optimal for the cobalt catalysts in both oxidation states. The method was optimized for the hydrogenation of indazole-containing enamide **2Ib** in up to a 20-gram scale reaction and applied to a variety of enamides and carboxylic acids with variation of the *N*-protecting group and arene. The performance of the cationic cobalt(I) precatalysts was more sensitive to the identity of the *N*-protecting group, as compared to the neutral cobalt(II) precatalysts. The neutral cobalt precatalysts were tolerant of carboxylic acid-containing substrates, while the cationic precatalysts were not. These findings for the effect of single-electron differentiation on catalyst activity demonstrate the importance of expanding the catalyst toolkit through the increased electronic states accessible to first-row transition metal catalysts. This method highlights the versatility of cobalt-catalyzed asymmetric hydrogenation, and provides a new route towards the chiral indazole-containing intermediate for the synthesis of the CGRP receptor-inhibitor **1**.

ASSOCIATED CONTENT

Data Availability Statement
The data underlying this study are available in the published article and its Supporting Information.

Supporting Information.
The Supporting Information is available free of charge at pubs.acs.org.
Experimental data, including synthesis and characterization of precatalysts, catalytic data, SFC traces, and NMR spectra (PDF).
Crystallographic information for **3Ib** (CIF) (CCDC 2240258).

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Funding Sources

The authors acknowledge the financial support from Biohaven, LTD, a National Science Foundation (NSF) Grant Opportunities for Academic Liaison with Industry (GOALI) grant (CHE-1855719), and the Princeton Catalysis Initiative.

ACKNOWLEDGMENT

The authors acknowledge the financial support from BioHaven, LTD, and a National Science Foundation (NSF) Grant Opportunities for Academic Liaison with Industry (GOALI) grant (CHE-1855719). Dr. Laura Wilson, Brandon Kennedy, and Dr. Yingru Zhang of Lotus Separations (Princeton, NJ) are gratefully acknowledged for technical expertise and assistance with SFC analyses. The authors gratefully acknowledge Sophie Gilbert, Dr. Piotr Gajewski, and Dr. Andre de Vries of Symeres (NL) for assistance in conducting the 20 gram scale hydrogenation experiment.

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