Heterogeneous Domino Catalysis

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# Multisite Organic–Inorganic Hybrid Catalysts for the Direct Sustainable Synthesis of GABAergic Drugs**

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*Dedicated to the MPI für Kohlenforschung on the occasion of its centenary*

***Abstract:*** *Multisite organic–inorganic hybrid catalysts have been prepared and applied in a new general, practical, and sustainable synthetic procedure toward industrially relevant GABA derivatives. The domino sequence is composed of seven chemical transformations which are performed in two one-pot reactions. The method produces both enantiomeric forms of the product in high enantiopurity as well as the racemate in good yields after a single column purification step. This protocol highlights major process intensification, catalyst recyclability, and low waste generation.*

Multifunctional materials feature unique properties with potential applications in nanotechnology and catalysis.[1] Lately, particular interest is rising in the design and preparation of multifunctional hybrid organic–inorganic solid materials for applications in domino catalysis and cascade reactions.[2] These might enable the maximization of chemical efficiency while benefiting from the advantages of heterogeneous catalysis. Despite the extensive research focused lately on the development of asymmetric domino and cascade reactions mediated by homogeneous catalysts,[3] investigations on the use of chiral catalytic solids are lacking.

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system.[4] Its deficiency is associated with several neurological and psychiatric disorders,[5] which has triggered extensive research in the synthesis and clinical application of GABA derivatives.[6] Figure 1 shows the structures of GABA and marketed analogues. All these derivatives have been commercialized in their racemic form although the enantiomers show divergent biological activities.[7] Phenibut[8] is a psychotropic drug. Rolipram exhibits varied biological activities[9] and is employed in the treatment of depression.[10] Baclofen[11] is used as a muscle relaxant and antispastic agent.[12] Pregabalin

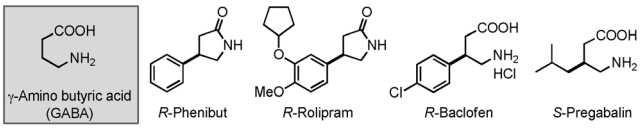
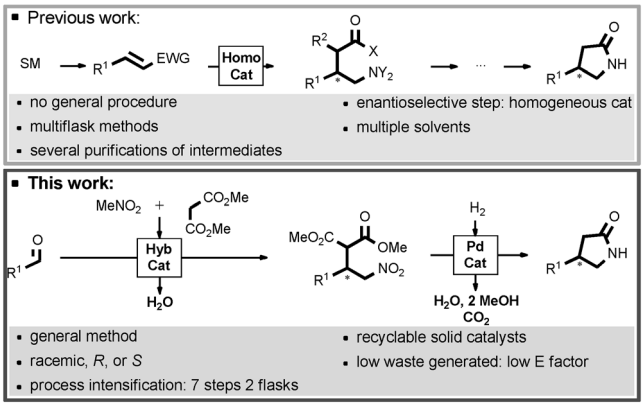



***Figure 1.*** Structures of GABA and GABA derivatives used as pharmaceuticals.

is the active ingredient in the drug Lyrica, which is used for the treatment of epilepsy, neuropathic pain, and generalized anxiety disorders.[13] In 2013, Lyrica occupied position 19 in the US retail sales of the pharmaceutical products market.

Due to the therapeutic potential of GABA derivatives, a plethora of synthetic protocols has been developed. Scheme 1 illustrates the general trend in the latest asymmetric




***Scheme 1.*** Previous and current approaches toward the catalytic synthesis of GABA derivatives. SM = starting material. EWG = electron-withdrawing group.

catalytic syntheses[14] that rely on a Michael-type addition. The initial α,β-unsaturated compound used in this transformation is prepared in (at least) one step and must be purified in order to assure maximum efficiency and stereoselectivity in the asymmetry-controlling step. Subsequent functional group modification toward the final product is achieved in at least two separate steps. These procedures are usually based on homogeneous non-recyclable catalysts and mainly utilize a stop-and-go strategy that features the isolation of intermediates, the use of multiple solvents as well as several column chromatographic and aqueous work-up procedures. Overall, this leads to a high waste generation. The pharmaceutical sector is often characterized by low

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process intensification and the highest Environmental (E) factor in the chemical industry, with typical values ranging from 25 to >100.[15] This has encouraged pharmaceutical companies to commence "green" chemistry programs.[16] Despite the great effort made to optimize the synthesis of a particular GABA analogue, a simple, general, and sustainable protocol to obtain all possible derivatives is still lacking. Scheme 1 shows our proposal for a general chemical synthesis of these relevant drugs by means of readily available solid catalysts in two one-pot operations and with very low waste generation. This protocol represents a conceptual and practical step forward with respect to the reported syntheses.

The synthetic route for the synthesis of GABA derivatives is shown in Figure 2. First, the aldehyde is reacted with

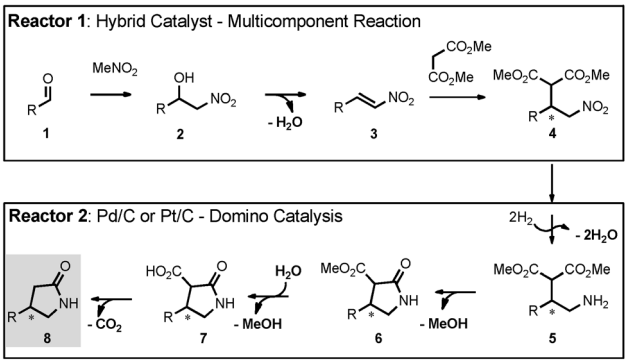


***Figure 2.*** Catalytic sequence of seven chemical transformations in a two-flask operation proposed for the preparation of GABA derivatives using a single solvent. R = aromatic or aliphatic chain. * Represents the generated chiral center.

nitromethane and dimethylmalonate in a multicomponent transformation to form compound **4**. The achiral transformation is catalyzed by commercially available solid catalysts, while the asymmetric version is catalyzed by urea-modified cinchona alkaloid derivatives on a mesoporous siliceous material with additional pending aminopropyl groups.[17] This multicomponent reaction forms two new C–C bonds (one of them in a stereoselective manner if desired) with high atom economy. The raw compound **4** is then transferred to the second reactor and subjected to the heterogeneous catalytic hydrogenation of the nitro group to the primary amine **5**. Then, spontaneous amide cyclization followed by thermal decarboxylation of the remaining ester group gives the desired final product **8** after the four-step sequence. Purification by a single column chromatography and recrystallization of the final product would ensure the purity of the compound as well as enhance the enantiopurity. Overall, a linear sequence of seven chemical transformations is performed with only two solid catalysts to directly give the desired GABA derivatives either in racemic or enantiopure form. The only by-products formed are $H_2O$, MeOH, and $CO_2$. One solvent could be used for the whole procedure, which is an additional benefit of our proposed reaction sequence.

To optimize the sequence, each transformation was examined independently and selected data is shown below

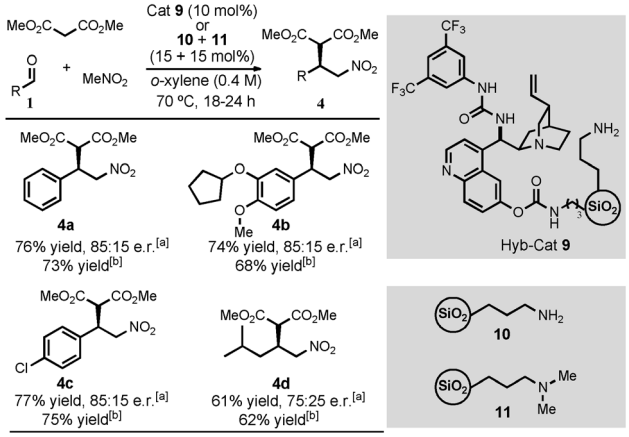


***Figure 3.*** Multicomponent reaction of aldehydes, nitromethane, and malonates. [a] Chiral solid catalyst **9** was used. [b] Composite catalyst **10** + **11** was used.

(a complete set of results can be found in the Supporting Information). Figure 3 shows the results attained for the multicomponent reaction of aldehyde **1** with nitromethane and dimethylmalonate. The chiral solid catalyst was prepared in both pseudo-enantiomeric forms starting either from quinine or quinidine and following a reported procedure (see Supporting Information for details on the preparation and characterization of the chiral solid catalyst).[17] Hybrid solid catalyst **9** derived from quinidine proved efficient in promoting the required asymmetric multicomponent transformation affording the Michael adducts **4** in good yields and reasonable enantiomeric ratios (Figure 3). The pseudo-enantiomeric solid catalyst derived from quinine produced the opposite Michael-adduct enantiomer with similar efficiency and a similar level of enantiocontrol (data shown in the Supporting Information, Scheme S1).

As many of the GABA pharmaceuticals are commercialized in a racemic form, the multicomponent transformation was assayed with a variety of commercial silica-based solid catalysts. The optimum catalyst should include an aminopropyl site that smoothly promotes the Henry condensation and also a stronger base that would facilitate the subsequent malonate Michael addition. Therefore, a composite solid catalyst was used combining an aminopropyl-functionalized silica material with a supported basic catalyst. Several organic bases supported on siliceous materials were screened and an enhanced performance was observed for commercially-available dimethylaminopropyl-functionalized silica. Extensive optimization of the reaction conditions can be found in the Supporting Information (Tables S1–S4). The best result in terms of yield and selectivity was achieved when the transformation was carried out in *o*-xylene at 70 °C for 18 h with 15 mol % of the aminopropyl-silica-based catalyst **10** combined with 15 mol % of the dimethylaminopropyl-silica-based solid **11**. Figure 3 shows that under these conditions, product **4a** derived from benzaldehyde (**1a**) is formed in 73 % yield. A substrate scope evaluation showed that the method is applicable to different starting materials with varied functionalities, which allows establishing the method as a general procedure for the synthesis of new GABA analogues.

  

The final part of our synthetic procedure implies transformation of compounds **4** into products **8** through a four-step one-pot sequence (see Figure 2). The procedure was supposed to proceed in the presence of a metal-supported catalyst under $H_2$ atmosphere. The initial catalyst screening (see Table S5 in the Supporting Information) showed that Pd/C and Pt/C can accomplish the nitro group reduction, which is followed by the three steps that yield the GABA analogues **8**, whereas the enantiopurity of the final compounds is maintained.

The generality of the transformation is shown in Figure 4 for several γ-nitro ester compounds **4a–i** that where successfully transformed to the GABA-analogues **8a–i** in good yields. Different substituents are tolerated in substrates bearing an aromatic ring. Chloride derivative **4c** endures the reaction conditions without extensive dehalogenation when Pt/C is used instead of Pd/C. If desired, the cyclohexyl derivative **8g** can be obtained by hydrogenation of the aromatic ring of **8a**.

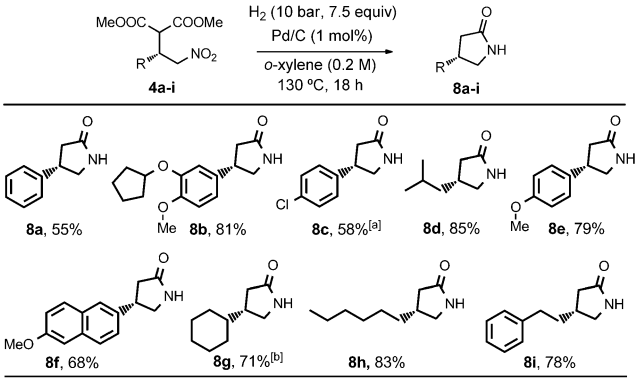


***Figure 4.*** Reduction–cyclization–hydrolysis–decarboxylation cascade reaction mediated by Pd/C. [a] Yield of the isolated products. Pt/C was used as a catalyst instead of Pd/C. [b] 20 bar (15 equiv) of $H_2$ and 36 h reaction time.

Once the two cascade reactions were fully optimized, the sequence of seven chemical transformations in two one-pot reactions was carried out with benzaldehyde **1a** as starting material. The results are shown in Figure 5. The initial three-component reaction occurred accordingly with the chiral solid catalyst or the composite solid **10** + **11**, affording adduct **4a**. After the transformation is completed, the excess nitromethane is recovered by distillation prior to the hydrogenation sequence. Subsequently, the *o*-xylene solution is transferred to the reactor containing the Pd/C catalyst (2 mol%) and subjected to hydrogenation. By these means, the desired phenibut **8a** was isolated in 35% yield for the racemate after column chromatography, and 38–40% yield of either the *R* or *S* enantiomer depending on the chiral catalyst used. Recrystallization of each enantiomer[14a,b] affords **8a** with high enantiopurity (95% *ee*). The seven-step reaction sequence was also demonstrated for (*R*)-rolipram **8b** and for the precursors of (*R*)-baclofen **8c** and (*S*)-pregabalin **8d**, and the results shown in Figure 5 are remarkable. The method

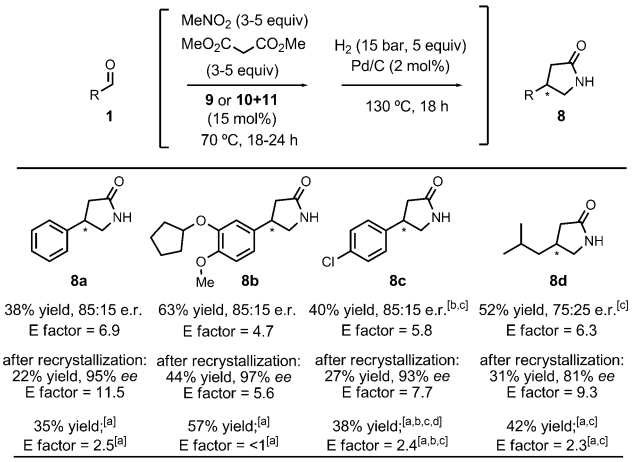


***Figure 5.*** Seven-step two-flask synthetic preparation of GABA derivatives. The *R* and *S* enantiomers were formed in very similar yields and selectivities with the corresponding chiral solid catalysts derived from quinidine, **9**, or quinine, pseudo-*ent* **9**. [a] Composite catalyst **10** + **11** was used. [b] Pt/C (2 mol%) was used for the hydrogenation step. [c] Baclofen and pregabalin were obtained by hydrolysis of the lactame with HCl at 100 °C for 24 h. [d] Scaled up to 1 g of product.

affords the desired products in good yields for a seven-step sequence (35 to 63%), and in many cases, with similar or higher yields than those reported for multiflask syntheses (details of the reported synthesis of GABAergics are shown in the Supporting Information: Tables S6–S8). Additionally, the procedure exhibits a low E factor with values which are lower than those reported for previous syntheses. We have roughly estimated the E factor for the reported procedures by only considering the main waste lines generated (water solutions used for work-up purification techniques have not been considered). Among the methods reported for the rolipram synthesis (Table S6), the lowest E factor observed is 5.5 with a chemical yield of 39% which is unfavorable compared with our method (Figure 5). We obtained an E factor of 4.7 for the chiral product and a remarkable E value of 1 for the racemate with high total yields of 63% and 57%, respectively. Similar data is shown for baclofen (Table S7). The procedure with the lowest E factor affords the product in 29% yield, whereas we obtained the chiral compound in 40% yield. Regarding the pregabalin synthesis (Table S8), there is only one protocol featuring yield and E factor values surpassing the results obtained here (Figure 5). However, no catalyst recycling was demonstrated, and the exclusive use of solid catalysts makes our strategy highly attractive. The multifunctional solid catalysis in a procedure comprising seven chemical transformations in two one-pot reactions presented here shows clear advantages in terms of practicability, cost, and waste generation. Furthermore, this protocol was shown to be suitable for large-scale preparation; the synthesis of baclofen **8c** was easily scaled to 1 g (35% yield after treatment with HCl).

In order to confirm the seven-step sequence depicted in Figure 2, the following experiments were performed. Intermediates **3**, **6**, and **7** were detected by GC-MS and NMR techniques during the reaction, and products **6d** and **7d** (as

  

a mixture, see Figure S1) were isolated from the reaction mixture after stopping the hydrogenation halfway.

Then, **6d**, **7d**, and **3a** were submitted to the reaction conditions, and the obtained results were similar to those obtained with the corresponding starting materials, confirming that intermediates **3**, **6**, and **7** are present in the synthesis and that the sequence consists of seven chemical transformations.

The solid catalysts could be used three times with minimal loss of activity (see Supporting Information). Temperature-programmed fourier transform infrared spectroscopy (TP-FTIR) of the fresh and used composite catalyst **10** + **11** showed similar spectra for both hybrid catalysts (Figure S2), which confirms that no poisoning of the amine groups occur.

In summary, we have developed a synthetic method for the direct preparation of GABA analogues in their racemic as well as each enantiomerically enriched form. The protocol highlights a major intensification of the process by the achievement of seven reactions in a two-flask operation by means of multifunctional hybrid organic–inorganic solid catalysts, and allows the synthesis of (*R*)-phenibut, (*R*)-rolipram, (*R*)-baclofen, and (*S*)-pregabalin in 35–63 % yield, high optical purity (up to 97 % *ee*), and with low E factors ($\leq$ 6.3). The solid catalysts are recyclable and the procedure can be scaled up to 1 g of product. This protocol meets all requirements demanded by "green" chemistry such as high process intensification, chemical efficiency, catalytic reactions, recyclability of catalysts/solvents, and low waste production. This methodology for the synthesis of GABA derivatives is perfectly suited for continuous flow applications.[18]

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