Synergy between chemo- and bio-catalysts in multi-step transformations†

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Cascade synthetic pathways, which allow multi-step conversions to take place in one reaction vessel, are crucial for the development of biomimetic, highly efficient new methods of chemical synthesis. Theoretically, the complexity introduced by combining processes could lead to an improvement of the overall process; however, it is the current general belief that it is more efficient to run processes separately. Inspired by natural cascade procedures we successfully combined a lipase catalyzed amidation with palladium catalyzed coupling reactions, simultaneously carried out on the same molecule. Unexpectedly, the bio- and chemo-catalyzed processes show synergistic behaviour, highlighting the complexity of multi-catalyst systems.

Introduction

Catalysis has played a prominent role in the development of new synthetic routes toward complex molecules, which have been of tremendous value for various disciplines such as the pharmaceutical sciences and food technology.[1–3] Although the complexity of molecules has increased, their synthesis generally involves a sequential array of relatively simple single-step transformations. Nature, on the other hand, carries out multi-step conversions *in complex systems*, with high overall atom and energy efficiency. There is a growing consensus that future synthetic processes should comprise comparable one-pot multi-step conversions, in cascade or in concert, in order to achieve a similar level of "sustainability" in organic synthesis.[4–8] Consequently, one of the current major challenges in synthetic chemistry is the transformation of simple single-step reactions to multi-step multi-component procedures and, more importantly, a comprehension of the *complex system* generated by integration of the processes in one-pot.[9,10] Here we report how the increase in complexity by carrying out bio- and chemo-catalyzed reactions in one reaction vessel surprisingly leads to synergistic effects between the two processes.

It is generally unknown how substrates, products and side-products of a reaction affect the progress of another reaction carried out in the same vessel, which is one of the corner stones of understanding the behaviour of complex catalyst systems. Theoretically, *multicatalyst systems* could lead to an improvement in the overall process; however, there is a general belief that it is more efficient to run processes separately. This is especially true if metal-mediated and bio-catalyzed processes are combined, because generally these are applied under substantially different conditions with limited functional group tolerance. Despite the fact that these types of combined processes would be very relevant for the production of pharmaceutically important compounds,[11,12] the only successful examples so far involve dynamic kinetic resolution procedures.[13,14] Clearly new strategies are required to face the current challenges. We therefore decided to investigate a simple cascade bio- and chemo-catalyzed transformation of a model substrate, 4-bromobenzylamine (**1a**), using the widely used catalysts lipase[15–17] and palladium, to invoke simultaneously an amidation and a C–N bond formation[18–21] (Scheme 1).

Lipases are used for the acylation of a wide scope of alcohols and amines. In particular Lipase B from *Candida antarctica* (Cal B) has shown, besides a broad applicability in different types of solvents, a remarkable thermo-stability, especially when anchored to a solid support.[22–24] There are several reports in which Cal B has been used in combination with a transition metal catalyst; however, this has been limited to racemization metal catalysts for the dynamic kinetic resolution of racemic alcohols and derivatives.[13,14] In our first combined system, we investigated the synergy between lipase catalyzed amidation and the Buchwald–Hartwig coupling (C–N bond formation). It was felt that if the known sensitive C–N coupling can be successfully incorporated into a bio-chemo cascade then the concept could be readily applied to other well-known coupling procedures.

Results and discussion

As shown in Scheme 1, the cascade process can follow several pathways: i) the lipase catalyzed amidation occurs simultaneously with the palladium catalyzed reaction; ii) the enzymatic reaction precedes the Pd catalyzed transformation, or iii) the reversed reaction order can dominate.

First the lipase-catalyzed reaction was subjected to pseudo-cascade conditions. 4-bromobenzylamine (**1a**) was submitted to enzymatic amidation by using the resin bound enzyme Novozym 435® as a catalyst, in the presence of common reagents used for Pd-catalyzed coupling (Pd precursors, and Cs_2CO_3 as base) in toluene at 100 °C. The amidation indeed proceeded under these basic conditions and also the presence of the palladium sources ($Pd(OAc)_2$, $Pd(dba)_2$) did not inhibit the enzyme activity. Thus, the enzyme proved to be surprisingly robust and active

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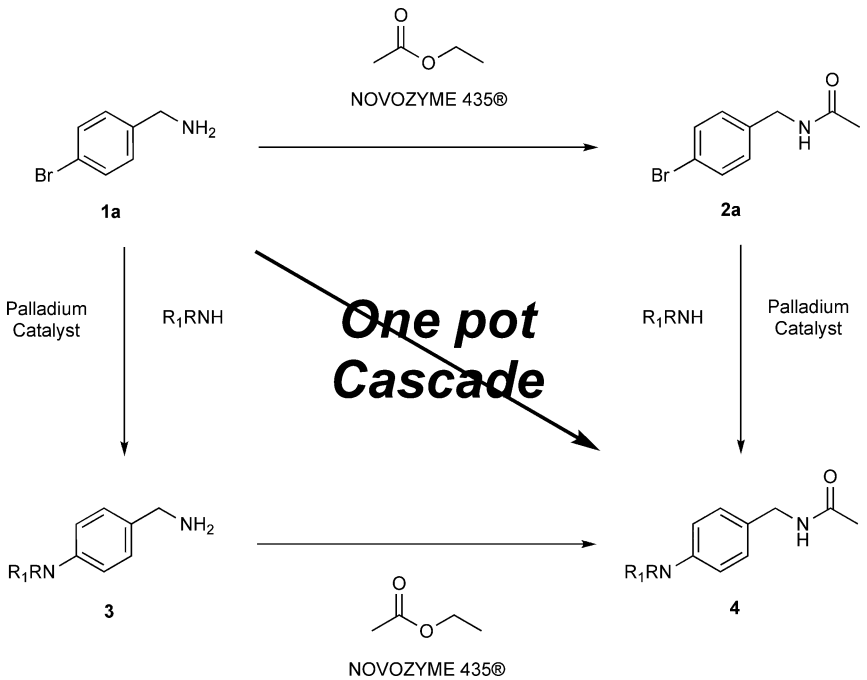


Scheme 1 Proposed cascade reaction combining an enzymatic amidation and a transition metal catalyzed C–N bond formation.

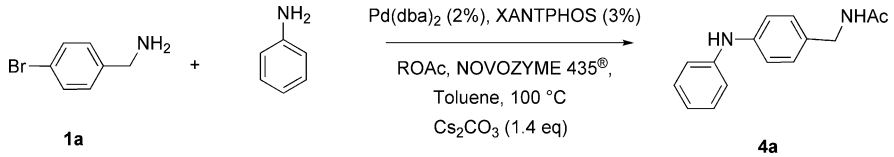
Table 1 Palladium catalyzed amination carried out on *N*-(4-bromobenzyl)acetamide (**2a**) in the presence of aniline and the most representative ligands used in the literature (entries 1–5)[a]; the combined amination/amidation cascade reaction carried out on 4-bromobenzylamine (**1a**) in the presence of aniline, Novozym 435® and the most representative ligands used in literature (entries 6–15)[b]

Entry	Ligand	AcOR	Substrate	Conversion (%)[c]	**2a** (%)[c,d]	**5** (%)[c,d]	**4a** (%)[c,d]	Cooperativity
1	$P^tBu_3H\ BF_4$[e]	NA[g]	**2a**	40	NA[g]	8	92	NA[g]
2	XANTPHOS[f]	NA[g]	**2a**	20	NA[g]	4	96	NA[g]
3	Ph-oC_6H_4-P^tBu_2[f]	NA[g]	**2a**	1	NA[g]	–	–	NA[g]
4	BINAP[f]	NA[g]	**2a**	12	NA[g]	25	75	NA[g]
5	P(*o*Tol)$_3$[e]	NA[g]	**2a**	9	NA[g]	25	75	NA[g]
6	$P^tBu_3H\ BF_4$[e]	EtOAc	**1a**	99	18	44	38	+
7	XANTPHOS[f]	EtOAc	**1a**	94	6	9	85	++
8	Ph-oC_6H_4-P^tBu_2[f]	EtOAc	**1a**	94	28	8	64	++
9	BINAP[f]	EtOAc	**1a**	97	59	37	4	–
10	P(*o*Tol)$_3$[e]	EtOAc	**1a**	99	92	8	–	0
11	$P^tBu_3H\ BF_4$[e]	MeOAc	**1a**	99	20	15	65	+
12	XANTPHOS[f]	MeOAc	**1a**	94	5	4	91	++
13	Ph-oC_6H_4-P^tBu_2[f]	MeOAc	**1a**	99	48	3	49	++
14	BINAP[f]	MeOAc	**1a**	92	89	4	7	0
15	P(*o*Tol)$_3$[e]	MeOAc	**1a**	99	97	3	–	–

[a] Reactions carried out at 100 °C in toluene; concentration of **2a**: 0.21 mm; aniline (1.04 eq); catalyst precursor: $Pd(dba)_2$ (2 mol%); Cs_2CO_3 as base (1.4 eq). [b] Reactions carried out at 100 °C in toluene; concentration of **1a**: 0.21 mM; aniline (1.04 eq); catalyst precursor: $Pd(dba)_2$ (2 mol%); Cs_2CO_3 as base (1.4 eq); Novozym 435® (100 mg); AcOR (3 eq). [c] Determined *via* GC analysis of the crude reaction mixtures after 24 h of stirring. [d] Percentage of the total of GC products. [e] 4 mol%. [f] 3 mol%. [g] Not Applicable.

at this high temperature (100% conversion into the expected product intermediate *N*-(4-bromobenzyl)acetamide **2a** after 2 h). In addition, the amidation runs described above were also carried out in the absence of Novozym 435®, in order to estimate the contribution from background reactions; the results showed a negligible conversion of substrate **1a** after 2 h and no amide **2a** was present. Further control experiments revealed that Cal B was sufficiently selective for 4-bromobenzylamine (**1a**) over aniline, making the latter suitable as a nucleophile for the palladium catalyzed amination reaction in the cascade process.

The amination reaction was studied using **2a** as the substrate, with palladium catalysts based on commonly used phosphorous ligands. Under the conditions applied the palladium catalysts provided low to moderate conversions (1–40%), with the main product being the aminated compound **4a** (See Table 1, entries 1–6). Following the traditional approach would imply optimization of



Scheme 2 Combined amidation and amination reaction using Novozym 435® and a palladium catalyst.

this single step prior to investigation of the cascade reaction; however, we decided to optimize the cascade process as a whole (Scheme 2).

A series of cascade reactions was set up using **1a** as the starting substrate, aniline as the amine nucleophile, ethyl or methyl acetate as the source of the acyl moiety and the same Pd ligands as used for the single-step amination reaction (Table 1, Scheme 2). In all cases the conversion of **1a** into the reaction products was >90% after 24 h, confirming that the enzymatic amidation reaction proceeded smoothly. More importantly, the amination reaction proved to be startlingly more efficient in the cascade process when compared to the single-step reaction, pointing to a positive cooperation between the two processes. As a second surprise we found that the organometallic catalyst that provided the highest conversion was not the same for the cascade process as for the single-step transformation, indicating that the cooperativity effect was also catalyst dependent. (Some of the catalyst systems did not show any cooperativity at all (entries 9, 10, 14, 15).) The cooperativity effect also varied with the acyl source. The use of either ethyl or methyl acetate indeed provided different results for the various catalytic systems (compare entry 6 *vs* 11, and 8 *vs* 13 in Table 1). These data clearly and unambiguously show that optimization of the separate reaction steps is not useful for the current cascade process.

To understand this intriguing cooperativity we investigated the influence of several additives on the single-step amination reaction of **2a**: a) the presence of the enzyme; b) the presence of deactivated enzyme (Novozym 435®, evacuated in order to remove absorbed water (3–5%); c) the presence of water; d) the presence of ethyl or methyl acetate; e) the presence of methanol (side product formed during the amidation reaction); f) the presence of Novozym 435®, methanol and methyl acetate, in order to mimic the situation when the amidation step has already occurred but the amination step is just beginning. All these amination reactions were studied using XANTPHOS as the ligand to form the palladium catalyst, because with this catalyst the maximum cooperativity was observed.

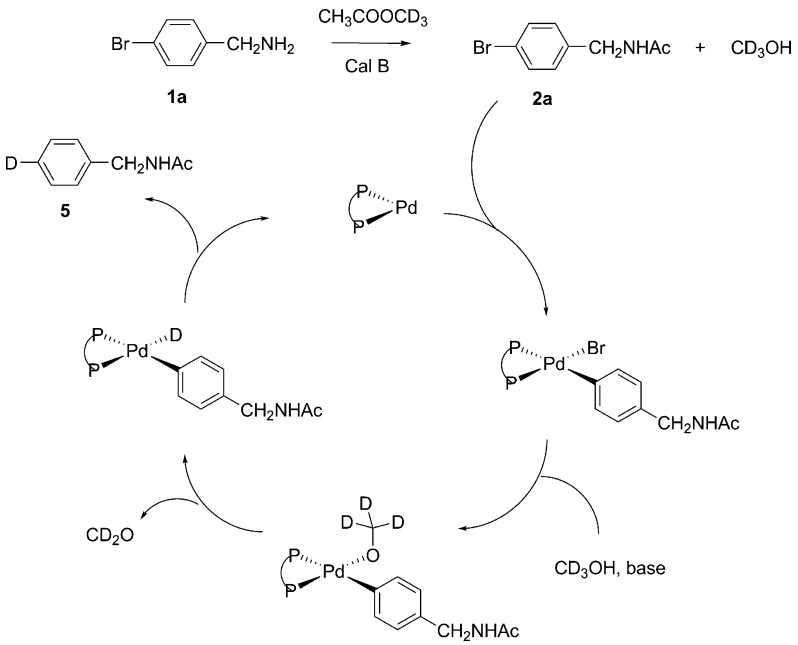
Whereas most control experiments showed similar or a small increase in conversion, the presence of 3 equivalents of methanol surprisingly led to complete conversion after 4 h, with 96% selectivity for the expected amination product **4a**. The most plausible explanation for the behaviour observed with methanol is the formation of small amounts of CsOMe in the reaction mixture, facilitated by the high temperature employed. This methoxide species is both a better base and more soluble in toluene than Cs_2CO_3. As a consequence the rate of the amination reaction is increased because the base is known to be involved in the rate-determining step, which is the deprotonation of the Pd–ammonium intermediate.[20,25]

All other results are also explained by this phenomenon. The presence of 3 equivalents of water, when reaction was carried out under the same conditions, provided a higher yield (40% conversion after 24 h), likely as a result of the formation of CsOH in the reaction mixture. A similar effect was observed when the amination reaction was carried out in the presence of Novozym 435® (the conversion of the starting substrate increased to 33% after 24 h); in this case sufficient amounts of water were introduced by the supported enzyme. Indeed, an amination reaction carried out using a batch of Novozym 435® that had been evacuated for 1 h at 0.1 mm Hg, gave the same activity as in the case where no enzyme was present (22% *vs.* 20% conversion). The above clearly demonstrates that the acceleration of the amination reaction under cascade conditions is due to the combination of the release of methanol, which is the byproduct formed during the lipase-catalyzed step, and, to a lesser extent, the presence of water introduced by the supported enzyme. Indeed the experiments carried out under the conditions of f) showed that the conversion of amide **2a** increased up to 76%, with almost complete selectivity for the product **4a**.

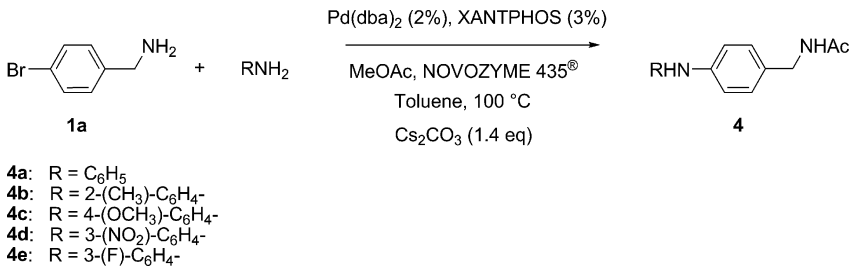
The amount of the dehalogenation product *N*-benzylacetamide (**5**) in the reaction mixture is dependent on the type of catalyst system and, more importantly, also on the ester-source used for the amidation step. The latter again points at an involvement of the alcohol side-product from the enzymatic reaction, which was indeed confirmed by labeling experiments. A cascade reaction carried out in the presence of CH_3COOCD_3 (using $pd(dba)_2/PBu_3H^+BF_4^-$ and Novozym 435® as catalysts) showed about 60% deuteration on the aromatic ring of the dehalogenated side-product (measured *via* GC/MS). In contrast, the other products did not have any deuterium incorporated. The formation of **5** therefore likely occurs through a β-hydride elimination reaction from a Pd-alkoxide species (Scheme 3). This process is dependent on the electronic and steric nature of the Pd species involved, accounting for the ligand effects observed in the formation of the side product.

The cascade reaction was investigated on **1a** applying various amine nucleophiles and using the experimental conditions that provided the highest amount of cascade products in the case of aniline (Scheme 4). In all processes the conversion of the starting substrate **1a** was almost complete after 24 h (>95%) and the selectivity for the expected cascade product **4** was always higher than 80% (GC or ^{1}H-NMR). In contrast to the cascade process, the single-step aminations carried out on intermediate **2a**, led to poor conversions (<25% after 24 h) indicating a positive cooperativity effect for all cascades investigated. Analogous results were obtained in the cascade process using 3-bromobenzylamine (**1b**) as the starting material and aniline as the nucleophile (97% conversion of **1b** after 24 h, 98% GC selectivity in the cascade product *N*-[3-(phenylamino)benzyl]acetamide (**4f**)), with the amination step proceeding much faster than in the reaction with *N*-(3-bromobenzyl)acetamide (**2b**) as starting substrate.

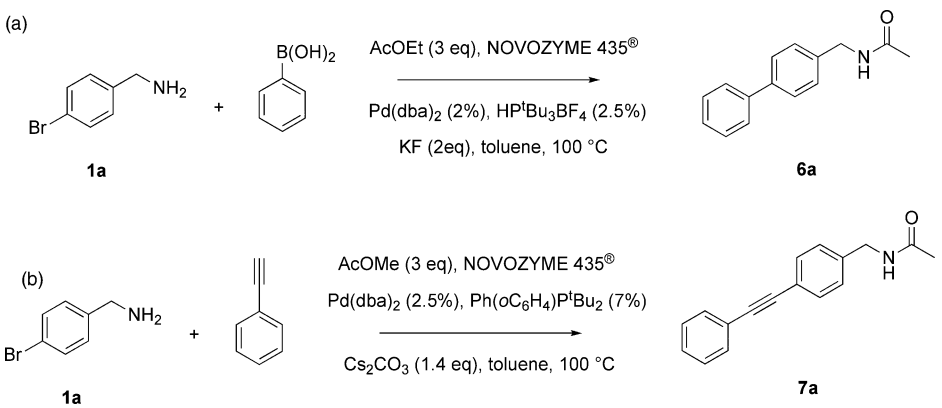
As suggested in the introduction, the validity of this concept was easily extended to two other Pd-catalyzed coupling reactions;



Scheme 3 The proposed mechanism for the origin of the dehalogenation product **5**.



Scheme 4 Combined amidation and amination reaction using various anilines.



Scheme 5 (a) Combined amidation and Suzuki reaction using Novozym 435® and a palladium catalyst. (b) Combined amidation and Sonogashira reaction using Novozym 435® and a palladium catalyst.

the Suzuki–Miyaura (Scheme 5a) and Sonogashira (Scheme 5b) reactions. In both cases the conversion of **1a** was complete after 20 h whereas the selectivity in the cascade products, **6a** and **7a**, was 70% and 89%, respectively. This shows that our findings are indeed rather general as several different chemo-bio cascade processes were successfully carried out.

Conclusions

In these cascade processes a *synergistic* effect was obtained between the two catalytic processes. The origin of this effect appeared to be an acceleration of the Pd-catalyzed step, mainly due to the presence of methanol generated during the lipase catalyzed

amidation reaction. This type of feedback mechanism is also often observed in Nature, in particular in the metabolic pathways of the cell, and is a consequence of the complexity of the reaction mixture. In order to achieve cascade catalytic systems which approach the complexity of the cell, an alternative approach to one pot catalytic systems needs to be developed. Importantly, the cooperativity effect is dependent on the palladium catalyst used and the alcohol side-product formed, highlighting that the optimal approach to efficient cascade processes may lie in the study of the system as a whole from the onset of investigation.

The classical approach to considering complicated processes normally involves the partitioning of the problem; for cascade processes this implies optimizing separate reactions before combining them (Figure 1). These procedures are only advantageous if the processes do not interact with each other, i.e in the absence of any synergy between the systems. An alternative, more counterintuitive approach, as demonstrated above, involves an optimization procedure of the *overall* cascade process after identification of a compatibility window. In this case, all factors affecting the outcome of the reaction are present during the optimization, which enables a more efficient search for optimal experimental conditions. As we could extend this cascade process to other substrates and other reactions we believe that this work represents a small but important step towards process intensification.

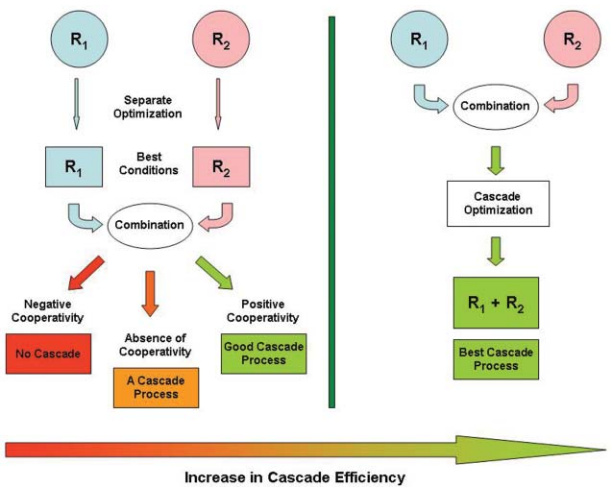


Fig. 1 Two different approaches to designing and developing a cascade process.

Experimental section

General considerations

Materials. The starting materials were purchased from commercial sources (Acros and Aldrich) and used without further purification. Methyl acetate-d_3 was prepared following a literature procedure.[26] Novozym 435® was purchased from Aldrich, stored at +4 °C and used as received. Toluene was distilled from sodium.[27] Ethyl acetate and methyl acetate were used directly from the commercial sources. All experiments were performed using standard Schlenk flask techniques under an argon atmosphere.

Analytical techniques. Separations were performed on silica gel (BIOSOLVE©, 60 Å, 0.063–0.200 mm). NMR spectra were recorded on a Varian INOVA 500 MHz and the data are reported in ppm. GC analyses were performed on a Shimadzu GC-17A instrument, column type DB-1 (J & W; 30 m x 0.32 mm). Mass spectra (EI, 70 eV) were recorded on an Agilent Technology 6890/5973-GC/MS instrument, column type HP-5 MS (30 m x 0.25 mm). Melting points were determined using a GALLENKAMP© apparatus and they should be considered estimates.

Amidation reaction on bromobenzylamine

Bromobenzylamine (**1**) (1.20 mmol), 200 mg Novozym 435®, ethyl acetate (3.60 mmol) and 6 mL toluene were inserted in a Schlenk flask under argon and the resulting mixture was heated up to 100 °C and stirred for 2 h. The mixture was then cooled down, diluted with ethyl acetate (10 mL) and extracted with 10 mL of 2% aqueous HCl solution. The water layer was extracted two times with 10 ml ethyl acetate and the combined organic layers were washed in sequence with water (10 mL), 5% aqueous sodium bicarbonate (10 mL), water (10 mL) and then dried on magnesium sulphate. The solvent was removed *in vacuo* to provide *N*-(bromobenzyl)acetamide (**2**).

***N*-(4-Bromobenzyl)acetamide (2a, white solid, 87%).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.43 (2H, d, *J* 8.2), 7.15 (2H, d, *J* 8.2), 5.75 (1H, bs), 4.37 (2H, d, *J* 6.0) and 2.02 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.2, 137.5, 132.0, 129.7, 121.6, 43.3 and 23.5; *m*/*z* (EI) 229 (M^+, 44%), 227 (47%), 186 (25%), 184 (28%) and 106 (100%); mp 120 °C (from ethyl acetate; lit.[28] 118.5–120 °C).

***N*-(3-Bromobenzyl)acetamide (2b, white solid, 93% isolated yield).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.37 (2H, m), 7.17 (2H, d, *J* 5), 6.45 (1H, bs), 4.33 (2H, d, *J* 6) and 1.98 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.5, 141.0, 130.8, 130.7, 130.4, 126.5, 122.9, 43.2 and 23.3; *m*/*z* (EI) 229 (M^+, 98%), 227 (100%), 186 (56%), 184 (57%) and 106 (100%); mp 79 °C (from ethyl acetate).

Amination reaction on *N*-(4-bromobenzyl)acetamide (2a)

Caesium carbonate (560 mg, 1.72 mmol), the chosen ligand (0.0367–0.0488 mmol), $Pd(dba)_2$ (14 mg, 0.0244 mmol) and *N*-(4-bromobenzyl)acetamide (**2a**) (275 mg, 1.20 mmol) were inserted into a Schlenk flask under an argon atmosphere. The system was then briefly evacuated and backfilled with argon (3 cycles). At this point the amine nucleophile (1.20 mmol), freshly deoxygenated toluene (6 mL) and the additive, if required, were inserted into the Schlenk flask under argon and the resulting mixture was heated up to 100 °C. The reaction was then analyzed by GC.

Amination/amidation cascade reaction

Caesium carbonate (560 mg, 1.72 mmol), $Pd(dba)_2$ (14 mg, 0.0244 mmol), the chosen ligand (L, 0.0366–0.0488 mmol) and the amine nucleophile (if solid, 1.25 mmol), were inserted into a Schlenk flask under an argon atmosphere. The system was then briefly evacuated and backfilled with argon (3 cycles). At this point freshly deoxygenated toluene (6 mL) was inserted into the Schlenk flask under argon and the mixture was briefly stirred (5 seconds). Then bromobenzylamine (**1a**) (1.20 mmol), the amine nucleophile (if liquid, 1.25 mmol), ethyl or methyl acetate (3.60 mmol) and 200 mg Novozym 435® were inserted into the

Schlenk flask under an argon atmosphere. The resulting mixture was then heated up to 100 °C and analyzed by GC. Pure samples of the final products *N*-[(phenylamino)benzyl]acetamides (**4**) could be obtained by filtering the crude mixtures on celite, concentrating the filtrates under vacuum and eluting the resulting crude oils on silica (gradient dichloromethane/methanol from 100:0 to 98:2).

***N*-[4-(Phenylamino)benzyl]acetamide (4a, pale yellow solid).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.26 (2H, dd, *J* 8 and 7.5), 7.14 (2H, d, *J* 8.5), 7.06 (2H, d, *J* 8), 7.01 (2H, d, *J* 7.5), 6.93 (1H, t, *J* 7.5), 6.46 (1H, bs), 6.07 (1H, bs), 4.31 (2H, d, *J* 5.5) and 1.97 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.5, 143.4, 142.8, 130.7, 129.6, 129.2, 121.1, 118.0, 117.9, 43.527 and 23.4; *m/z* (EI) 240 (M^+, 100%), 197 (29%) and 182 (92%); mp 103 °C (from CH_2Cl_2/MeOH).

***N*-[4-(2-Methylphenylamino)benzyl]acetamide (4b, yellow oil).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.21 (2H, d, *J* 8), 7.15 (3H, m), 6.95 (1H, dd, *J* 8 and 6.5), 6.91 (2H, d, *J* 8), 5.92 (1H, bs), 4.34 (2H, d, *J* 5.5), 2.25 (3H, s) and 2.00 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.1, 143.8, 141.2, 131.2, 130.1, 129.3, 128.9, 127.0, 122.5, 119.3, 117.6, 43.6, 23.5 and 18.1; *m/z* (EI) 254 (M^+, 100%), 211 (26%) and 196 (81%).

***N*-[4-(4-Methoxyphenylamino)benzyl]acetamide (4c, white solid).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.12 (2H, d, *J* 8.5), 7.06 (2H, bs), 6.86 (4H, m), 5.78 (1H, bs), 4.33 (2H, bs), 3.80 (3H, s) and 2.00 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.0, 155.7, 144.9, 135.7, 129.4, 122.5, 115.9, 114.9, 55.8, 43.6 and 23.5; *m/z* (EI) 270 (M^+, 100%), 255 (43%), 227 (11%) and 212 (40%); mp 121–123 °C (from CH_2Cl_2/MeOH).

***N*-[4-(3-Nitrophenylamino)benzyl]acetamide (4d, red solid).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.83 (1H, t, *J* 2), 7.70 (1 H, dd, *J* 8 and 2), 7.37 (1H, t, *J* 8), 7.27 (3H, m), 7.11 (2H, d, 8.5), 6.06 (1H, bs), 5.81 (1H, bs), 4.41 (2H, d, *J* 5.5) and 2.05 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.1, 149.9, 145.2, 140.6, 133.2, 130.3, 129.6, 122.1, 120.3, 115.0, 110.4, 43.6 and 23.6; *m/z* (EI) (M^+, 100%), 268 (81%), 242 (46%) and 227 (66%); mp 158 °C (from CH_2Cl_2/MeOH).

***N*-[4-(3-Fluorophenylamino)benzyl]acetamide (4e, yellow oil).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.17 (3H, m), 7.06 (2H, d, *J* 8.5), 6.74 (2H, m), 6.58 (1H, m), 5.92 (2H, bs), 4.35 (2H, d, *J* 5.7) and 2.01 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.2, 164.0 (d, *J* 244), 145.4 (d, *J* 11.8), 141.7, 131.8, 130.7 (d, *J* 9.7), 129.3, 119.3, 112.8, 107.2 (d, *J* 20.7), 103.7 (d, *J* 24.4), 43.5 and 23.5; δ_F (470.5 MHz; $CDCl_3$; $CFCl_3$) –112.2; *m/z* (EI) 258 (M^+, 100%), 215 (31%) and 200 (74%).

***N*-[3-(Phenylamino)benzyl]acetamide (4f, pale yellow solid).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.27 (2H, dd, *J* 8.5 and 7.5), 7.21 (1H, t, *J* 7.5), 7.07 (2H, d, *J* 8.5), 6.99 (1H, d, *J* 8), 6.94 (2H, m), 6.81 (1H, d, *J* 7.5), 6.04 (1H, bs), 5.88 (1H, bs), 4.35 (2H, d, *J* 6) and 1.99 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.3, 143.9, 143.0, 139.8, 129.9, 129.6, 121.5, 120.2, 118.4, 117.0, 116.5, 43.968 and 23.465; *m/z* (EI) 240 (M^+, 100%), 197 (58%) and 180 (20%); mp 135–137 °C (from CH_2Cl_2/MeOH).

Suzuki/amidation cascade reaction

Phenyl boronic acid (148 mg, 1.21 mmol), potassium fluoride (188 mg, 3.23 mmol), $Pd(dba)_2$ (12.5 mg, 0.0217 mmol) and $P^tBu_3H^+$ BF_4^- (8 mg, 0.0270 mmol) were inserted into a Schlenk flask under an argon atmosphere. The system was then briefly evacuated and backfilled with argon (3 cycles). At this point freshly deoxygenated toluene (6 mL) was inserted into the Schlenk flask under argon and the mixture was briefly stirred (5 seconds). Then 4-bromobenzylamine (**1a**) (1.08 mmol), ethyl acetate (3.60 mmol) and 200 mg Novozym 435® were inserted into the Schlenk flask under an argon atmosphere. The resulting mixture was then heated up to 100 °C and analyzed by GC. A pure sample of the final product *N*-[4-phenylbenzyl]acetamide (**6a**) could be obtained by filtering the crude mixture on celite, concentrating the filtrate under vacuum and eluting the resulting crude oil on silica (gradient dichloromethane/methanol from 100:0 to 98:2).

***N*-[4-Phenylbenzyl]acetamide (6a; light brown solid).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.57 (4H, m), 7.45 (2H, t, *J* 7.5), 7.36 (3H, m), 5.73 (1H, bs), 4.49 (2H, d, *J* 5.5) and 2.06 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.3, 140.9, 140.8, 137.4, 129.0, 128.6, 127.7, 127.6, 127.3, 43.7 and 23.5; *m/z* (EI) 225 (M^+, 100%) and 182 (66%); mp 182 °C (from CH_2Cl_2/MeOH; lit.[29] 180–182 °C).

Sonogashira/amidation cascade reaction

Caesium carbonate (560 mg, 1.72 mmol), 2-(ditertbutylphosphino)biphenyl (22.5 mg, 0.0756 mmol), $Pd(dba)_2$ (15.5 mg, 0.0270 mmol) were inserted into a Schlenk flask under an argon atmosphere. The system was then briefly evacuated and backfilled with argon (3 cycles). At this point freshly deoxygenated toluene (6 mL) was inserted into the Schlenk flask under argon and the mixture was briefly stirred (5 seconds). Then 4-bromobenzylamine (**1a**) (1.08 mmol), phenylacetylene (1.51 mmol), methyl acetate (3.60 mmol) and 200 mg Novozym 435® were inserted into the Schlenk flask under an argon atmosphere. The resulting mixture was then heated up to 100 °C and analyzed by GC. A pure sample of the final product *N*-[4-(2-phenylethynyl)benzyl]acetamide (**7a**) could be obtained by filtering the crude mixture on celite, concentrating the filtrate under vacuum and eluting the resulting crude oil on silica (gradient dichloromethane/methanol from 100:0 to 98:2).

***N*-[4-(2-Phenylethynyl)benzyl]acetamide (7a; light brown solid).** δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.53 (2H, m), 7.50 (2H, d, *J* 8.0), 7.35 (3H, m), 7.26 (2H, d, *J* 8.0), 5.81 (1H, bs), 4.45 (2H, d, *J* 6.0) and 2.04 (3H, s); δ_C (125.7 MHz; $CDCl_3$; Me_4Si) 170.1, 138.7, 132.1, 131.8, 128.6, 128.5, 128.0, 123.4, 122.8, 89.8, 89.2, 43.7 and 23.5; *m/z* (EI) 249 (M^+, 100%), 206 (66%), 191 (30%) and 178 (31%); mp 156 °C (from CH_2Cl_2/MeOH).

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