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Chemoenzymatic Cascades

Stereoselective Three-Step One-Pot Cascade Combining Amino- and Biocatalysis to Access Chiral γ-Nitro Alcohols**

*Christian Ascaso-Alegre, Raquel P. Herrera, and Juan Mangas-Sánchez**

Abstract: The combination of small-molecule catalysis and enzyme catalysis represents an underexploited area of research with huge potential in asymmetric synthetic chemistry due to both compatibility of reaction conditions and complementary reactivity. Herein, we describe the telescopic synthesis of chiral nitro alcohols starting from commercially available benzaldehyde derivatives through the one-pot three-step chemoenzymatic cascade combination of a Wittig reaction, chiral-thiourea-catalysed asymmetric conjugate addition, and ketoreductase-mediated reduction to access the corresponding target compounds in moderate to excellent overall isolated yields (36–80 %) and high diastereomeric and enantiomeric ratios (up to >97:3). This represents the first example of the combination of an organocatalysed asymmetric conjugate addition via iminium ion activation and a bioreduction step catalysed by ketoreductases.

By constructing artificial cascades, in which the product of a given reaction acts as the substrate for the next, synthetic chemists imitate the efficient metabolic routes in living organisms to make complex molecules.[1,2] These processes provide many practical and environmental advantages as no intermediate purification or isolation is required, thus reducing time, effort, and waste. Moreover, highly reactive, labile, or toxic species can be easily transformed in the reaction mixture, leading to higher yields. Biocatalytic cascades are particularly convenient for these processes as enzymes normally work under the same reaction conditions (pH, temperature, pressure), and the outstanding chemoselectivity they display, minimises the risk of cross-reactivities that can potentially lead to the formation of side products. Some of these processes have already been applied at a large scale for the synthesis of pharmaceuticals.[3] These systems can also be constructed by combining chemo- and biocatalysts. In this manner, the synthetic abilities of the different catalytic worlds can be brought together to work synergically and enable access to enantioenriched compounds from simple and readily available non-chiral starting materials.[4,5] This is especially relevant in the combination of transition metal (TM) catalysis and biocatalysis,[6,7] which has become a very dynamic field in recent years. However, and despite the relative similarities between enzyme and small-molecule catalysis, examples of cascade processes involving organo- and biocatalysis are still scarce in the literature.[8] Furthermore, these reports are restricted to the combination of enamine catalysis (aldol or Mannich-type reactions) promoted by proline-based catalysts (PBC) with lipases (*Ca*LB), ketoreductases (KREDs) and transaminases (TAs) to access chiral amino alcohols (Scheme 1a),[9] diols (Scheme 1b),[10,11] lactones (Scheme 1c),[12] or *N*-heterocycles.[13]

Chiral γ-nitro ketones and alcohols are important building blocks in the synthesis of different active pharmaceutical ingredients[14,15] and can be efficiently synthesised via iminium-catalysed asymmetric Michael addition of nitromethane over α,β-unsaturated carbonyl compounds.[16,17] Recent efforts by the groups of Hilvert, Poelarends, and others have shown that this reaction can also be performed via enzymatic catalysis using different biocatalysts such as carboligases and tautomerases,[18–21] or artificial enzymes bearing non-natural cofactors that enable iminium catalysis.[22] However, the use of prolinol[23] and thiourea-based[24] organocatalysts continues to be the preferred method as they have been shown to be a very efficient tool to enable this transformation through a bifunctional mechanism involving carbonyl activation via iminium ion formation and nitro group activation via hydrogen-bonding interactions.[25]

With this in mind, we envisaged that by combining the excellent selectivity aminocatalysis offers for asymmetric C–C bond formation and the exquisite efficiency ketoreductases display in the stereoselective reduction of carbonyl compounds, these two processes can be potentially combined sequentially in the same vessel to access synthetically relevant chiral γ-nitro alcohols (Scheme 1d).

In order to establish the basis for a combined asymmetric nitromethane addition followed by a bioreduction, we

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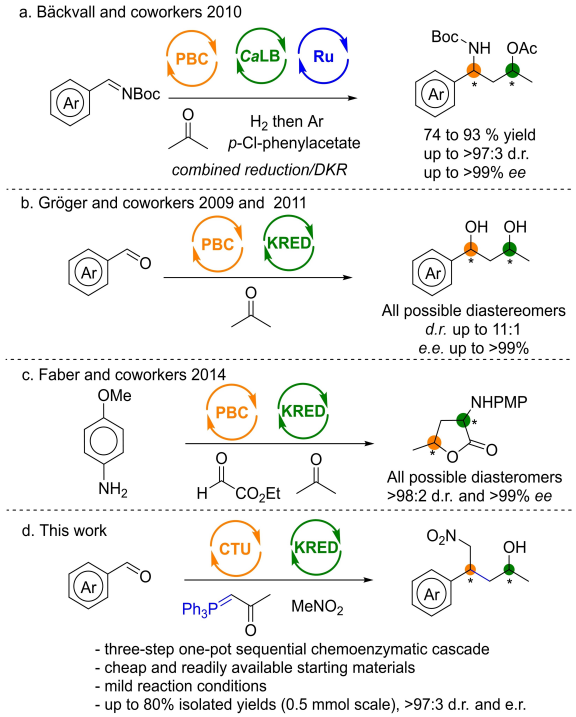


Scheme 1. Examples of the combination of organo- and biocatalysts to access chiral compounds. PBC: Proline-based catalyst. CTU: Chiral thiourea.

initially investigated the chiral cyclohexanediamine-based thiourea (CTU, Figure 1) developed by Wang and co-workers (*R*,*R*)-**I** for the Michael addition of nitromethane over commercially available 4-phenyl-3-buten-2-one (**2a**) as it has been demonstrated to be an efficient catalyst for this transformation.[24] Initial reaction under the previously reported conditions described by Wang and confirmed the exquisite stereoselectivity and efficacy previously reported for this organocatalyst (Table 1, entry 2).[24] We then carried out a comprehensive reaction optimisation including solvent, catalyst loading, nitromethane concentration and temperature. Specifically, different enzyme-compatible solvents were tested at a 15 mol% catalyst loading and using 20 eq. of $MeNO_2$ (entries 1–6), observing high to excellent yields (73–95 %) in most cases with cyclohexane as the best solvent after 5 days at room temperature. Satisfyingly, in all cases, the corresponding γ-nitro ketone (*R*)-**3a** was obtained in

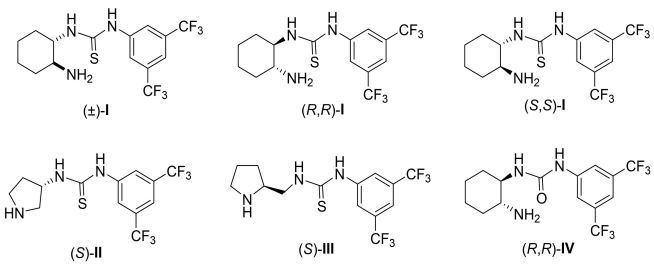
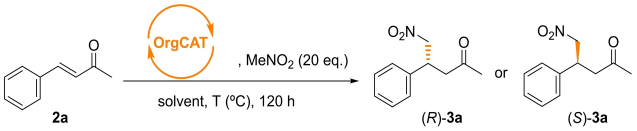


Figure 1. Structures of the organocatalysts **I–IV** screened in the conjugate addition of nitromethane over benzalacetone **2a**.

Table 1: Investigation of different organocatalysts and conditions in the asymmetric conjugate addition of nitromethane over benzalacetone **2a**.



Entry	Organocatalyst	Solvent	Yield [%]	e.r.
1	(±)-**I**	EtOAc	91	n.a.
2	(*R*,*R*)-**I**	EtOAc	73	>99:1 (*R*)
3	(*R*,*R*)-**I**	toluene	88	>99:1 (*R*)
4	(*R*,*R*)-**I**	cyclohexane	95	>99:1 (*R*)
5	(*R*,*R*)-**I**	MTBE	82	>99:1 (*R*)
6	(*R*,*R*)-**I**	*i*PrOH	36	92:8 (*R*)
7	(*S*)-**II**	EtOAc	75[a]	*rac*
8	(*S*)-**III**	EtOAc	85[a]	55:45 (*S*)
9	(*R*,*R*)-**IV**	EtOAc	28	85:15 (*R*)
10	(*R*,*R*)-**I**	EtOAc	<3[b]	n.a.
11	(*R*,*R*)-**I**	EtOAc	49[c]	81:19 (*R*)
12	(*R*,*R*)-**I**	cyclohexane	76[d]	>99:1 (*R*)
13	(*R*,*R*)-**I**	cyclohexane	72[e]	>99:1 (*R*)
14	(*R*,*R*)-**I**	cyclohexane	91[f]	>99:1 (*R*)
15	(*R*,*R*)-**I**	cyclohexane	72[g]	>99:1 (*R*)
16	(*R*,*R*)-**I**	cyclohexane	50[h]	>99:1 (*R*)
17	(*R*,*R*)-**I**	cyclohexane	58[i]	96:4 (*R*)
18	(*S*,*S*)-**I**	cyclohexane	83	>99:1 (*S*)

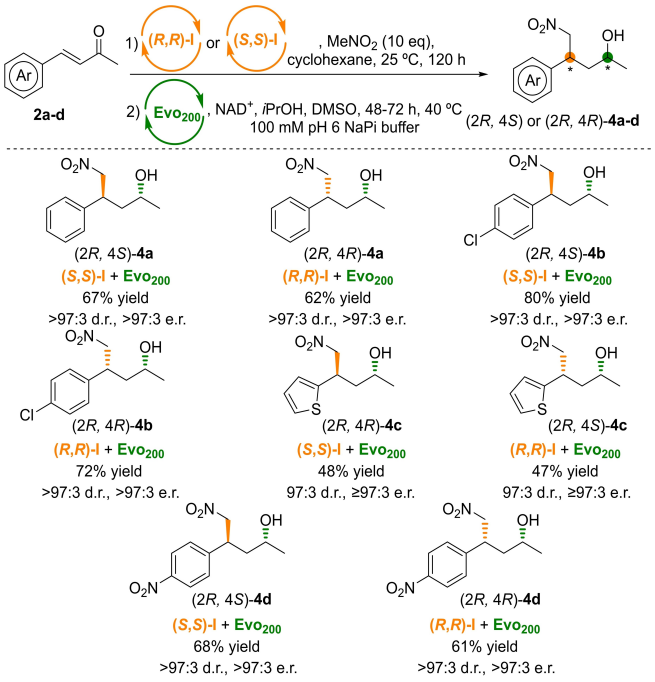
Yields are for the isolated product after column chromatography; enantiomeric ratios were determined by HPLC on a chiral stationary phase. Absolute configurations are based on previously reported data.[24] n.a.: not applicable. [a] 48 h reaction. [b] *p*-TsOH 15 mol% added as additive. [c] NEt_3 15 mol% added as additive. [d] 10 mol% catalyst. [e] 5 mol% catalyst. [f] 15 eq. $MeNO_2$. [g] 10 eq. $MeNO_2$. [h] 5 eq. $MeNO_2$. [i] 48 h, 40 °C.

enantiopure form. Since 2-propanol is generally used as a sacrificial substrate in the subsequent ketoreductase step, the asymmetric conjugate addition was also tested using 2-propanol as the solvent (entry 6). Unfortunately, a significant drop in both activity (36 % yield) and stereoselectivity (92:8 e.r.) was observed.

We hypothesised that product release upon reaction is rate-limiting therefore, the use of additives and secondary amine-based catalysts [Figure 1, (*S*)-**II**, (*S*)-**III**] were investigated in efforts to speed up the process. Specifically, we explored the use of chiral prolinamide thioureas that were proved to be efficient catalysts for the addition of ketones over nitrostyrenes and other asymmetric transformations via enamine catalysis.[26–29] The use of (*S*)-**II** and (*S*)-**III** as catalysts resulted in a significant increase in the reaction rate with the product obtained in high yields after 48 h (entries 7 and 8) although in both cases a complete loss of stereoselectivity was observed, obtaining **3a** in either racemic form or very low enantiomeric ratio. The analogous cyclohexane diamine urea catalyst (*R*,*R*)-**IV** was also tested although the ability of this catalyst to promote the asymmetric addition of nitromethane was found to be drastically reduced, obtaining (*R*)-**3a** in 28 % isolated yield and in 85:15 e.r. (entry 9). The addition of catalytic amounts of acid (*p*-TsOH, entry 10 or AcOH) resulted in no product being detected which suggests that non-acidic media is required for effective

nitromethane deprotonation. The addition of base (NEt_3) resulted in a lower yield (49%) and a drop in selectivity (81:19 e.r., entry 11). Lower catalyst loadings (Table 1, entries 12 and 13) led to a slight decrease in yield (from 95 to 72%) although no reduction in the stereoselectivity was found. Similarly, we also investigated the influence of $MeNO_2$ loadings observing no effect on the stereoselectivity at lower $MeNO_2$ equivalents and a drop in yield when 10 eq. were used (Table 1, entries 12–16). Finally, the influence of the temperature was also investigated in efforts to speed up the process. Using 15 mol% of (*R*,*R*)-**I**, a 58% isolated yield was obtained in 48 h at 40 °C although, in this case, a drop in the stereoselectivity of the reaction was detected (from >99:1 to 96:4 e.r., entry 17).

With the optimised conditions in hand (entry 14), we next examined the combination of the CTU-mediated asymmetric conjugate addition with a bioreduction step catalysed by KREDs. Production of the final products in racemic form was initially attempted using $NaBH_4$ as the reducing reagent, resulting in the formation of **2a** via retro-Michael (nitromethane elimination). Non-selective reduction was successfully carried out using NH_3BH_3 in THF. For the asymmetric reduction step, we selected the commercially available and enantiocomplementary KREDs Evo_{200} and Evo_{030}. Initial tests revealed that starting from enantiomerically pure (*R*) and (*S*)-**3a**, both enzymes enabled the access to all four diastereomers in excellent d.r. and conversions that ranged from 29 to 53% after 24 h using 1 mg mL^{-1} enzyme concentration and in >97:3 d.r. (determined by ^{1}H NMR over the reaction crudes, figures S14,15). These results suggest that the biocatalytic reduction in both cases is fully stereoselective. The two-step cascade was then constructed by combining both catalytic steps following a sequential approach. To our delight, starting from commercial enone **2a** and using both (*R*,*R*)-**I** and (*S*,*S*)-**I** organocatalysts (15 mol% loading), 10 eq. of $MeNO_2$, cyclohexane as the solvent and Evo_{200} as KRED, the corresponding chiral γ-nitro alcohols (2*R*,4*R*)-**4a** and (2*R*,4*S*)-**4a** could be isolated in 62 and 67% yields after column chromatography, respectively, and in excellent diastereomeric and enantiomeric ratios (>97:3 d.r. and e.r.) (Scheme 2). This process constitutes the first example of a one-pot system combining an asymmetric organocatalysed step via iminium ion activation followed by a bioreduction step to form two new stereogenic centres from a prochiral compound. Unfortunately, only traces of (2*S*,4*R*)-**4a** and (2*S*,4*S*)-**4a** were detected when Evo_{030} was used. Control experiments revealed that this enzyme does not tolerate the presence of nitromethane in the reaction mixture. We next went on exploring the scope of this process by screening different α,β-unsaturated ketones (**2b–d**) obtained from either commercial sources (**2c**) or synthesised via the Wittig reaction between different benzaldehyde derivatives (**1b** and **1d**) and ylide **5**. For the *p*-Cl and *p*-NO_2 derivatives **2b** and **2d**, the corresponding chiral alcohols were obtained in moderate to high isolated yields (48 to 81%) and in excellent diastereomeric and enantiomeric ratios (>97:3). Lower yields were observed in the case of the thienyl-derived enone **2c**, with 47 and 48% isolated yields for the *syn* and *anti* products



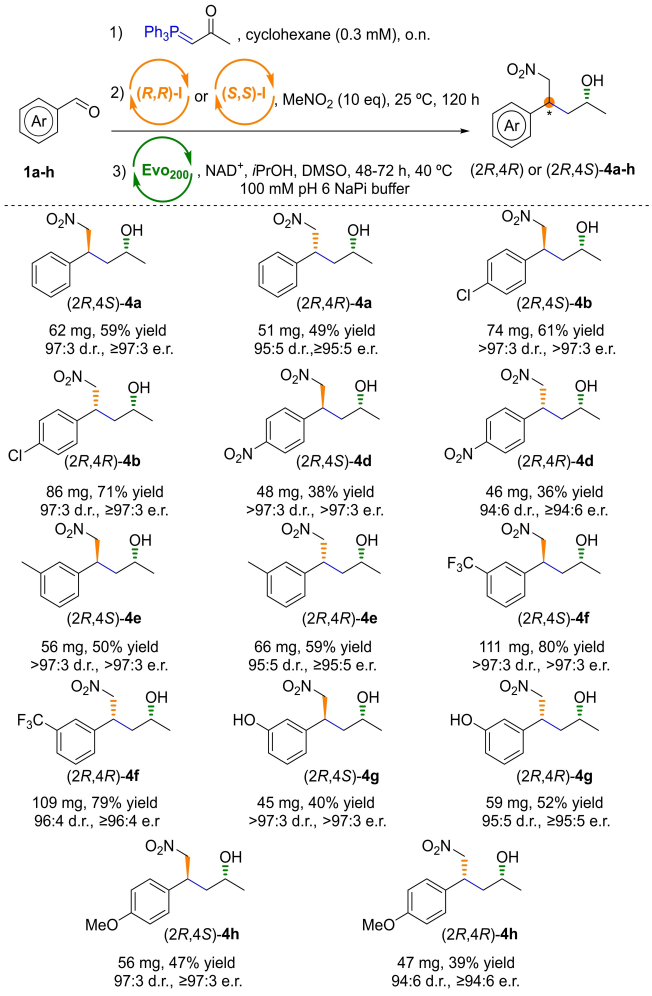
Scheme 2. Two-step sequential cascade to access chiral γ-nitro alcohols from enones combining cylohexanediamine-derived thioureas and ketoreductases. Conversions and diastereomeric and enantiomeric ratios were determined by either ^{1}H NMR spectroscopy or HPLC on a chiral stationary phase, respectively. Yields are for the isolated product after column chromatography. Reaction conditions: 15 mol% (*R*,*R*)-**I** or (*S*,*S*)-**I**, 10 eq. $MeNO_2$, 0.66 mg mL^{-1} (*anti*) or 1 mg mL^{-1} (*syn*) total Evo200 KRED loading, 10% *i*PrOH. 30% DMSO, 100 mM pH 6 phosphate buffer, 5 mM NAD^+.

respectively, and in 97:3 d.r. in both cases. Both steps were examined individually using (*S*,*S*)-**I** as the catalyst, obtaining the corresponding chiral γ-nitro ketone (*S*)-**3c** in 47% isolated yield and in 94:6 e.r., suggesting that the loss of stereoselectivity and lower productivity in the overall process is caused by the organocatalysed step, with the biocatalytic reduction being highly efficient (Table S1).

After the successful combination of both catalytic steps, and since the Wittig reaction proceeds under similar reaction conditions with triphenylphosphine oxide as the sole by-product, we envisaged that the whole synthetic route could be carried out in the same reaction vessel adding the different components successively with no product isolation and, therefore, a three-step sequential telescopic cascade could be constructed to access the target products from commercially available benzaldehyde derivates.

Using the *p*-methoxy derivative as the model substrate, the reaction between 4-methoxybenzaldehyde (**1h**) and ylide **5** in cyclohexane (0.3 M) at 80 °C was carried out for 24 h followed by the organocatalytic asymmetric 1,4-addition of nitromethane at room temperature for 120 h in a one-pot sequential process to form the chiral γ-nitro ketone (*R*)-**3h**, with no loss in stereoselectivity observed in the process. Encouraged by this result, we next examined the three-step cascade by coupling the KRED-mediated bioreduction step using Evo_{200} under the conditions previously optimised.

Initial purification of the starting materials was performed to prevent any interaction with the organocatalysed step. We then explored the synthesis of a broad panel of chiral γ-nitro alcohols starting from commercially available benzaldehyde derivatives **1a–h** bearing electron-withdrawing and electron-donating substituents at a 0.5 mmol scale (Scheme 3). Remarkably, in all cases the final products (2*R*,4*S*)-**4a–h** and (2*R*,4*R*)-**4a–h** were obtained in excellent diastereomeric and enantiomeric ratios which highlights the outstanding synthetic value of multistep catalytic cascade processes to access chiral compounds in a straightforward manner. Generally, the synthesis of the *syn* products (2*R*,4*R*)-**4a–h** proved to be more challenging, with higher enzyme loadings required to achieve high conversions (1 mg mL^{-1} total enzyme loading vs 0.66 mg mL^{-1} to access the *anti*-configured products). We also detected a small decrease in the diastereomeric ratio in the *syn*-configured products (from >97:3 to 94:6 in the case of **4d** and **4h**). Considering the high stereoselectivity observed in the nitromethane conjugate addition catalysed by (*R*,*R*)-**I**, these results suggest that Evo$_{200}$ displays a slightly lower stereoselectivity towards the (*R*)-configured nitro ketones **3a–h**. Despite observing no significant nitromethane related enzyme inhibition, a stepwise addition over 48 to 72 h was found to be optimal to afford good yields, thus suggesting some enzyme degradation over time.



Scheme 3. Telescopic three-step sequential synthesis of chiral γ-nitro alcohols from readily available aldehydes. Conversions, diastereomeric ratios and enantiomeric excesses determined by either ^{1}H NMR or HPLC on a chiral stationary phase. Isolated yields after column chromatography. Conditions: 0.5 mmol benzaldehyde derivative **1a–h**, 1.4 eq. ylide, 15 mol% (*R*,*R*)-**I** or (*S*,*S*)-**I**, 10 eq. $MeNO_2$, 0.66 mg mL^{-1} (*anti*) or 1 mg mL^{-1} (*syn*) total Evo200 KRED loading over 48 and 72 h respectively, 10% *i*PrOH. 30% DMSO, 100 mM pH 6 phosphate buffer, 5 mM NAD^+.

In the case of the 3-OH derivative **4g**, allylic alcohol obtained from the KRED-mediated reduction of **2g** was observed as a by-product, which suggested that the organocatalytic reaction was limiting the overall yield. We decided to study both steps individually, which revealed that, whereas the Wittig reaction proceeded almost quantitatively and the enone **2g** was isolated in high yield (73%), a moderate yield (53%) was obtained in the asymmetric nitromethane conjugate addition over **2g**, thus limiting higher productivities in the overall cascade. Nevertheless, (2*R*,4*S*)-**4g** and (2*R*,4*R*)-**4g** could be isolated in 40 and 52% yields, respectively, and in enantiopure form, highlighting the importance of these cascade systems to synthesise chiral products more efficiently. Similarly, yields ranging between 39 and 47% were obtained in the case of the 4-OMe derivative **4h**, which indicates that the conjugate addition over enones bearing electron-donating groups are less efficient. In the case of the *p*-NO_2 derivatives (2*R*,4*S*)-**4d** and (2*R*,4*R*)-**4d**, moderate yields of 38 and 36% were obtained, respectively. In this case, both the Wittig reaction and the organocatalysed step proceeded in high conversion, with the bioreduction step being the limiting step in the overall process. The cascade proved to be highly productive on derivatives bearing other EWG. For instance, 3-CF_3 derivatives (2*R*,4*S*)-**4f** and (2*R*,4*R*)-**4f** were isolated in remarkable 80% and 79% yields and the 4-Cl substituted products (2*R*,4*S*)-**4b** and (2*R*,4*R*)-**4b** were obtained in 61 and 71% isolated yields, respectively.

In summary, we have demonstrated how primary amine catalysis via iminium ion activation can be efficiently combined in a cascade process with oxidoreductases to access chiral γ-nitro alcohols, which are important intermediates in the asymmetric synthesis of high value-added compounds. Additionally, we have also shown that this cascade can be further extended to start from commercially available benzaldehyde derivatives to access the corresponding α,β-unsaturated prochiral ketones via the Wittig reaction. Under a one-pot set-up in which the different components were added sequentially, a large set of chiral γ-nitro alcohols could be synthesised in moderate to excellent overall yields (38–80%) after three steps without significant modification of the reaction conditions. All products were also obtained in high diastereomeric and enantiomeric ratios (up to ≥97:3 d.r. and e.r.). This constitutes the first example of the combination of an asymmetric C–C bond formation reaction via iminium catalysis followed by a reduction step through enzyme catalysis. This study demonstrates the potential of multicatalytic cascade systems to access enantiomerically enriched compounds under environmentally be-

nign conditions and will hopefully inspire further research in this area.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Asymmetric Synthesis · Biocatalysis · Chemoenzymatic Cascades · One-Pot Processes · Organocatalysis

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