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A facile lipase-catalyzed KR approach toward enantiomerically enriched homopropargyl alcohols

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Paweł Kafarski on the occasion of his 70th birthday and Ryszard Ostaszewski on the occasion of his 60th birthday as well as in honor of their profound contribution to the field of polish biocatalysis.

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ABSTRACT

Compounds possessing propargylic (prop-2-ynylic) system are very important building blocks for organic chemistry. Among them, preparation of enantiomeric homopropargyl alcohols (but-3-yn-1-ols) constitutes a key-challenge for asymmetric synthesis and thus drawn tremendous attention from the synthetic community in the last few decades. In this work, the catalytic performance of a set of commercial lipases has been investigated for enantioselective transesterification of 1-phenylhomopropargylic alcohols under kinetically–controlled conditions. Lipase from *Burckholderia cepacia* (BCL) immobilized either on ceramic (Amano PS-C II) or diatomaceous earth (Amano PS-IM) turned out to be the most active and enantioselective enzyme preparations ($E \gg 500$) furnishing both resolution products of the racemic 1-phenylbut-3-yn-1-ol in highly enantiomerically enriched form (up > 99% ee). Variable reaction parameters, such as the acyl-group donor reagent as well as solvent, were additionally screened to establish their impact on the stereochemical outcome. For optimal biocatalytic systems established with model substrate, the enzymatic transformations were extended toward preparative-scale KR of 8 other differently *para*-phenyl-substituted homopropargylic *sec*-alcohols, which resulted in the synthesis of (*S*)-alcohols (96–100% ee) and the respective (*R*)-acetates (92–100% ee) in 19–44% yield, accordingly. Additionally, the crystal structure of (1*R*)-1-(4-nitrophenyl)but-3-yn-1-yl acetate has been evaluated for the first time and helped to assess stereopreference of the studied BCL.

1. Introduction

The acetylenic derivatives play a fundamental role in organic chemistry as they constitute extremely valuable building blocks for synthesis of architecturally more complex compounds possessing broad spectrum of applications. The terminal ethylenic functional group is very reactive and highly useful in plethora of modern synthetic endeavors [1]. In this context, organic compounds bearing an acetylene unit are prone to undergo vast number of chemical transformations including: (i) additions of various molecules to carbon–carbon triple bond [i.e. halogens, hydrogen halides or cyanide, boranes, water in the presence of acids or Hg(II) salts, azides under copper(I)-catalyzed 1,3-dipolar cycloaddition (CuAAC) conditions], (ii) selective reductions of alkyne functionality into *Z*- or *E*-olefins or full reductions to paraffins, (iii) ozonolysis into carboxylic acids and classical (iv) alkylations and/or substitution with electrophyllic partners. Moreover, toward the propargyl moiety such reactions as: (v) crosscouplings (i.e. Castro-Stevens, Sonogashira, Cadiot-Chodkiewicz, etc.), (vi) cyclotrimerizations, (vii) silylformylation-allylsilylations, (viii) eneyne metathesis, and (ix) ring annulations can be accomplished as well.

Interestingly, terminal acetylenic functional group are a common structural motif found in many natural products originating from bacteria [mycomycin (**I**) [2–4]; cepacin B (**II**) [5]; smenothiazole B (**III**) [6,7]; apramides: A (**IV**) and G (**V**) [8]; jamaicamide B (**VI**) [9]; dragonamides: A (**VII**) [10,11], B [12] and E [13]; spongidepsin (**VIII**) [14–17]], plants [sterculynic acid (**IX**) [18]], marines [chondriol (**X**) [19]; rhodophytin (**XI**) [20]; *trans*-kumausyne (**XII**) [21,22]; dideoxypetrosynol A (**XIII**) [23,24]] and other nautical organisms such as cephalaspidean mollusk [kulolide (**XIV**) [25]] (Fig. 1). Since their biological activities are very interesting and well-documented, over the past few decades, there have been many elegant methodologies developed for the synthesis of the above-mentioned derivatives.

Moreover, among terminal acetylenic functionalities especially the propargylic moiety seems to be very important from the view-point of

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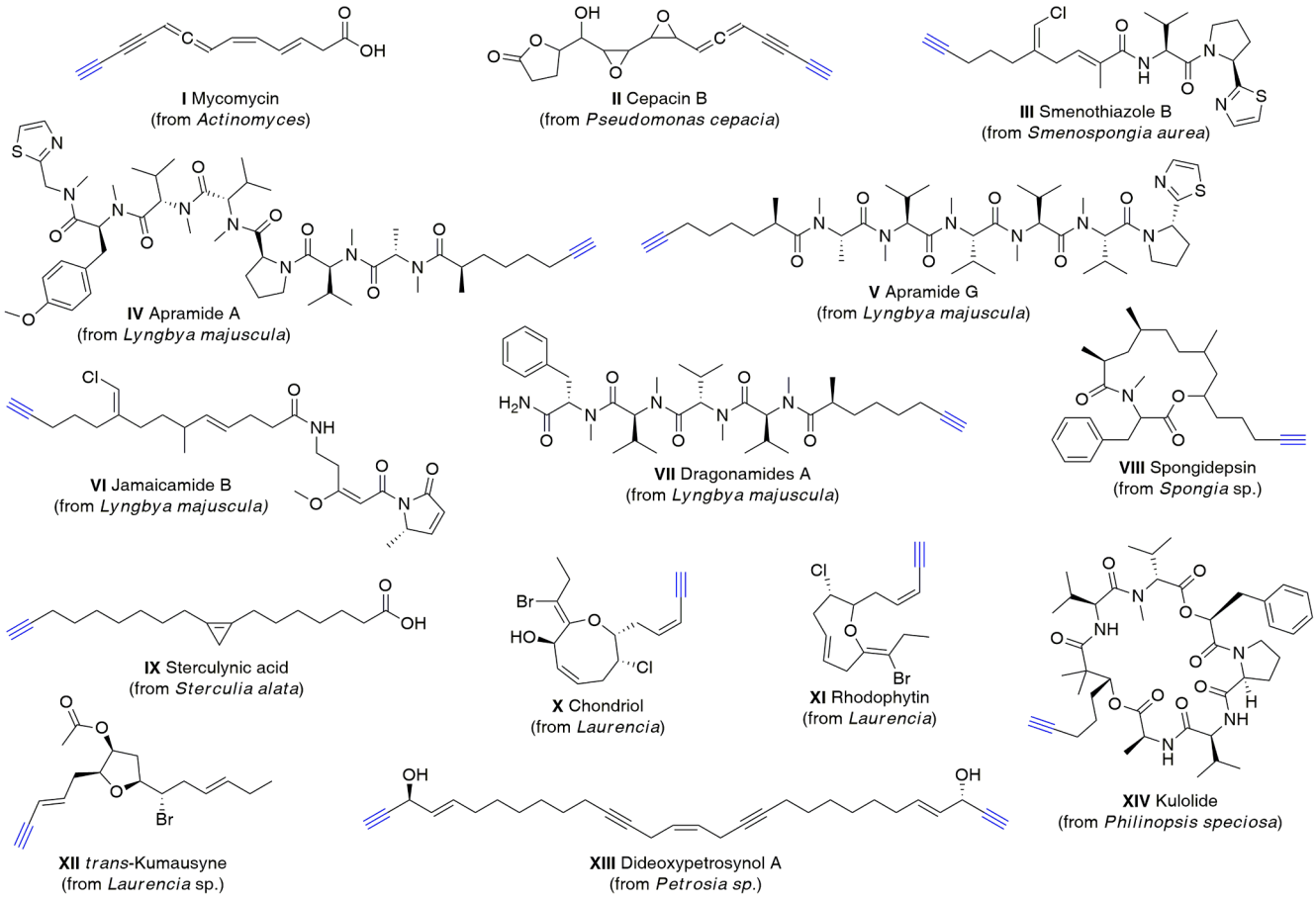


Fig. 1. Examples of natural products possessing terminal acetylenic functionality **I–XIV**.

biological activity. This stems from the fact that 2-propynyl group constitutes a privileged motif for numerous synthetic pharmaceuticals (Fig. 2, **XV–XIX**) and agrochemicals (Fig. 2, **XX–XVI**).

The most prominent examples reaching the blockbuster status in the pharma industry are the specific selective irreversible inhibitors of the mitochondrial isoenzymes of monoamine oxidase: type A (MAO-A) [clorgiline, **XVI** (*Clorgilinum*®)] and type B (MAO-B) [selegiline, **XV** (*Emsam*®, *Eldepryl*®, *Zelapar*®, etc.); pargyline, **XVII** (*Eutonyl*®); rasagiline, **XVIII** (*Azilect*®)], which are mainly used as medicines to treat symptoms in early Parkinson's disease. Besides the above-mentioned therapeutic agents, worth mentioning is the late-stage non-selective muscarinic acetylcholine receptor agonist [talsaclidine, **XIX** (*WAL-2014*)] developed for the treatment of Alzheimer's disease. The propargyl group can also be found in the chemical structures of various commercialized protoporphyrinogen-IX oxidase (PPO) inhibitors used worldwide to combat pathogens of arable crops. Among them so-called oomycetes fungicides [mandipropamid, **XX** (*Revus*®)] and peroxidizing herbicides [flumioxazin, **XXI** (*Pestanal*®); flumipropyn, **XXII** (*S 23121*®); oxadiargyl, **XXIII** (*Topstar*®); azafenidin, **XXIV** (*Azafenidin*®); thidiazimin, **XXV** (*UNII-Z1USL6USPO*®); pyrazogyl, **XXVI** (*AEB 172391*®)] deserve special attention.

Approximately more than 50% of all pharmaceuticals and agrochemicals comprise at least one stereogenic center [26–30]. Therefore, the current market of chiral drugs dramatically requires not only an efficient tool box (advanced '*chiral technologies*') to synthesize enantiomeric APIs in a facile manner on an industrial scale, but also a wide array of non-racemic building blocks obtainable in consistency with the restrictions imposed by regulatory agencies (i.e. FDA, EMA, etc.) [31,32]. One of such potentially useful chiral synthons for the synthesis of medicines are homopropagylic alcohols containing phenyl substituent. In turn, these compounds can be transformed into other valuable pharmaceutical intermediates, such as: 5-substituted dihydrofuran-3-ones (*via* gold-catalyzed reaction methodology) [33] or 2,3-dihydrofurans (*via* molybdenum-mediated cycloisomerization) [34] and 3,4-allenols (*via* Crabbé homologation) [35]. The optically active homopropargylic alcohols have been mostly synthesized through asymmetric addition of various nucleophilic regents [either a metalloallenes (i.e. allenyltri-*n*-butylstannanes [36–39], allenylboronic esters [40–44], allenyltrichlorosilane [45], 10-TMS-9-borabicyclo [3.3.2]decanes [46], allenylzinc [47]) or propargyls (i.e. propargyl halides in the presence of low-valent metal such as chromium [48,49] or indium [50,51], propargyl borolane [52], propargyldiisobutylaluminium [53])] to aldehydes in the presence of chiral catalysts or auxiliaries. Among chiral catalysts for enantioselective carbonyl propargylations the Lewis acids [i.e. BINOL–Ti(IV) complexes], Lewis bases (i.e. helical chiral 2,20-bipyridine *N*-monoxides) and Brønsted acids [i.e. BINOL–derived phosphoric acids (BINOL–PAs) and carboxylic acids] are the most common (see papers cited above [36–53]). In turn, catalysts composed of chiral aminoalcohols (i.e. pseudoephedrine) and diamines [i.e. (*S*)-1-[(1-methyl-2-pyrrolidinyl)methyl]piperidine] are willingly applied as well since especially aminoalcoholic ligands are low-cost, easy accessible and highly modular. A few other catalysts also proved to be effective for this transformation [i.e. tethered bis(8-quinolinato) (TBOx) chromium complex, Cr(II)-carbazole tridentate ligand complex, etc.] (also see the papers cited above [36–53]).

Nevertheless, the chirality inducement in the case of asymmetric prop-2-ynylation of aldehydes is often highly unsatisfactory (< 90% ee) and still remains challenge. Notable, most of the reported methods are also restricted by limitations concerning use of reagents that are relatively expensive, low-reactive, difficult to prepare, sensitive to air and/or moisture and often need post-reaction treatment of the crude mixture to remove some covalent additives (i.e. TMS ethers by TBAF, boranes by

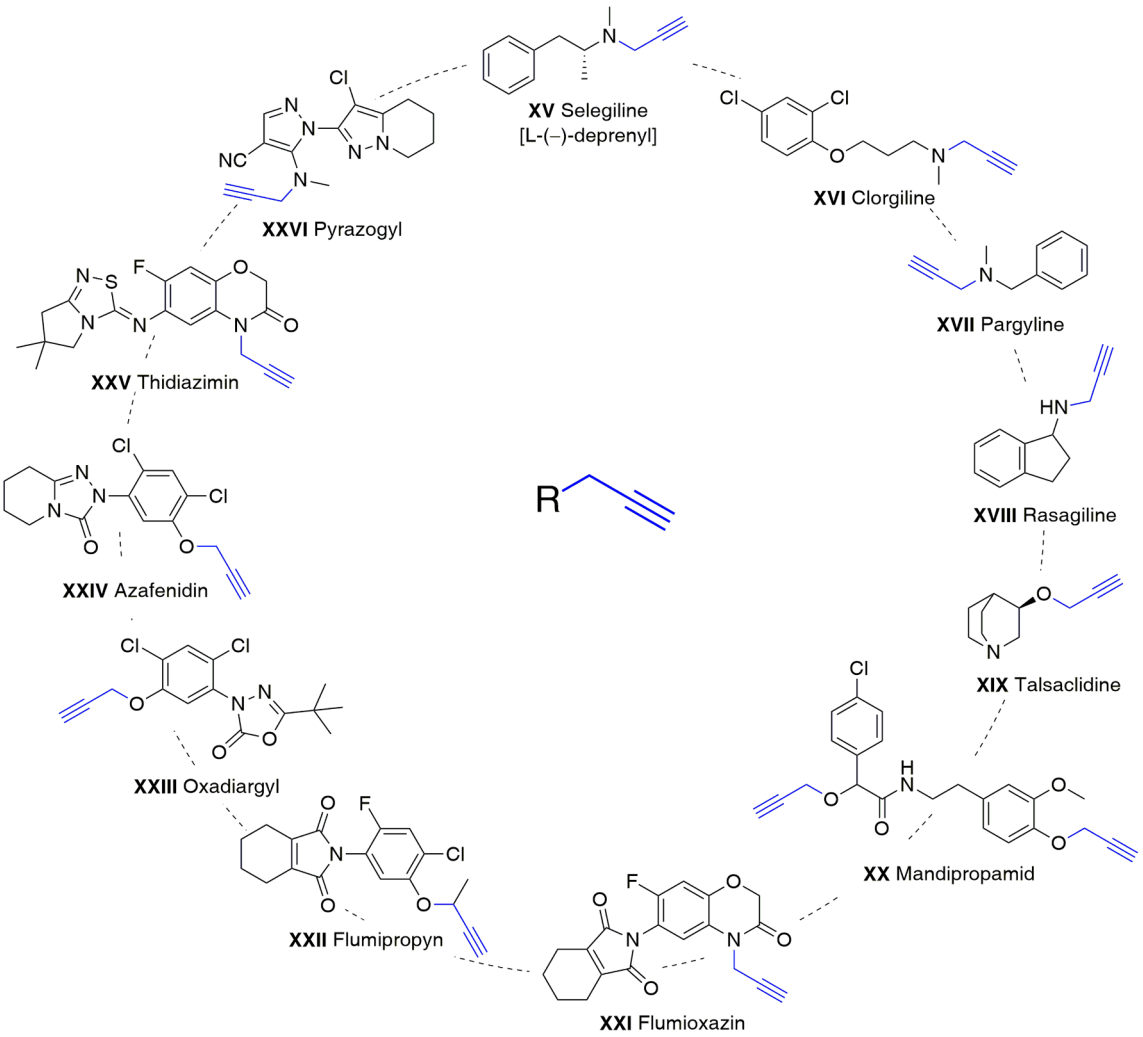


Fig. 2. Representative chemical structures of compounds with propargylic moiety used as pharmaceuticals (**XV–XIX**) and agrochemicals (**XX–XVI**).

H_2O_2/NaOH or $BF_3{\cdot}OEt_2$) from the propargylated products leading to tedious purifications. The difficulties associated with regioselectivity of propargylations concerning competing allenylation of carbonyl substrates is also arduous to circumvent. Moreover, employing chiral catalysts based on highly toxic metals largely deny the possibility of using thus-prepared synthons in manufacturing of pharmaceuticals. Therefore, the choice of lipases as catalysts for asymmetric functionalization of homopropargylic alcohols rests not only on practical considerations (particularly the ease of handling, stable to air/water and highly selective in action relative to the metal-based catalysts), but also on safety of usage (non-toxic and fully biodegradable).

In view of the considerable attention, which the above-mentioned alkynols have received from chemists all over the world as well as our continual interests in expanding the repertoire of biocatalytic approaches toward preparation of small-molecule chiral synthons valuable for pharmaceutical sciences, here we wish to report our new results on lipase-catalyzed enantioselective synthesis of non-racemic homopropargylic alcohols with excellent level of enantiomeric enrichment obtainable using simple kinetic resolution (KR) methodology.

2. Experimental section

General details concerning reagents, solvents, catalysts (enzymes) and methods used as well as analytical data for the obtained compounds are available in Supporting Information.

2.1. Synthesis

2.1.1. General procedure for the synthesis of racemic homopropargyl alcohols, rac-3a–i

The appropriate aldehyde **1a–i** (10 g) was added to H_2O (100 mL) containing KI (1.5 equiv), $SnCl_2$ dehydrate (1.5 equiv) and propargyl bromide (**2**) as 80 wt% in toluene solution (1.5 equiv). Next, after 10 min of stirring saturated aqueous NH_4Cl (70 mL) solution was added. The stirring was continued for 15 h at 35 °C. Further extraction with Et_2O (4 × 250 mL) gave an organic phase which was washed with H_2O (600 mL), brine (600 mL), and subsequently dried over anhydrous $MgSO_4$ and concentrated. The oily residue was chromatographed on silica gel by using two independent columns sequentially. At first, traces of the aldehydic substrate were removed by eluting with CH_2Cl_2/hexane (60:40, v/v) in accordance to dry column vacuum chromatography (DCVC) technique [54], and then pure product was obtained by eluting the second batch with a mixture of $CHCl_3$/acetone (99:1, v/v) as an eluent in a conventional column chromatography manner. The desired alcohols *rac*-**3a–i** were thus synthesized with 8–40% yield, respectively.

2.1.2. General procedure for the synthesis of racemic homopropargyl esters, rac-4a–i

To a solution of the racemic propargyl alcohol *rac*-**3a–i** (500 mg) in dry CH_2Cl_2 (5 mL), Et_3N (1.5 equiv) and catalytic amount of DMAP (15 mg) were added. Next, the mixture was cooled to 0–5 °C in the ice

bath, and one of the appropriate acyl chloride (1.5 equiv) dissolved in dry CH_2Cl_2 (2 mL) was added dropwise. Afterward, the cooling bath was removed, and the resulting mixture was stirred at room temperature for 12 h. The crude mixture was diluted with CH_2Cl_2 (10 mL), subsequently quenched with H_2O (20 mL), the water phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layer was washed with saturated water solution of $NaHCO_3$ (40 mL), brine (40 mL), and dried over anhydrous $MgSO_4$. After filtering of the drying agent, and evaporation of the residuals of solvent under reduced pressure the crude product was purified by double column chromatography on silica gel, at first, using mixture of $CHCl_3$/acetone (99:1, v/v), then using *n*-hexane/AcOEt (80:20, v/v) as eluent, thus obtaining desired esters *rac*-**4a–i**, *rac*-**5a** and *rac*-**6a** with 19–93% yield, respectively.

*2.1.3. General procedure for analytical-scale lipase-catalyzed KR of rac-**3a***

In a typical procedure, the model racemic alcohol *rac*-**3a** (25 mg, 0.17 mmol) was dissolved in organic solvent (500 μL), and subsequently, vinyl acetate (44 mg, 0.51 mmol, 47 μL) and the respective lipase preparation (10 mg, 40%, w/w) were added. Thus composed reaction mixture was stirred in thermo-stated glass vial (V = 4 mL) placed in anodized aluminum reaction block at 30 °C and 800 rpm. The progress of enzymatic kinetic resolution (EKR) process was monitored by GC and chiral HPLC analyses until the required conversion was achieved (ca. 50%). The samples were prepared by withdrawing the suspension (50 μL) from the reaction mixture, dilution it with portion of the respective organic solvent (500 μL), and centrifugation of the enzyme using laboratory centrifuge (6000 rpm). After evaporation of the volatiles from taken supernatant, the crude oil was dissolved in *n*-hexane-*i*-PrOH (1.5 mL, 3:1, v/v) and analysed by GC and HPLC. The same procedure was repeated with vinyl butanoate (59 mg, 0.51 mmol, 65 μL) and vinyl decanoate (102 mg, 0.51 mmol, 115 μL), but using catalytic system composed of Amano PS-IM (10 mg) suspended in $PhCH_3$ (500 μL).

*2.1.4. General procedure for preparative-scale lipase-catalyzed KR of rac-**3a–i***

To a solution of the respective racemic alcohol *rac*-**3a–i** (100 mg) in $PhCH_3$ (2 mL), vinyl acetate (3 equiv) and lipase Amano PS-IM (40 mg, 40%, w/w) were added at once. The enzymatic system was stirred in thermo-stated glass vial (V = 4 mL) placed in anodized aluminum reaction block at 30 °C and 800 rpm. The progress of EKR process was monitored by GC and chiral HPLC analyses and proceeded until the required conversion was achieved (ca. 50%). After removal of the enzyme by filtration on Schott funnel, washing it with portion of $PhCH_3$ (3 mL), and evaporation of the solvent under vacuum, the crude reaction mixture was purified by column chromatography on SiO_2 using mixture of $CHCl_3$/acetone (99:1 v/v) as an eluent to afford the respective EKR optically active products (*S*)-(−)-**3a–i** and (*R*)-(+)-**4a–i**.

*2.1.5. General procedure for hydrolysis of (R)-(+)-**4b** to establish its enantiomeric excess*

To a solution of optically active acetate (*R*)-(+)-**4b** (20 mg, 0.09 mmol, > 99% ee) in MeOH (2 mL) anhydrous K_2CO_3 (24 mg, 0.17 mmol) was added in one portion. The resulting mixture was stirred for 2 h at room temperature. Next, the volatiles were evaporated under vacuum, and the crude oil was diluted with CH_2Cl_2 (2 mL) and rinsed with H_2O (2 × 2 mL). The combined organic phase was dried over anhydrous $MgSO_4$, the drying agent was filtered off, and the permeate was concentrated under vacuum. Finally, the remaining crude oil was subjected to a short-pad SiO_2 column chromatography and purified using mixture of $CHCl_3$/acetone (99:1, v/v) as the eluent yielding enantiomeric (*R*)-(+)-**3b** (14 mg, 0.07 mmol, 86%, > 99% ee) as colorless oil.

2.1.6. X-ray structure

*2.1.6.1. Procedure of crystal growth of (R)-(+)-**4f**.* Colourless single crystal of sufficient quality for a structure analysis with conventional X-ray diffraction (XRD) method was prepared by dissolving (*R*)-(+)-**4f** (20 mg, 96% ee) in boiling $PhCH_3$ (1 mL). After refluxing the content of the flask for additional 5 min, the hot solution was slightly cooled, then transferred into glass vial (4 mL), tightly twisted, and left to cool to room temperature. Next, a screw cap was replaced by Parafilm "M"® appropriately perforated by needle to obtain single tiny hole in the center of its' surface. The system was stored at room temperature, and crystal growth was allowed to proceed for 14 days by slow evaporation of the solvent.

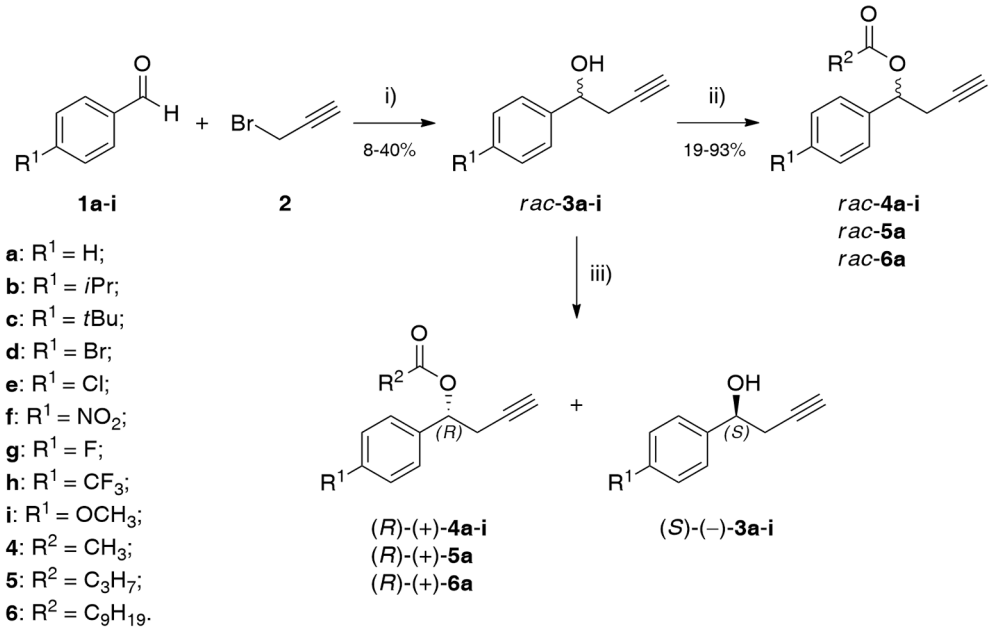
*2.1.6.2. Crystal structure determination of (R)-(+)-**4f**.* Single crystal of (*R*)-(+)-**4f**, suitable for X-ray diffraction studies were selected under polarizing microscope and measured with mirror monochromated CuKα radiation on an Oxford Diffraction κ-CCD Gemini A Ultra diffractometer. Cell refinement, data collection and data reduction were performed with the CRYSALIS^{PRO} software [55]. Using Olex2 [56], the structure was solved with the ShelXT [57] structure solution program and refined with the SHELXL − 2018 [58] refinement package using Least Squares minimization. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms attached to carbon atoms were added to the structure model at geometrically idealized coordinates and refined as riding atoms. An absolute configuration (*R*) for the compound molecule (+)-**4f** was determined using anomalous dispersion effects. Flack parameter [59] calculated from 694 selected quotients (Parsons' method) [60] equals − 0.09(18). Further analysis of the absolute structure was performed using likelihood methods with PLATON [61]. A total of 842 Bijvoet pairs (coverage of 1.00) were included in the calculations. The resulting value of the Hooft parameter [62] was −0.01(16). **Crystal Data** for $C_{12}H_{11}NO_4$ (M = 233.22 g/mol): orthorhombic, space group $P2_12_12_1$, a = 7.1787(3) Å, b = 8.0720(3) Å, c = 20.0382(7) Å, V = 1161.16(7) Å^3, Z = 4, T = 293.0(1) K, μ(CuKα) = 0.853 mm^{-1}, $Dcalc$ = 1.334 g/cm^3, 6067 reflections measured (11.82° ≤ 2Θ ≤ 134.192°), 2072 unique (R_{int} = 0.0594, R_{sigma} = 0.0508) which were used in all calculations. The final R_1 was 0.0457 (I > 2σ(I)) and wR_2 was 0.1236 (all data). CCDC 1,880,174 contains the supplementary crystallographic data for compound (*R*)-(+)-**4f**. This can be obtained free of charge on application to CDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: (+44)1223-336-033; email: deposit@ccdc.cam.ac.uk). The Crystal data and structure refinement parameters for (*R*)-(+)-**4f** can be found in Table S1 in Supplementary material.

3. Results and discussion

In this work, our principal desire was to broaden the scope and generality of lipase-catalyzed kinetic resolution (KR) of 1-*para*-substituted-phenylbut-3-yn-1-ols. In this regard, our efforts focused on chemoenzymatic synthesis of enantiomerically enriched homopropargylic alcohols **3a–i** consisting of KR methodology as a key step. The synthetic pathway is outlined below (Scheme 1).

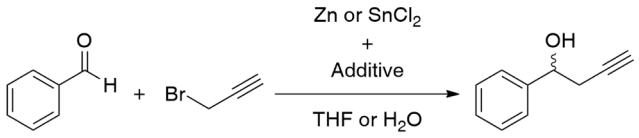
*3.1. Synthesis of the racemic starting materials, rac-**3a–i***

In the first step, the requisite racemic alkynols *rac*-**3a–i** were planned to be prepared through routine coupling of propargyl bromide (**2**) with a suitably functionalized benzaldehyde derivatives **1a–i** promoted by the respective metal. Hitherto so-called Barbier-type propargylation of the carbonyl compounds has been thoroughly studied and even reported in a comprehensive review article [63], however, each year novel improved modifications of this reaction appear. Hence, from a wide repertoire of available synthetic protocols, we have initially limited our investigations toward those, which employs zinc as the mediator. This was due to the fact that zinc is significantly less harmful for environment and human life when compared to lead, indium, tin, aluminum, gallium or other metals commonly used in such



Scheme 1. Lipase-catalyzed KR of racemic homopropargyl alcohols *rac*-**3a–i**. Reagents and conditions: (i) **2** as 80 wt% in $PhCH_3$ solution (1.5 equiv), KI (1.5 equiv), $SnCl_2$ (1.5 equiv), H_2O, 10 min at RT, aq. $NH_4Cl_{sat.}$, then 15 h at 35 °C; (ii) acyl chloride (1.5 equiv), Et_3N (1.5 equiv), DMAP (cat.), dry CH_2Cl_2, 10 min at 0–5 °C, then 12 h at RT; (iii) vinyl ester (3 equiv), lipase (40% w/w), organic solvent (1 mL/50 mg of substrate), 4–24 h at 30 °C, 800 rpm (magnetic stirrer).

Table 1
Synthesis of *rac*-**3a** *via* Barbier-type propargylation of benzaldehyde (**1a**) performed at 1 g-scale.



Entry	Propargyl bromide[a]	Zn[b]	$SnCl_2$[c]	Additive	Solvent	*t* [h]	*T* [°C]	Yield[d] [%]	Ref.
1	1 eq	1 eq	–	aq. $NH_4Cl_{sat.}$	THF	4	RT	20	[64]
2	1.5 eq	5 eq	–	aq. $NH_4Cl_{sat.}$	THF	24	RT	56[e]	[56]
3	1.3 eq	3 eq	–	aq. $CaCl_{2sat.}$ + aq. $NH_4Cl_{sat.}$	THF	1	RT	69[e]	[65]
4	1.5 eq	–	1.5 eq	TBABr[f] (0.3 eq)	H_2O	8	50	12	[66]
5	1.5 eq	–	1.5 eq	aq. $NH_4Cl_{sat.}$ + KI (1.5 eq)	H_2O	15	35	38	[67]

[a] 80 wt% in toluene.
[b] Granulated zinc was used.
[c] Anhydrous $SnCl_2$ was used.
[d] Isolated yield after column chromatography.
[e] Contaminated in ca. 10% (w/w) with forming an allenic by-product in accordance to gas chromatography (GC) indications.
[f] Tetrabutylammonium bromide.

couplings. In this regard, we examined a few Zn-mediated Barbier-type conditions toward model benzaldehyde **1a** using propargyl bromide (**2**) as 80 wt% in $PhCH_3$ solution and various additives in THF as solvent (see Table 1, entries 1–3). Unfortunately, in the first attempt using equimolar amounts of all reagents, the product *rac*-**3a** was isolated in very low 20% yield. After detailed examination of the available literature, we came across that the low reaction yields with granulated zinc might be due to the fact that a surface process is involved.

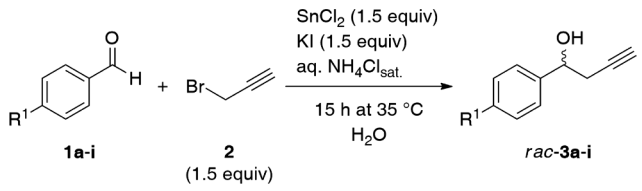
Therefore, to overcome this inconvenience, we decided to increase molar excess of zinc metal and propargylating agent **2** up to 5 equiv and 1.5 equiv, respectively. Successfully, this simple stoichiometric ratio adjustment as well as elongation of the reaction time up to 24 h revealed some improvement in the reaction yield (56%). However, it turned out that the desired Barbier adduct *rac*-**3a** was contaminated with an allenic by-product, which is inseparable *via* the convenient SiO_2-column chromatography, as the close proximity of these two alcohols induce similar physical properties furnishing the same R_f -value. In the next attempt to obtain *rac*-**3a**, we have followed procedure reported by Bieber et al. [65]. A slightly decreased amounts of both **2** and metallic zinc as well as additional utilization of saturated aqueous $CaCl_2$ solution have led to obtain product *rac*-**3a** in good 69% yield after just 1 h. Unfortunately, in this case the propargylation conditions also rendered very low regioselectivity because the corresponding allenol was detected at similar level of contamination as before. Since a significant quantities of hard-to-eliminate allenic alcohol were formed during the above-mentioned attempts, next we adopted purification procedure elaborated by Fu et al. [68]. This simple method is based on selective precipitation of homopropargylic alcohol in the presence of corresponding allenol accomplished by using equimolar mixture of $AgNO_3$ and $CaCO_3$ in aqueous acetone. In our hand, the separation protocol was only partially efficient as after treatment of the filtered-off precipitant with 1 M HCl the silver acetylide species hydrolysed to *rac*-**3a**, however, traces of allenic alcohol still remained in the solution. It was probably because of allenol being trapped in the precipitate or wrongly adjusted stoichiometry toward side-product. After repeating two-fold precipitation procedure the overall reaction's yield dropped

significantly (approx. by half of the initial value), and thus we finally abandoned ($AgNO_3$-$CaCO_3$)-based purification method. This disappointing observation led us to change our synthetic strategy once again. In aiming to suppress the metallotropic rearrangement between propargyl and allenyl species (responsible for the formation of allenic by-product) we have tested stannous chloride ($SnCl_2$) as the mediator instead of Zn and excluded organic solvent from the reaction medium. Inspired by paper published by Masuyama and co-workers [66], in the first trial we used equimolar quantities of **2** and anhydrous $SnCl_2$ in presence of 0.3 equiv of TBABr. In the course of this reaction the starting material **1a** was totally converted into the corresponding alcohol *rac*-**3a** after 8 h of stirring the mixture at 50 °C. However, the yield of propargylation was very poor (12%) as the complex mixture of by-products was formed. Nevertheless, contribution of allenic alcohol in overall contamination was marginal, and thus at that point, we turned our efforts toward modifications of $SnCl_2$-mediated Barbier reaction. Hopefully, when the reaction was assisted by addition of 1.5 equiv of KI and aq. $NH_4Cl_{sat.}$ instead of TBABr/H_2O, the desired propargylic adduct *rac*-**3a** (completely free from allenic alcohol !!!) could be isolated in an improved 38% yield. As this method turned out to be superior to others especially in terms of reaction's regioselectivity, therefore, a set of racemic phenyl-1-alkynols *rac*-**3a–i** having varying functional group diversity, such as: −*i*Pr, −*t*Bu, −Br, −Cl, $-NO_2$, −F, $-CF_3$ and $-OCH_3$, at the *para*-position of the phenyl ring have been synthesized at 10 g-scale using the commercially available and cheap arenecarbaldehydes **1a–i** as starting material (Table 2). Gratifyingly, the conducted reactions resulted in a similarly high selectivity albeit with poor to moderate isolated yields (8–40%) of the racemic alcohols *rac*-**3a–i**. It turned out that especially synthesis of *rac*-**3f** is challenging as in this case a parallel $SnCl_2$-mediated reduction of the nitro group was observed. In conclusion, although the efficiency of the employed method is significantly limited due to the formation of ca. 14-component reaction mixture (according to GC) that hinders isolation of desired products *rac*-**3a–i**, we did not optimize it further as it was not our major goal.

3.2. Synthesis of the racemic analytical standards, rac-4a–i

As per our planned strategy, the synthesis of racemic esters required as an analytical standards for enzymatic reactions was performed. The respective racemic acetates *rac*-**4a–i** as well as single butyrate *rac*-**5a** and decanoate *rac*-**6a** were obtained from the corresponding alcohols

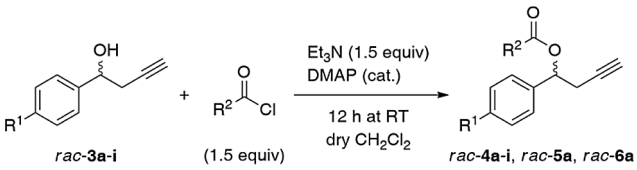
Table 2
Synthesis of the racemic homopropargyl alcohols *rac*-**3a–i** performed at 10 g-scale.



Entry	Product	R^1	Yield[a] [%]
1	*rac*-**3a**	H	33
2	*rac*-**3b**	*i*Pr	11
3	*rac*-**3c**	*t*Bu	20
4	*rac*-**3d**	Br	40
5	*rac*-**3e**	Cl	23
6	*rac*-**3f**	NO_2	8
7	*rac*-**3g**	F	31
8	*rac*-**3h**	CF_3	29
9	*rac*-**3i**	OCH_3	13

[a] Isolated yield after column chromatography.

Table 3
Synthesis of the racemic esters *rac*-**4a–i**, *rac*-**5a** and *rac*-**6a**.



Entry	Product	R^1	R^2	Yield[a] [%]
1	*rac*-**4a**	H	CH_3	26
2	*rac*-**5a**	H	C_3H_7	33
3	*rac*-**6a**	H	C_9H_{19}	28
4	*rac*-**4b**	*i*Pr	CH_3	30
5	*rac*-**4c**	*t*Bu	CH_3	19
6	*rac*-**4d**	Br	CH_3	20
7	*rac*-**4e**	Cl	CH_3	70
8	*rac*-**4f**	NO_2	CH_3	49
9	*rac*-**4 g**	F	CH_3	83
10	*rac*-**4 h**	CF_3	CH_3	93
11	*rac*-**4i**	OCH_3	CH_3	20

[a] Isolated yield after column chromatography.

rac-**3a–i** by standard DMAP-catalyzed acylation using 1.5 equiv of acyl chlorides, excess of Et_3N as a base trapping the hydrochloric acid formed, and dry CH_2Cl_2 as the solvent. The representative results are summarized in Table 3.

Surprisingly, most of the esterification reactions gave ester products in poor-to-moderate yields (19–49%), and therefore it was postulated that homopropagylic compounds are likely to be base-sensitive and/or prone to be acylated at terminal acetylenic group as well. Only three derivatives bearing the following −Cl, −F and $-CF_3$ substituent seemed to be resistant toward dual amine mixture (Et_3N/DMAP) as good-to-excellent yields (70–93%) in their cases could be obtained. It is worth to underline that most of the prepared esters (i.e. *rac*-**6a** and *rac*-**4b–i**) had never been synthesized.

With a set of racemic alcohols *rac*-**3a–i** and esters *rac*-**4a–i**, *rac*-**5a** and *rac*-**6a** in hand, our next task was to elaborate analytical methods (GC and HPLC) for enzymatic experiments. In particular, it was important to set up a reliable chiral HPLC method, able to follow the reactions directly, and to improve the synthetic performances of lipase-catalyzed reactions. In this context, we developed peculiar chiral HPLC methods (giving a good baseline separation) for model substrate *rac*-**3a** and its corresponding esters *rac*-**4a**, *rac*-**5a** and *rac*-**6a** in order to resolve the enantiomers directly from the crude mixtures in a single run, allowing to define the enantiomeric excess, and fully characterize enantioselectivity of the performed reactions very fast (see Supplementary material). Fortunately, no interference was observed at the retention times of interest among model substrate *rac*-**3a** and its esters. For the rest of the substrates *rac*-**3b–i** and their acetates *rac*-**4b–i** we elaborated chiral-stationary-phase HPLC conditions for individual racemates and not for the mixtures of both pairs of respective alcohol and ester enantiomers. It is worth to mention that one of the synthesized racemic acetates, that is: 1-[4-(propan-2-yl)phenyl]but-3-yn-1-yl acetate (*rac*-**4b**), had to be hydrolyzed before HPLC analysis due to lack of peaks separation of this derivative in the chromatograms when using available by us chiral columns [Chiralcel OD-H and Chiralpak AD-H].

3.3. KR of rac-3a–i using lipase-catalyzed transesterification

Although lipases are the catalysts of choice when ones desire to proceed kinetic enantiomeric resolution of chiral alcohols, very little is reported with regard to lipase-catalyzed separation of the racemic homopropargylic *sec*-alcohols. To the best of our knowledge, the report by Burgess and co-workers [69] is the only example of the use of lipases

toward synthesis of enantiomerically enriched phenyl-substituted alkynyl alcohols, and is limited only to kinetic resolution (KR) of racemic 1-phenylbut-3-yn-1-ol (*rac*-**3a**), which resulted in moderate level of enantioselectivity ($E = 28$) yielding optically active alcohol (*S*)-(−)-**3a** in > 95% ee and the respective acetate (*R*)-(−)-**4a** in moderate 72% ee. In this case it was native lipase from *Pseudomonas fluorescens* (Amano AK) that was used as biocatalysts for the studied transformations of *rac*-**3a**. The other enzymatic example of enantiomeric resolution of 1-phenylbut-3-yn-1-ol (*rac*-**3a**) was published by Prof. Herradon's research group [70]. However, this report concerns enantioselective transesterification of *rac*-**3a** using acylase I (AA-I) as biocatalyst instead of the lipase. Nevertheless, this method was also far from optimal ($E = 89$) allowing to obtain enantioenriched alcohol (*S*)-(−)-**3a** in 95% ee and the corresponding optically active butyrate (*R*)-(−)-**4a** in 92% ee. The rest of the literature reports turned to lipases' performances were focused rather on 2-heteroaryl substituted homopropargyl alcohols [71–73] or their aliphatic derivatives [74]. In example, Takano et al. [75] reported (lipase PS)-catalyzed resolution of 4-hydroxy-5(4-methoxyphenoxy)-1-pentyne, however, regardless of high optical purity of both KR products obtained, disadvantages of this reaction which limits this procedure of being preparative are hazardous CH_2Cl_2 used as the solvent and long reaction time (4 days).

Therefore, in this paper we turned our attention to novel and more efficient lipase-catalyzed kinetic resolution of titled homopropargylic alcohols *rac*-**3a–i**. We decided to perform those enzymatic transformations in a transesterification mode using vinyl esters as the acylating agents. It was made by us deliberately since non-aqueous variant of KR process is more desirable from industrial point of view due to less harmful isolation procedure. In the first step of analytical-scale enzymatic studies we performed an extensive screening of 17 commercial enzyme preparations including lipases and one esterase (pig liver esterase, PLE) to identify a lead candidate biocatalyst for the enantioselective acetylation (Table 4). The enzymes were tested in a model reaction comprising a racemic substrate *rac*-**3a** used at 25-mg scale in a solution of 3 equiv of vinyl acetate as an acetyl group donor and *tert*-butyl methyl ether (TBME) as solvent frequently used in lipase-catalyzed reactions, and stirred at 30 °C using a magnetic stirrer. All the assays were regularly traced by GC and HPLC analyses and finally arrested either upon 50% conversion was reached or 24 h have passed. These reaction conditions allowed us a clear characterization of the behaviour of the different biocatalysts of various bacterial, fungal and mammalian origin.

Table 4
Enzyme screening for enantioselective transesterification of *rac*-**3a** under KR-conditions in TBME.

Entry	Enzyme preparation[a]	*t* [h]	Conv.[b] [%]	ee_s[c] [%]	ee_p[c] [%]	*E*[d]
1	Novozym 435	24	14	16	99	233
2	Lipozyme 435	24	15	17	99	235
3	Chirazyme L-2, C-2	24	< 5	N.D.[e]	N.D.[e]	N.D.[e]
4	Chirazyme L-2, C-3	24	< 5	N.D.[e]	N.D.[e]	N.D.[e]
5	TL-Immobead 150	24	< 1	N.D.[e]	N.D.[e]	N.D.[e]
6	Lipozyme TL IM	24	30	43	98	151
7	Lipozyme RM IM	24	0	N.D.[e]	N.D.[e]	N.D.[e]
8	PS-Immobead 150	24	20	24	> 99	252
9	Amano PS-IM	24	49	96	98	392
10	Amano PS-C II	4	50	99	98	922
11	Chirazyme L-10	24	58	98	72	27
12	Amano PS	24	26	35	> 99	280
13	Amano Lipase M	24	0	N.D.[e]	N.D.[e]	N.D.[e]
14	Amano AK	24	37	56	94	57
15	Amano Lipase F-AP15	24	< 1	N.D.[e]	N.D.[e]	N.D.[e]
16	Lipase AY Amano 30	24	< 1	N.D.[e]	N.D.[e]	N.D.[e]
17	PLE	24	< 3	N.D.[e]	N.D.[e]	N.D.[e]

[a] Conditions: *rac*-**3a** 25 mg, lipase 10 mg, TBME 500 μL, vinyl acetate 44 mg, 53 μL (3 equiv), 30 °C, 800 rpm (magnetic stirrer).

[b] Based on GC, for confirmation the % conversion was calculated from the enantiomeric excess of the unreacted alcohol (ee_s) and the product (ee_p) according to the formula conv. = $ee_s/(ee_s + ee_p)$.

[c] Determined by chiral HPLC analysis by using a Chiralcel OD-H column.

[d] Calculated according to Chen *et al.* [76], using the equation: $E = \{\ln[(1 - conv.)(1 - ee_s)]\}/\{\ln[(1 - conv.)(1 + ee_s)]\}$.

[e] Not determined due to a low conversion rate.

From the first set of experiments it turned out that limited number of the studied enzymes were suitable for the enantioselective acetylation of *rac*-**3a**. Unfortunately, most of them were completely inactive (i.e. Lipozyme RM IM and Amano Lipase M) or remained a residual activity (i.e. Chirazyme L-2, C-2, Chirazyme L-2, C-3, TL-Immobead 150, Amano Lipase F-AP15, Lipase AY Amano 30, and PLE). In turn, lipases from *Candida antartica* type B immobilized on acrylic resins (Novozym 435 and Lipozyme 435) catalyzed *rac*-**3a** enantiomers' resolution with excellent enantioselectivity ($E > 200$) resulting in the formation of almost enantiomerically pure acetate (*R*)-(+)-**4a** (99% ee), nevertheless, the rates of reactions were very poor as the conversion reached only approx. 15% after 24 h, and thus the remaining alcohol (*S*)-(−)-**3a** was isolated with significantly diminished enantiomeric excesses (16–17% ee). An improved activity toward the racemic substrate *rac*-**3a**, albeit still moderate, exhibited the subsequent enzyme preparations: Lipozyme TL IM, PS-Immobead 150, Amano PS, and Amano AK. It is worth to mention that among them especially PS-Immobead 150 and Amano PS catalyzed KR of *rac*-**3a** with superb enantioselectivity ($E > 250$) leading to isolation of enantiomerically pure ester (*R*)-(+)-**4a** (> 99% ee), however, only unsatisfactory 20–26% conversions could be afforded in those cases, and thus the slower reacting enantiomer (*S*)-(−)-**3a** was afforded with moderate 24–35% ee. Surprisingly, in contrary to the results reported in the literature [69], in our hands Amano AK turned out to be slightly more efficient in terms of enantioselectivity ($E = 57$) than in the paper published by Burgess et al. ($E = 28$), however, enantiomeric excesses of KR products were still unsatisfactory. To our delight, the enzyme screening procedure revealed that other two immobilized preparations based on lipase from *Burckholderia cepacia* (BCL) and one native lipase from *Alcaligenes* sp. (ASL) were the most promising in terms of reaction rate and enantioselectivity. In example, BCL immobilized on diatomaceous earth (Amano PS-IM) exhibited high activity reaching 49% conversion after 24 h, thus allowing isolation of both KR products in highly enantiomerically enriched forms (96–98% ee). Notably, BCL immobilized on ceramic (Amano PS-C II) was even more efficient in the enantioselective acylation of *rac*-**3a** allowing 50% conversion to be achieved after amazingly short reaction time (just 4 h) almost without any decrease of the enantiomeric selectivity in KR manner. In this context, (Amano PS-C II)-catalyzed KR of *rac*-**3a** yielded homochiral alcohol (*S*)-(−)-**3a** (> 99% ee) and the forming optically active acetate (*R*)-(+)-**4a** (98% ee) with close to the highest enantioselectivity value ($E = 922$). In turn, Chirazyme L-10 although catalyzed resolution of model *rac*-**3a** with moderate enantioselectivity ($E = 27$), it allowed to obtain (*S*)-(−)-**3a** with 98% ee. As the highest activity and stereoselectivity discrimination during the transesterification process of *rac*-**3a** was observed in the case of Amano PS-C II, Amano PS-IM and Chirazyme L-10, both BCL and Chirazyme L-10 lipase preparations were selected for further optimization studies. It is also interesting to note that all the enzymatic reactions proceeded very cleanly without the formation of propargyl–allenyl isomerization by-products.

In general, the nature of the reaction medium has been known to hold strong influences on the catalytic performance of the enzymes mainly due to modulation of biocatalysts' enantioselectivity and stability. Therefore, evaluation of the solvent impact on reaction rate and stereochemical outcome should always be taken into account as one of the most critical factor for biocatalysis. Similarly to the reaction conditions used in our previous contribution, the effect of the solvent on the BCL- and ASL-catalyzed enantioselective transesterification of model racemic substrate *rac*-**3a** was studied in detail (Table 5). In this regard, several organic solvents characterized by different log*P* (0.20–3.00) values were employed. To obtain comparable results we

Table 5
Solvent screening for enantioselective transesterification of *rac*-**3a** with vinyl acetate catalyzed by immobilized lipases from *Burckholderia cepacia* (Amano PS-IM or Amano PS-C II) and native lipase from *Alcaligenes* sp. (Chirazyme L-10) under KR conditions.

Entry	Lipase[a]	Solvent (log *P*)[b]	*t* [h]	Conv.[c] [%]	ee_s[d] [%]	ee_p[d] [%]	*E*[e]
1	Amano PS-IM	Acetone (0.20)	24	25	33	> 99	275
2		THF (0.40)	24	24	32	> 99	272
3		TBME (0.96)[f]	24	49	96	98	392
4		*t*-Amyl alcohol (1.09)	24	48	91	99	637
5		Cyclohexane (2.50)	24	51	> 99	97	348
6		$PhCH_3$ (2.52)	24	48	91	> 99	637
7		Hexane (3.00)	24	50	97	98	420
8	Amano PS-C II	Acetone (0.20)	4	14	16	> 99	233
9		THF (0.40)	4	16	19	> 99	240
10		TBME (0.96) [f]	4	50	99	98	922
11		*t*-Amyl alcohol (1.09)	4	38	60	> 99	368
12		Cyclohexane (2.50)	4	50	97	96	207
13		$PhCH_3$ (2.52)	4	46	84	> 99	532
14		Hexane (3.00)	4	51	99	96	259
15	Chirazyme L-10	Acetone (0.20)	24	24	30	94	43
16		THF (0.40)	24	28	36	93	39
17		TBME (0.96)[f]	24	58	98	72	27
18		*t*-Amyl alcohol (1.09)	24	55	89	72	18
19		Cyclohexane (2.50)	24	70	> 99	42	11
20		$PhCH_3$ (2.52)	24	59	99	68	26
21		Hexane (3.00)	24	66	> 99	51	15

[a] Conditions: *rac*-**3a** 25 mg, lipase 10 mg, organic solvent 500 μL, vinyl acetate 44 mg, 47 μL (3 equiv), 30 °C, 800 rpm (magnetic stirrer).
[b] Logarithm of the partition coefficient of a given solvent between *n*-octanol and water according to ChemBioDraw Ultra 13.0 software indications.
[c] Based on GC, for confirmation the % conversion was calculated from the enantiomeric excess of the unreacted alcohol (ee_s) and the product (ee_p) according to the formula conv. = $ee_s/(ee_s + ee_p)$.
[d] Determined by chiral HPLC analysis by using a Chiralcel OD-H column.
[e] Calculated according to Chen et al. [76], using the equation: $E = \{\ln[(1 - conv.)(1 - ee_s)]\}/\{\ln[(1 - conv.)(1 + ee_s)]\}$.
[f] The results were taken from Table 1 for comparison.

decided to carry out the KR reactions deliberately for 24 h (in the case of Amano PS-IM and Chirazyme L-10) and 4 h (in the case of Amano PS-C II), respectively. Of all these solvents used, different non-polar, water-immiscible solvents such as already tested TBME as well as 2-methyl-2-butanol (*t*-amyl alcohol), cyclohexane, toluene ($PhCH_3$) and hexane gave the best conversion of starting material *rac*-**3a**. In turn, when both biocatalysts were suspended in polar and/or water-miscible solvents [acetone or tetrahydrofuran (THF)] then lipases maintained modest activity (barely 14–28% conversion could be achieved depending on KR conditions), thus furnishing slower-reacting enantiomer (*S*)-(−)-**3a** with inferior ee-values (up to 33%). As shown in Table 5, lipase Amano PS-C II suspended in TBME appeared to be superior to the majority of other tested catalytic systems as furnishing astonishing enantiomeric resolution of the model racemate *rac*-**3a** resulting in almost single enantiomers: (*S*)-(−)-**3a** (> 99% ee) and (*R*)-(+)-**4a** (98% ee). Interestingly, Amano PS-C II was also very efficient in cyclohexane and hexane while both resolution products could be afforded with excellent enantiomeric excess (96–99%).

Although Amano PS-C II turned out to be ultra-selective catalyst toward resolution of *rac*-**3a** enantiomers, we did not chose this lipase for further enzymatic investigations, as it has been already withdrawn from the offer of commercial suppliers, and optimization of the preparative-scale reactions based on it would be useless from the viewpoint of potential industrialization of such process. Moreover, if we considered seriously DKR approach, very active biocatalysts such as Amano PS-C II were not favorable. This obviously stems from the fact that for successful DKR, the enantiomers' resolution rate should never exceed the racemization rate too much, to avoid depletion of the resolved enantiomer as this could result in an decrease of the ester reaction product's enantiomeric purity. In turn, Chirazyme L-10 was excluded from further enzymatic studies from similar reason as the Amano PS-C II lipase (it is no longer commercially available) as well as because it furnished aggravated results in terms of enantioselectivity values (*E* = 11–43).

Although one can see that Amano PS-IM catalyzed transestrification of *rac*-**3a** very selectively in TBME, cyclohexane, and hexane leading to isolation of the remaining alcohol (*S*)-(−)-**3a** in 96–100% ee range and the forming acetate (*R*)-(+)-**4a** in 97–98% ee, however, it was *t*-amyl alcohol and $PhCH_3$, which furnished the most enantioselective (*E* = 637) transformations. Moreover, reactions conducted in $PhCH_3$ showed a slight increase of enantiomeric excess of (*R*)-(+)-**4a** (> 99% ee) compared to that performed in *t*-amyl alcohol, in which the formation of optically active acetate (*R*)-(+)-**4a** was afforded with 99% ee. Taking into account all the above results as well as utility in DKR approach, we found $PhCH_3$ more suitable as the reaction medium for the further screening experiments and potential DKR application.

Another variable parameter, which often play a pivotal role on enantioselectivity and reaction rate is the type of the acyl group donor reagent. Among vinyl esters highly applicable in KR approaches, those which acidic parts consist of long aliphatic (fatty) chain is desirable as their employment often leads to an impressive enhancement of the catalytic activity and stereoselectivity of lipases in transestrification reactions. Therefore, in the next set of experiments three different vinyl esters were used: vinyl acetate, vinyl butanoate, and vinyl decanoate (Table 6).

The influence of alteration of chain length in the acylating agent's acidic moiety on the course of the racemic alcohol *rac*-**3a** transestrification was examined using 3 equiv of the appropriate vinyl ester under catalysis of Amano PS-IM suspended in $PhCH_3$ as solvent. Consideration of the results summarized in Table 6 leads to the conclusion that reactivity and enantioselectivity were hardly affected by the nature of vinyl ester. All the examined acyl group donors behaved in a similar manner except that the reaction was slightly slower in the case of vinyl butanoate affording only 43% conversion. Moreover, as evidenced by HPLC the performance of Amano PS-IM in $PhCH_3$ under influence of various vinyl esters remained constant and mostly lead to highly selective transformations (*E* = 354–637) of the racemic starting material *rac*-**3a** into optically active esters (*R*)-(+)-**4a**, (*R*)-(+)-**5a** and (*R*)-

Table 6
The acyl donor reagent screening for (Amano PS-IM)-catalyzed KR of *rac*-**3a** in $PhCH_3$ after 24 h.

Entry	Acyl donor reagent	Conv.[a] [%]	ee_s[b] [%]	ee_p[b] [%]	*E*[c]
1	Vinyl acetate [d]	48	91	> 99	637
2	Vinyl butanoate [e]	43	76	> 99	459
3	Vinyl decanoate [f]	49	94	98	354

[a] Based on GC, for confirmation the % conversion was calculated from the enantiomeric excess of the unreacted alcohol (ee_s) and the product (ee_p) according to the formula conv. = $ee_s/(ee_s + ee_p)$.
[b] Determined by chiral HPLC analysis by using a Chiralcel OD-H column.
[c] Calculated according to Chen *et al.* [76], using the equation: $E = \{\ln[(1 - conv.)(1 - ee_s)]\}/\{\ln[(1 - conv.)(1 + ee_s)]\}$.
[d] Conditions: *rac*-**3a** 25 mg, Amano PS-IM 10 mg, $PhCH_3$ 500 µL, vinyl acetate 44 mg, 47 µL (3 equiv), 30 °C, 800 rpm (magnetic stirrer). The results were taken from Table 5 for comparison.
[e] Conditions: *rac*-**3a** 25 mg, Amano PS-IM 10 mg, $PhCH_3$ 500 µL, vinyl butanoate 59 mg, 65 µL (3 equiv), 30 °C, 800 rpm (magnetic stirrer).
[f] Conditions: *rac*-**3a** 25 mg, Amano PS-IM 10 mg, $PhCH_3$ 500 µL, vinyl decanoate 102 mg, 115 µL (3 equiv), 30 °C, 800 rpm (magnetic stirrer).

(+)-**6a** of very high enantiomeric purity (98–100% ee) leaving thereby slower reacting stereoisomer (*S*)-(−)-**3a** in lower enantioenrichment (76–94% ee). Thus, basically any of them can be used, however, for convenience and simplicity of product isolation as well as for reasons of the price of acyl donors, for the rest of KR studies we decided to employ vinyl acetate.

In order to establish the scope and limitation of the developed enantiomer separation methodology, the optimized biocatalytic conditions were applied for the rest of the synthesized homopropargylic alcohols *rac*-**3b–i** with different electronic and steric properties (Table 7). Moreover, at this step of investigations in order to inspect if the developed enzymatic process is susceptible to scaling up, we decided to examine the respective 4-fold linear enlargement of all the previously set parameters including the amounts of racemic substrates *rac*-**3a–i**, vinyl acetate concentration, lipase quantities and solvent volume under the optimized reaction conditions. As can be seen from the results collected in Table 7, in almost all cases an excellent *E*-values can be reached regardless of the variety of the substrate used, thus allowing the isolation of non-racemic acetates in very high [92–97% ee for (*R*)-(+)-**4a**, **d**, **e**, **f**, **g**, **i**], an excellent [99% ee for (*R*)-(+)-**4b**] and total [> 99% ee for (*R*)-(+)-**4c** and (*R*)-(+)-**4h**] enantiopurity. On the other hand, using the established KR methodology a recovery of the remaining optically active alcohols could be obtained with very high [96% ee for (*S*)-(−)-**3d** and (*S*)-(−)-**3f** (for 50% conv.)], excellent [98–99% ee for (*S*)-(−)-**3b**, **e**, **g**, and **i**] and perfect [> 99% ee for (*S*)-(−)-**3a**, (*S*)-(−)–**3c**, (*S*)-(−)-**3f** (for 51% conv.) and (*S*)-(−)–**3h**] optical purity. Under our standard reaction conditions, good yields of both resolution chiral products can be afforded from racemic starting materials.

Table 7
The (Amano PS-IM)-catalyzed preparative-scale KR of *rac*-**3a–i** in $PhCH_3$.

Entry	Substrate[a]	*t* [h]	Conv.[b] [%]	ee_s[c] [%]/Yield[d] [%]	ee_p[c] [%]/Yield[d] [%]	*E*[e]
1	*rac*-**3a**	24	49	95/36	97/35	246
2		25	51	99/35	95/36	206
3		26	51	> 99/34	95/35	206
4	*rac*-**3b**	72	50[f]	99/34	99[g]/32	1057
5	*rac*-**3c**	72	50	> 99/34	> 99/29	1057
6	*rac*-**3d**	72	50	96/34	96/25	194
7	*rac*-**3e**	72	51	98/39	95/34	180
8	*rac*-**3f**	72	50	96/43	96/42	194
9		74	51	> 99/29	97/43	348
10	*rac*-**3g**	72	52	99/33	92/44	126
11	*rac*-**3h**	72	50	> 99/30	> 99/20	1057
12	*rac*-**3i**	72	51	99/19	96/22	259

[a] Conditions: *rac*-**3a–i** 100 mg, Amano PS-IM 40 mg, $PhCH_3$ 2 mL, vinyl acetate (3 equiv), 30 °C, 800 rpm (magnetic stirrer).
[b] Based on GC, for confirmation the % conversion was calculated from the enantiomeric excess of the unreacted alcohol (ee_s) and the product (ee_p) according to the formula conv. = $ee_s/(ee_s + ee_p)$.
[c] Determined by chiral HPLC analysis by using a Chiralcel OD-H or Chiralpak AD-H column, respectively.
[d] Isolated yield after column chromatography using mixture of $CHCl_3$/acetone (99:1, v/v) as eluent.
[e] Calculated according to Chen *et al.* [76], using the equation: $E = \{\ln[(1\text{cconv.})(1 - ee_s)]\}/\{\ln[(1 - conv.)(1 + ee_s)]\}$.
[f] Based on GC.
[g] Determined by chiral HPLC after K_2CO_3-mediated hydrolysis of the remainder acetate (*R*)-(+)-**4b** into the corresponding alcohol (*R*)-(+)-**3b**.

It is important to mention that in all cases except the reaction carried out with non-substituted derivative *rac*-**3a** the KRs required to be conducted for at least 72 h to achieve ca. 50% conversion value as *para*-substituted derivatives *rac*-**3b–i** were enzymatically less reactive. The performed experiments revealed that this extremely enantioselective Amano PS-IM lipase has an acyl binding site which offers an optimum environment to host homopropargylic alcohols bearing phenyl rings with electron-donating bulky groups such as: –*i*Pr and –*t*Bu or with a smaller electron-withdrawing $–CF_3$ substituent. In those cases, kinetic resolution process proceeded with the highest possible enantioselectivity values (*E* = 1057) allowing to isolate both stereoisomeric forms with excellent enantiomeric purities (> 99% ee). A marginally lower enantioselectivities (*E* = 246–348) were observed in the cases of those derivatives bearing simple phenyl ring with hydrogen atoms *rac*-**3a** or which *para*-position in the phenyl ring was occupied by $-OCH_3$ (*rac*-**3i**) and $-NO_2$ (*rac*-**3f**) groups, respectively. All these shown to be suitable substrates here, and gave the desired resolution products in a very high 95–99% ee range. In turn, racemic compound possessing hydrogen bioisostere (fluorine atom) at the *para*-position (*rac*-**3g**) as well as those with electron-withdrawing groups, such as −Br (*rac*-**3d**) and −Cl (*rac*-**3e**) were slightly worse substrates for (Amano PS-IM)-catalyzed KR approach (*E* = 126–194). Noteworthy, in order to obtain enantiomerically pure (*S*)-(−)-**3a** (> 99% ee) and (*S*)-(−)-**3f** (> 99% ee), time of the preparative-scale reactions had to be slightly elongated up to 26 h and 74 h (Table 7, entries 3 and 9), respectively.

3.4. Assignment of the stereochemistry of the EKR products

The stereochemistry of the obtained chiral non-racemic products was determined by comparison of their specific rotation signs with relevant data reported in literature (see Table S2 in Supplementary material). This assignment leads to a conclusion that Amano PS-IM follows the empirical rule formulated by Kazlauskas [77], according to which the (*R*)-enantiomer of a secondary alcohols possessing two much differing in size substituents attached to the asymmetric centre is preferentially transformed into ester when the lipases are utilized as the catalysts. Unexpectedly, the specific rotation sign for optically active *para*-nitro derivative **3f** was in contrary to the rest of the enantiomeric alcohols synthesized in the same enzyme-catalyzed kinetic resolution manner and measured as a methanolic solution. Such result was contradictive to the so-called Tschúgaeff rule [78], which assumes that optically active compounds with a single asymmetric atom belonging to homologous series should have the same sign of optical rotation. Moreover, the stereochemical outcome of the reaction conducted with *rac*-**3f** was uncertain since inconsistent results were obtained when compared with literature data concerning specific rotation signs of that particular non-racemic alcohol **3f** [42]. This finding surprised us because it was unlikely that toward only one compound from the same homologous series the enantioselectivity was reversed in the case of Amano PS-IM. In addition, our uncertainty was strengthen when comparing the HPLC retention times for enantiomeric **3f** and the rest of optically active alcohols obtained in the lipase-catalyzed kinetic

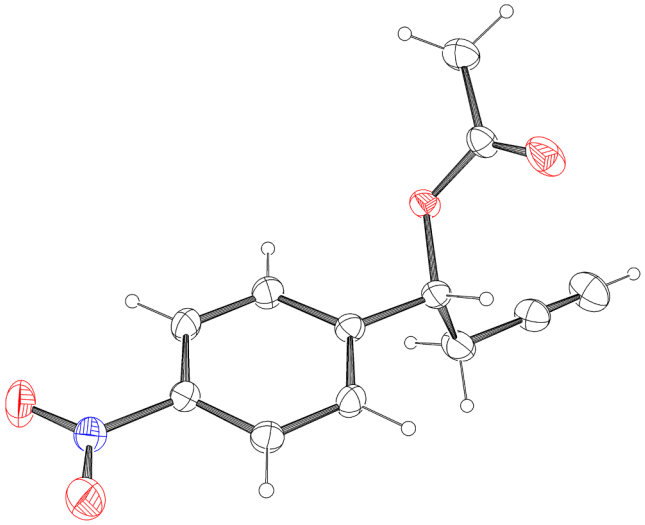


Fig. 3. An ORTEP plot of (*R*)-(+)-**4f** enantiomer. Thermal ellipsoids were drawn at 50% probability and hydrogen atoms omitted for clarity (C black, H gray, N blue, O red). The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC-1880174.

resolution of *rac*-**3a–h**. The HPLC chromatograms clearly showed the same tendency in the order of the peaks among derivatives studied on Chiralcel OD-H column. In all cases, the first minor peak consequently represents the residual traces of (*R*)-enantiomer, while the second major peak obviously corresponded to opposite (*S*)-enantiomer (see Supplementary material). However, when compared retention parameters for acetate possessing nitro group (+)-**4f** with other chiral esters resolved on the same HPLC column, the tendency was reversed. As we were strongly puzzled with these results, therefore we decided to perform the polarimetric measurement again using this time $CHCl_3$ (according to Jain and co-workers [42]) instead of MeOH in which whole homologous series was done. We suspected that it might be the solvent that influences the sign of optical rotation. To our surprise, when we have repeated the polarimetric measurement for a solution of homochiral **3f** (> 99% ee) in $CHCl_3$ it turned out that the sign of optical rotation was reversed $\{[\alpha]_D^{22} = -33.33$ (*c* 1.05, $CHCl_3)\}$ when compared with the corresponding methanolic solution $\{[\alpha]_D^{23} = +4.76$ (*c* 1.05, MeOH)} of the same alcohol's sample, which confirmed our assumption that it was the solvent effect. Moreover, as we could not believe in unexpected inversion of the Amano PS-IM enantiomeric preference toward *para*-nitro-substituted derivative *rac*-**3f**, therefore to confirm if the absolute configuration was properly attributed by us, a single-crystal X-ray analysis was additionally performed for controversial optically active derivative. However, from the pair of enzymatically resolved enantiomeric products, we could prepare single crystal of sufficient quality only for acetate (+)-**4f**. Moreover, despite the lack of heavy atom in molecule of (+)-**4f**, Flack parameter value was enough to determine properly the configuration. To our delight the performed XRD inspection undoubtedly proved that (+)-**4f** is (*R*)-configurated at the stereogenic carbon atom (Fig. 3), so the alcohol (−)-**3f** must be (*S*)-configurated, and thus the Amano PS-IM stereopreference toward *rac*-**3f** is consequently consistent with Kazlauskas' rule [77]. The ORTEP drawing of (*R*)-(+)-**4f** was prepared using freeware crystallographic software (ORTEP-3 for Windows) developed by Louis J. Farrugia [79].

4. Conclusion

Exploring new routes to optically active homopropargyl alcohols we have merged simple organic chemistry methodology with classical lipase-catalyzed kinetic resolution of the corresponding racemates. In this regard, a series of racemic *para*-substituted 1-phenylbut-3-yn-1-ols have been synthesized *via* Barbier-type propargylation of the respective arenecarbaldehydes using 3-bromo-1-propyne (propargyl bromide, **2**) and $SnCl_2$ assisted by KI in saturated aqueous NH_4Cl solution. Subsequently, the model substrate (1-phenylbut-3-yn-1-ol, *rac*-**3a**) was tested with the collection of 17 different hydrolytic enzymes suspended each in a solution of vinyl acetate as acyl donor in TBME, appropriately. Using enantioselective transesterification synthetic variant carried out under kinetically-controlled conditions at analytical scale, it turned out that the lipases from *Burkolderia cepacia* (i.e. Amano PS-IM and Amano PS-C II) exhibited excellent enantioselectivity (E > 200 at 30 °C). Further screening of reaction media on stereochemical outcome revealed that Amano PS-C II was superior to Amano PS-IM in terms of catalytic activity and selectivity. However, due to criterion of availability of both commercial preparations, it was BCL immobilized on diatomite (Amano PS-IM), which was selected for investigations on the acyl-group donors' effect as well as up-scaling studies. The examined Amano PS-IM demonstrated great catalytic flexibility toward the substrate scope as the variation of the substitution pattern on the phenyl ring was very well-tolerated by this enzyme. The synthesized propargyl alcohols with electron-donating or electron-withdrawing functional groups are all suitable substrates for this methodology allowing to achieve excellent enantiomeric enrichment (92–100% ee) and fair to very good 19–44% isolated yields for both resolution products, respectively. Nevertheless, the collected experimental data concerning preparative-scale reactions clearly indicate that enantioselectivities were the best for derivatives possessing –*i*Pr (*rac*-**3b**), –*t*Bu (*rac*-**3c**), and $-CF_3$ (*rac*-**3h**) groups in the *para* position, thus reaching the highest possible *E*-value for lipase-catalyzed KR approach. The enantiomers of all of the tested substrates with (*R*)-configuration were transesterified with vinyl acetate preferentially by Amano PS-IM. Noteworthy, the developed method provides significantly increased enantioselectivity for the secondary homopropargylic alcohols compared to literature and might be considered as highly useful starting-point for other synthetic campaigns. Currently, DKR methodology based on the elaborated catalytic system toward homopropargyl alcohols is under development in our laboratories.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.01.050.

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