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Enzyme-catalyzed kinetic resolution of spirocyclic secondary amines obtained by ring-closing metathesis, as well as synthesis of cyclopentane[c]pyrrole and -pyridines by the Pauson-Khand reaction

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RESEARCH ARTICLE

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ABSTRACT

As herein defined; a ring closing metathesis (RCM) reaction of *N*-anchored homoallylic dienes followed by enzymatic kinetic resolution and ring closing enyne metathesis (RCEM) with an intramolecular Pauson-Khand reaction of *N*-tethered homopropargylic enynes are described for the first time. RCM afforded azaspirodeca and -undecadiene with 78 and 82% chemical yields, as well as azaspironona and decadienecarboxylates with 65 and 70% chemical yields, respectively. Furthermore, RCEM protocol resulted in conjugated diene 50% chemical yield. Moreover, intramolecular Pauson-Khand reaction is also applied to enynes, which yielded cyclopenta[*c*]pyrrole-carboxylate as diastereomeric mixtures; besides cyclopenta[*c*]pyridin-one and cyclopenta[*c*]pyridin-carboxylate frameworks as single diastereomers. Above all, secondary amines (azaspirodeca and undecadiene) have been efficiently resolved through an enzyme-catalyzed reaction in a moderate ee up to 77 and 20% ee, with their corresponding esters up to 75 and 55% ee, in the presence of CAL-B (being the most effective biocatalyst) and recombinant from *Aspergillus oryzae*. Both CAL-B and CAL-A-*CLEA* afforded reverse enantiomeric separation of them for the first time.

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1. Introduction

Spirocyclic structures exist in many natural products [1]. In particular, spirocyclanes having a nitrogen atom incorporated at the ring junction, represents a synthetic goal in the past decade. Many biologically substantial alkoloids containing this structural motif, such as anticancer homoharringtonine (Figure 1) [2,3], antivascular cell adhesion molecule-1 (VCAM-1) [4,5], induction agent; halichlorine and immunosuppressive compound; FR901483 [6] have received numerous synthetic interests in the past decades [7-9].

For the synthesis of numerous natural products and the discovery (Figure 2) several synthetic methodologies have been applied [10-14]. RCM and RCEM catalyzed by ruthenium and molybdenum are recently used ones developed by Schrock and Grubbs [10-15], respectively [16,17].

In this context, enantiomerically enriched azaspirodeca [18] and -undecadienes [18] obtained by the RCM reaction up to 77% ee with corresponding esters up to 75% ee for the first time. Azaspironona and decadiene-carboxylates [18,19] with good chemical yields by the same method.

The enyne metathesis reaction catalyzed by metal alkalidenes is also a solely powerful and atom-economical means of generating carbocycles and heterocycles from enyne precursors [20,21]. Generally, special reaction conditions [22] such as; ethylene atmosphere as we applied; yielded the vinyl-azaspirodeca-diene-carboxylate (**14b**) Diels Alder precursor. Spirocyclic compounds, especially those containing nitrogen and oxygen heteroatoms, are a reoccurring structural motif in a number of natural products and biologically active compounds [23,24].

The most important transformation that incorporates cobalt complexed alkynes and maintains cyclopentenones is PKR-Pauson-Khand Reaction; upon combination of alkenes and cobalt complexed alkynes, intermolecularly or intramolecularly [25-27] to build up cyclopentanone-pyrrole and pyridines with spirocyclic motifs on homoallylic and homopropargylic imines. Cyclopentenone ring systems are also used as building blocks to obtain natural cyclopentenoids [28], especially having spiro junction cyclopenta[*c*]-pyran; pyridine analog and cyclopenta [*c*]-furan; pyrrole analog units. Within this sphere, we applied the PKR protocol to obtain cyclopenta[*c*]pyrrole-carboxylates (**8a-b**) with high diastereoselectivities, as well as cyclopenta[c]

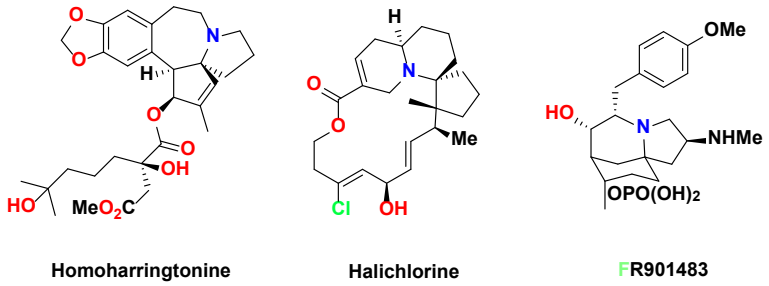


Figure 1. Examples of azaspirocyclane compounds.

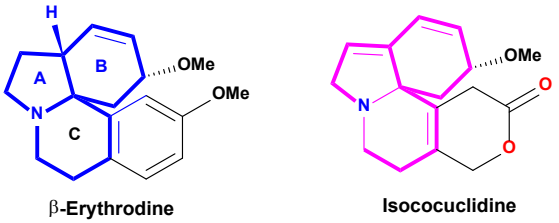
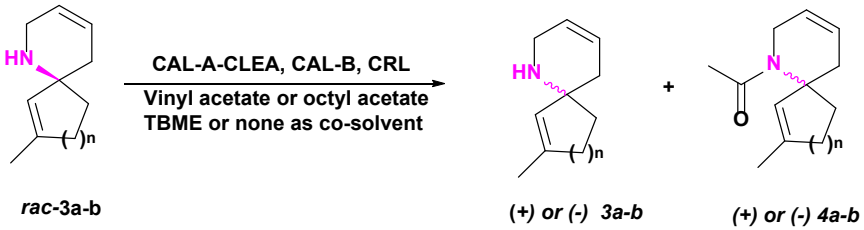


Figure 2. Naturally occurring alkaloids containing azatricycles.



Scheme 1. Enzyme-catalyzed acyl transfer reaction.

pyridine-carboxylate (**11b**) together with cyclopenta[*c*] pyridin-one (**13b**), as single diastereomers.

Nitrogen containing enantiopure compounds, such as amines, amino acids, and their derivatives, are important chiral building blocks and final products in the pharmaceutical and fine chemical industries [29,30]. Furthermore, the production of secondary amines in enantiopure form is important in this regard [31], based on the fact that it is the desired goal from the physicological and environmental point of view [32]. However, there are a few examples on the resolution of secondary amines in the literature, although such building blocks are commonly used in pharmaceuticals [33,34].

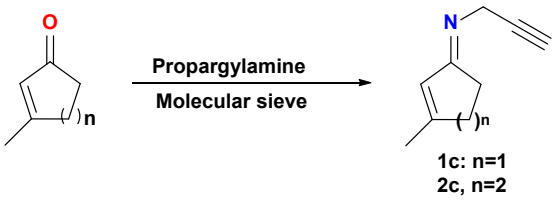
Although the reported strategies include enzymatic kinetic and dynamic kinetic resolution methods for obtaining chiral amines [34-36]; finding the appropriate biocatalytic method possesses a huge challenge [35,36]. Therefore, the resolution of secondary amines by enzyme-catalyzed acylation is a relatively rare process [34], since there are many parameters that affect the optimal conditions [37]. Especially enzyme: substrate fit, lock-and-key mechanism is difficult to achieve because of the steric effects. Due to the fact that; substrate structure is one of the key factors for high enantioselectivity [37-39]. These are restricted conditions that prevent enantiopurity**.** This situation is also valid for tertiary alcohols not gaining dominance over enzyme: substrate conformity [40].

We have already reported initial studies on the enzyme catalyzed resolution of aromatic-ring fused cyclic tertiary alcohols of α-indanone and α-tetralone [41] showing the results of enzymatic resolution of racemic tertiary allylic, homoallylic and homopropargylic alcohols [42]. Within this sphere, we first report the results of the enzymatic kinetic resolution of racemic azaspirodeca and -undecadiene (Scheme 1).

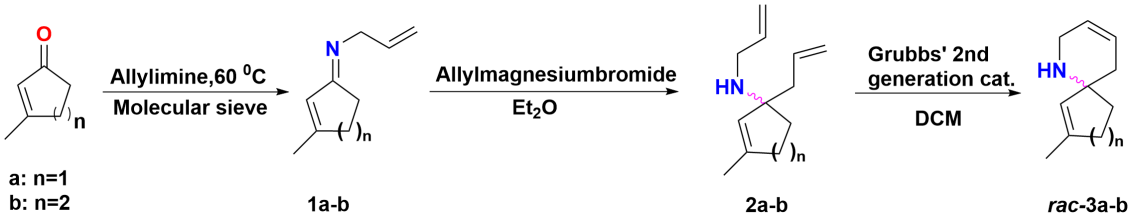
2. Experimental

2.1. General

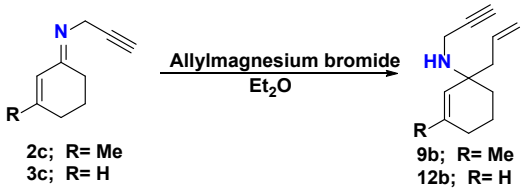
All experiments were carried out in pre-dried glassware (1 h, 150 °C) under an inert atmosphere of Argon. The following reaction solvents were distilled from the indicated drying agents: dichloromethane (P_2O_5), tetrahydrofuran (sodium, benzophenone). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on the JEOL ECS-400 spectrometer. ^{1}H (400 MHz) and ^{13}C NMR were recorded in $CDCl_3$, and the chemical shift was expressed in ppm as the internal standard relative to $CDCl_3$ (δ 7.26 and 77.0 for ^{1}H and ^{13}C NMR, respectively). Infrared spectra were recorded on a Thermo Nicolet IS10 ATR-FT-IR spectrophotometer**.** HRMS spectra were detected on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC / MS instrument at the Central Laboratory in METU. Optical rotations were measured employing a Rudolph Research Analytical Autopol II automatic polarimeter. Flash column chromatography was performed using thick-walled glass columns with flash grade (Merck Silica Gel 60). Reactions were appropriately monitored by thin layer chromotography using precoated silica gel plates (Merck Silica Gel PF-254), visualized by UV light and polymolybden phosphoric acid in ethanol. All extracts were dried over anhydrous magnesium sulfate and solutions were concentrated under vacuum using a rotary evaporator. Homoallylic 1a, 1b, and homopropargylic imines, **1c-3c**, were prepared by a reported procedure [18,47]. Also, *N*-homoallylic 5a, 5b and *N*-homopropargylic carbamates 7a, 7b, 10b were synthesized according to the modified literature procedure [18,47]. All reactions were monitored by thin layer chromatography (TLC).



Scheme 2. Synthesis of homopropargyl imines.



Scheme 3. Synthesis of *rac*-**3a** and *rac*- **3b** by RCM.



Scheme 4. Grignard reaction of homopropargylamines.

2.1.1. Synthesis of homoallyl (1a, 1b) and homopropargyl imines (1c-3c)

A sealable tube was charged with a 0.5 M solution of cyclic ketone; 3-methyl-2-cyclopentenone or -cyclohexenone; (0.98 g, 10 mmol) in benzene (20 mL). Allylamine or propargylamine (1.16 g, 3.55 mmol) and crushed molecular sieves (1/1 ratio, w/w) were then added, the tube sealed and the reaction mixture heated to 55-60 °C. After being stirred overnight, the solution was diluted with ether and filtered. The ether was carefully removed by vacuum evaporation at low temperature. Benzene was removed by blowing nitrogen gas over the solution to give the pure imine product as orange-yellow oil used directly in the next step [18]. (Schemes 2 and 3).

2.1.2 Synthesis of azaspirodecadiene (rac-3a) and azaspiroundecadiene (rac-3b) by RCM

The construction of parent azaspirodecadiene (**3a**) and azaspiroundecadiene (**3b**) units was synthesized by addition of *N*-allylamine in the presence of commercially available 3-methyl-cyclopentenone and cyclohexenone, followed by the addition of allylmagnesium bromide to the corresponding homoallylimines (**1a**, **1b**); diene precursors (**2a**, **2b**) subjected to the RCM reaction in the presence of Grubbs' 2nd generation catalyst as shown in (Scheme 3).

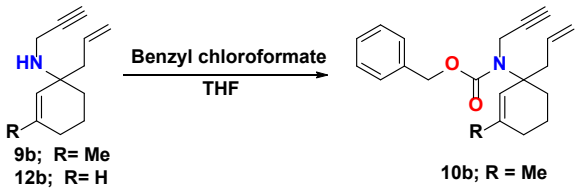
2.1.3. General procedure for the enzymatic kinetic resolution of rac-3a and rac-3b

For 100 mg of substrate, *rac*-**3a** and *rac*-**3b** and 1 mL acyl donor with 50 mg of the enzyme were shaken at a suitable temperature (38-40 °C) with or without cosolvent. The reaction was followed by TLC. When it came to the end, the mixture was filtered and the residue concentrated under vacuo. Followed by flash-column chromatography, the crude mixture was purified using suitable ethylacetate/hexane and triethylamine as an eluent (Scheme 1).

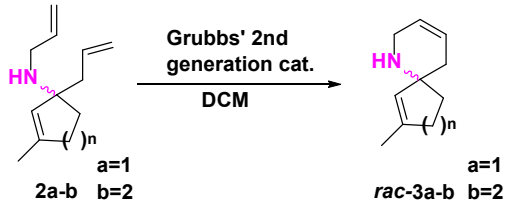
2.1.4. Synthesis of N-homoallylic (2a, 2b) and N-homopropargylic enamines (9b, 12b)

To a stirred solution of Mg turnings (0.36 g,15 mmol) and iodine (2 pieces) in dry diethyl ether (15 mL) at room temperature equipped with a reflux condenser, a mixture of allylbromide (1.33 g, 11 mmol) in anhydrous diethyl ether (7 mL) was added dropwise. The mixture was allowed to reflux for 25 min. Then cooled down to 0 °C followed by the addition of the corresponding imine (**1a**, **1b** or **2c**, **3c**) (0.96 g, 7mmol) in dry diethyl ether (5 mL) was added dropwise. The resultant mixture was stirred for 4 h. The reaction mixture was hydrolyzed with a saturated ammonium chloride solution (20 mL). The resulting mixture was extracted with diethyl ether (3×30 mL). The combined organic phase was washed with brine (20 mL) and dried over $MgSO_4$ and evaporated in vacuo. The crude products were purified by flash column chromatography with a mixture of ethylacetate/hexane and triethylamine in suitable ratios (Scheme 4).

1-Allyl-3-methyl-N-(prop-2-yn-1-yl) cyclohex-2-enamine (**9b**): Color: Thick yellow oil. Yield: 1.39 g, 83 %. FT-IR (KBr *ν*, cm^{-1}): 3311 (C≡C-H (C sp-H), 3238 (N-H streching), 3010 (C sp^2-H), 2971 (C sp ^{3}-H), 2901 ((CH_3), Csp^3-H), 2090 (-C≡C-, stretching), 1661 (-C=C- stretching, cyclohexene ring and -C=C- stretching of allyl group (matching)), 1102 (-CH_2-N-), 1249 and 647 (C≡C-H, (C sp -H twisting), 961 and 885 (C sp^2-H twisting, specific for terminal alkenes). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.76-5.91 (m, 1H, CH), 5.35 (s, 1H, CH), 5.21 (broad singlet, N-*H*), 5.09 (dd, *J* = 1.2 and 12.1 Hz, 1H, CH) 5.07 (dd, J= 2.0 and 7.2 Hz, 1H, CH), 3.31 (d, *J* = 2.8 Hz, 2H, C*H*$_2$-N), 2.26 (dd, *J*= 1.2 and 8.4 Hz, 1H, one of the allylic methylene protons), 2.21 (dd, *J* =7.2 and 11.8 Hz, 1H, the other allylic methylene proton), 2.17 (t, *J* = 2.4 Hz, 1H, C≡C-*H)*, 1.84-1.91 (m, 2H, CH_2), 1.67 (s, 3H, CH_3), 1.64 (dd, *J* = 1.6 and 4.4 Hz Hz, 1H, one of the proton of



Scheme 5. Synthesis of homopropargylic carbamate **10b.**



Scheme 6. Synthesis of *rac*- **3a**-**3b** by RCM.

CH_2), 1.62 (dd, *J* =2.4 and 5.6 Hz, 1H, the other proton of CH_2), 1.55 (d, *J* = 2.4 Hz, 1H), 1.52 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 136.9, 134.0, 126.9, 117.9, 83.4, 70.5, 54.9, 44.7, 35.1, 31.6, 29.7, 23.8, 19.5. HRMS-ESI $C_{13}H_{20}N$, $[M+H]^+$ Calculated mass; 190.1596, Found mass; 190.1613.

1-Allyl-N-(prop-2-yn-1-yl)cyclohex-2-enamine (**12b**): Color: Dark Brown oil. Yield: 1.10 g, 72 %. FT- IR (KBr, *ν*, cm^{-1}): 3317, (C≡C-H (C sp-H), 3092, 2130 (-C≡C-, stretching), 1650. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.69-5.90 (m, 1H, CH), 5.05 (dd, *J* = 2.0 ve 10.0 Hz, 1H, CH), 5.01 (t, *J* = 1.0 Hz, 1H, CH), 5.00 (ddd, *J* = 1.2, 3.2 ve 4.0 Hz, 1H), 4.97 (pd, *J* = 1.2 ve 5.6 Hz, 1H), 3.39 (dd, *J* = 2.4 ve 5.0 Hz, 1H, CH_2-*N*), 3.38 (dd, *J* = 2.4 ve 5.4 Hz, 1H, CH_2-N), 3.26 (t, *J* = 2.8 Hz, 1H, *N*-H), 2.15 (dd, *J* = 2.4 ve 4.4 Hz, 1H, one of the allylic methylene protons), 2.13 (t, *J* = 2.6 Hz, 1H, C≡C-*H*), 2.10 (dd, *J* = 0.4 ve 6.0 Hz, 1H, the other allylic methylene proton), 2.08 (d, *J* = 7 Hz, 1H, CH) , 1.83 (dd, *J* = 4.0 ve 10.6 Hz, 1H, CH), 1.77 (dd, *J* = 3.6 ve 12.2 Hz, 1H, CH), 1.62 (dd, *J* = 1.2 ve 2.8 Hz, 1H, CH), 1.56 (dd, *J* = 3.6 and 10.6 Hz, 1H, CH), 1.50 (dd, *J* = 3.2 and 6.2 Hz, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 134.4, 133.3, 118.0, 117.0, 83.5, 82.0, 71.2, 70.2, 54.8, 43.6, 41.2, 35.3, 32.4, 19.5. $C_{12}H_{18}N$, HRMS-ESI, $[M+H]^+$ Calculated mass; 176.1439, Found mass; 176.1423.

2.1.5. Synthesis of N-homopropargylic carbamate (10b)

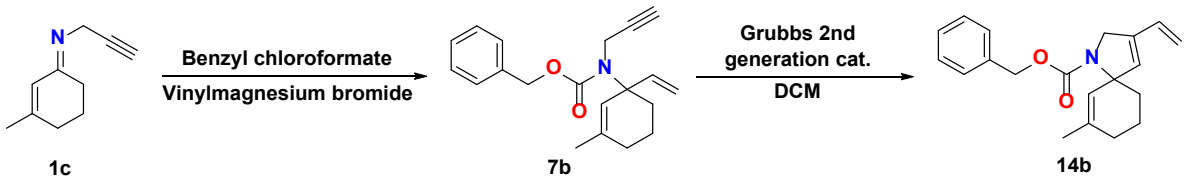
A portion of (47 mg, 2.64 mmol) corresponding enyne (**9b**) was dissolved in THF (3 mL), benzyl chloroformate (47 mg, 2.75 mmol) was added, and the mixture was heated at 60 °C for 1 hour. The mixture was partitioned between water (20 mL) and Et_2O (20 mL), and the layers were separated. The organic layer was washed with a sat'd $NaHCO_3$ solution and the brine was dried over $MgSO_4$, filtered concentrated under reduced pressure. The crude products were purified by flash column chromatography with a mixture of ethylacetate/hexane and triethylamine in appropriate ratios [18,47]. (Scheme 5).

Benzyl (1-allyl-3-methylcyclohex-2-en-1-yl)(prop-2-yn-1-yl) carbamate (**10b**): Color: Yellow oil. Yield: 910 mg, 72 %. FT-IR (KBr *ν*, cm^{-1}): 3072 (aromatic, (Csp^2-H)), 3310 (C≡C-H (C sp-H), 3025 (C sp^2-H), 2942 (Csp ^{3}-H), 2911 ((CH_3), Csp^3-H), 2250 (-C≡C-, stretching), 1697 (C=O stretching), 1655 (-C=C- stretching, signals belong to the cyclohexene and aromatic ring are matched) 1606 (-C=C- stretching, allyl group), 1266 (-CH_2-N-), 1141 (-CH_2-*C-O*- stretching), 1241 and 696 (C≡C-H, (C sp -H twisting), 908 and 766 (C sp^2-H twisting, specific for terminal alkenes). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.25-7.38 (m, 5H,-C_6H_5), 5.68-5.78 (m, 1H, CH), 5.16 (dd, *J*= 2.4 and 12.6 Hz, 1H, one of the terminal vinylic protons), 5.08 (dd, *J*= 2.0 and 12.6 Hz, 1H, the other terminal vinylic proton), 5.52 (s, 1H, CH), 5.00 (s, 1H, Ph-*CH*$_2$-O), 4.97 (d, *J*= 5Hz, 2H, Ph-C*H2*-O), 4.07-4.12 (m, 2H, *N*-CH_2), 2.32-2.38 (m, 2H, CH_2), 2.02 (s, 1H, C≡C-*H)*, 1.88-1.93 (m, 2H, CH_2), 1.84-1.87 (m, 2H, CH_2), 1.52-1.62 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 189.3 (ester carbonyl carbon), 137.8, 134.3, 128.4, 127.7, 127.5, 125.3, 123.5, 118.3, 117.8, 86.1, 81.3, 65.8, 37.7, 30.4, 29.8, 24.0, 23.6, 19.5, 18.7. $C_{21}H_{26}NO_2$. HRMS-ESI, $[M+H]^+$ Calculated mass; 324.1964, Found mass; 324.1971.

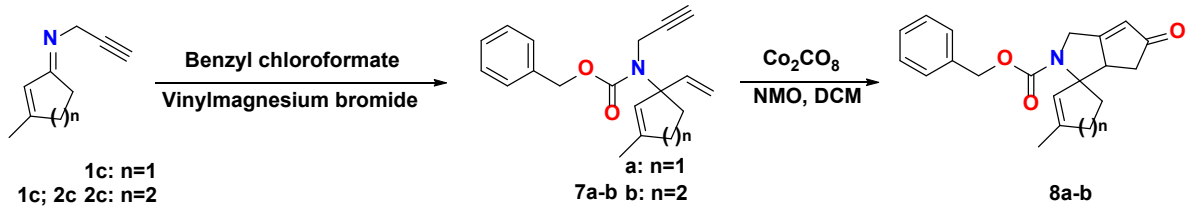
2.1.6. General procedure for Ring Closing Metathesis (RCM)

The *N*-homoallylic diene skeletons (2.23 g, 1.26 mmol) (**2a**-**b** or **5a**-**b**) and (2.39 g, 1.26 mmol) *p*-TsOH monohydrate were dissolved in DCM (15 mL) and heated at reflux for 30 min. After cooling to room temperature, Grubbs' second generation catalyst (50 mg, 5 mol %) was added, and then the mixture was heated at reflux for additional 2 h. The reaction was monitored by TLC. At the end of the reaction, the crude product was concentrated under vacuo and aqueous $NaHCO_3$ solution was added to the residue. After the addition of solid K_2CO_3 to make the solution basic, the organic components were extracted with CH_2Cl_2. The organic solution was dried on $MgSO_4$ and concentrated to obtain the crude product. It was purified by flash column chromatography using suitable ethylacetate/ hexane and triethylamine as eluent (Scheme 6).

8-Methyl-1-azaspiro[5.5]undeca-3,7-diene (**3b**): Color: Thick dark brown oil. Yield: 560 mg, 82 %. FT-IR (KBr, *ν*, cm^{-1}): 3245 (N-H), 3016 (CH_2, Csp^2-H, cyclohexene ring), 2986 (CH_3 (sp^3 -H), 2969 (CH_3 (Csp^3-H), 1660 (-C=C- stretching, cyclohexene ring), 1076 (-CH_2-N-), 1437 (-C=C- stretching, tetrahydropyridine ring). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 5.64 (d, *J* = 11.6 Hz, 1H, CH), 5.61 (d, *J* = 11.6 Hz, 1H, CH), 5.31 (s, 1H, CH), 3.32 (d, *J* = 10.4 Hz, 1H, N-C*H*$_2$-), 3.29 (d, *J* = 14.4 Hz, 1H, *N*-CH_2), 1.87-1.93 (m, 2H, CH_2, cyclohexene allylic methylene protons), 1.85 (d, *J* = 5.2 Hz, 1H, CH_2, tetrahydropyridine ring one of the methylene protons, CH), 1.82 (d, *J* = 5.6 Hz, 1H, tetrahydropyridine ring the other methylene proton, CH), 1.63 (dd, *J* = 6.0 and 13.6 Hz, 1H, one of the cyclohexene methylene protons, CH), 1.58 (s, 3H, CH_3), 1.54 (dd, *J* = 6.0 and 10..8 Hz, 1H, the other cyclohexene methylene proton, CH), 1.50 (broad singlet, N-***H***), 1.49 (d, *J* = 6.4 Hz, 1H, one of the cyclohexene methylene protons, CH), 1.47 (d, *J* = 1.6 Hz, 1H, the other cyclohexene methylene proton, CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 135.6, 127.5, 125.5, 124.3, 49.4, 41.4, 37.1, 33.5, 29.7, 23.9, 19.3. HRMS-ESI, $C_{11}H_{18}N$, $[M+H]^+$ calculated mass; 164.1439, found mass; 164.1459.



Scheme 7. Synthesis of **14b** by ring-closing enyne-metatesis.



Scheme 8. Synthesis of 8a-b by Pauson-Khand reaction.

2.1.7. General procedure for ring-closing enyne metathesis (RCEM)

The *N*-homopropargylic enyne skeleton (390 mg, 1.26 mmol) (**7b**) and (2.39g, 1.26 mmol) *p*-TsOH monohydrate were dissolved in DCM (15 mL) and heated at reflux for 30 min. After cooling to room temperature, Grubbs' second-generation catalyst (50 mg, 5 mol %) was added, and then the mixture was heated at reflux for an additional 2 h. The reaction was monitored by TLC. At the end of the reaction, the crude product was concentrated under vacuo and aqueous $NaHCO_3$ solution was added to the residue. After the addition of solid K_2CO_3 to make the solution basic, the organic components were extracted with CH_2Cl_2. The organic solution was dried on $MgSO_4$ and concentrated to obtain the crude product. It was purified by flash column chromatography using suitable ethylacetate/ hexane and triethylamine as eluent (Scheme 7).

Benzyl 7-methyl-3-vinyl-1-azaspiro[4.5]deca-3,6-diene-1-carboxylate) (**14b**): Color: Light Brown oil. Yield: 50 %. FT-IR (KBr, *ν*, cm^{-1}): 3011 (Csp^2-H, aromatic), 2970 (CH_3 (sp^3-H), 2920 (CH_3 (Csp^3-H), 1703 (-O-***C=O***),1520 and 1492 (aromatic -C=C- stretching), 1075 (-CH_2-N-), 1228 (-CH_2-***C-O-***stretching) cm^{-1} 892 ve 697 (C sp^2-H twisting, specific for terminal alkenes). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.38 (d, *J*=4.4 Hz, 1H,CH_2-*Ph)*, 7.34 (d, *J*= 5.6 Hz, 1H, CH_2-*Ph*), 7.33 (d, *J*= 4.8 Hz, 2H, CH_2-*Ph*), 7.29 (d, *J*= 3.6 Hz, 1H, CH_2-Ph), 5.76-5.82 (m, 1H, C=C*H*, internal vinylic proton), 5.62 (t, *J*=4.4 Hz, 1H, *H*C=C-C-CH_3), 5.55 (s,1H, C=C*H*), 5.28 (d *J*=0.4 Hz, 1H, HC=C*H2*, one of the terminal vinylic proton) 5.27 (s, 1H, HC=C*H2*, the other terminal vinylic proton), 5.16 (d, J= 3.6 Hz, 2H, -Ph-C*H*$_2$-O), 4.40 (d, *J* = 2.4 Hz, 1H, N-C*H*$_2$), 4.19 (d, J=2.4 Hz, 1H, N-C*H*$_2$), 2.31 (dd, *J*= 4.0 ve 11.6 Hz, 1H, C*H*$_2$ one of the allylic methylene protons), 2.28 (dd, *J*=4.4 ve 9.4 Hz, 1H, C*H*$_2$ the other allylic methylene proton), 2.07 (dd, *J*= 9.6 and 21.2 Hz, 1H, one of the methylene protons, CH_2),1.76 (dd, *J*= 2.0 and 17.6 Hz, 1H, the other methylene proton, CH_2), 1.19 (dd, *J*=6.4 and 22.6 Hz, 1H, CH_2, one of the methylene protons), 1.41 (d, *J*= 5.6 Hz, 1H, CH_2, the other methylene proton), 1.24 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 157.2, 142.5, 139.1, 137.8, 131.2, 128.9, 128.7, 128.6, 128.5, 128.0, 127.9, 119.4, 112.1, 71.5, 69.2, 67.5, 39.2, 31.6, 29.8, 27.5. HRMS-ESI, $C_{20}H_{24}NO_2$, $[M+H]^+$ Calculated mass; 310.1729, Found mass; 310.1788.

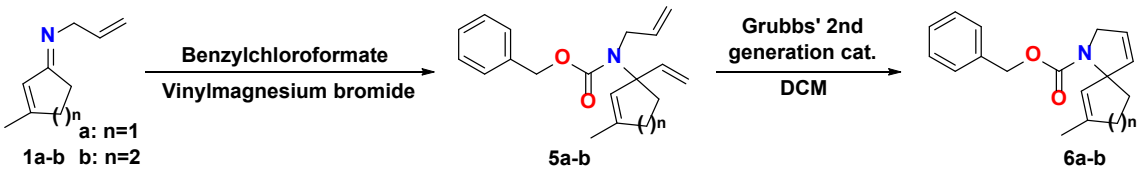
2.1.8. General procedure for the Pauson-Khand reaction (PKR)

To a solution of corresponding enynes (**7a**, **7b**, **10b**, or **12b**) (230 mg, 1.13 mmol) in DCM (15 mL) was added $Co_2(CO)_8$ (0.683 g, 2 mmol) and stirred for 2 h with TLC monitoring. Subsequently, NMO (1.32g, 11.3 mmol) was added and stirred overnight. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography using EtOAc/hexane and triethylamine as the eluent (Scheme 8).

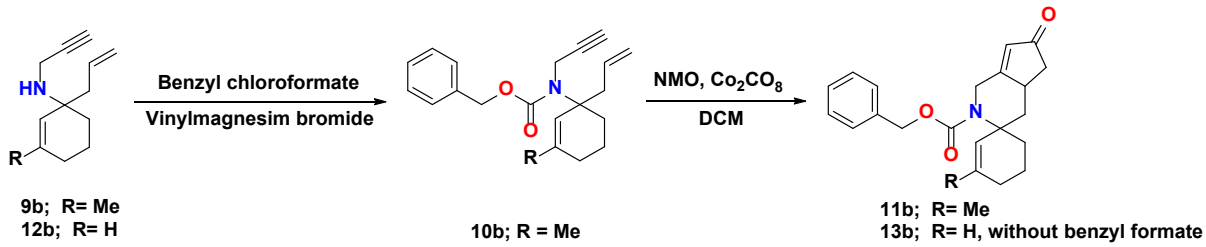
Benzyl 3-methyl-5'-oxo-3', 5', 6', 6a'-tetrahydro-2'H-spiro [cyclohex[2]ene-1,1'-cyclopenta[c]pyrrole]-2'-carboxylate (**8b**): Color: Dark Brown Liquid. Yield: 1.25 g, 65%. FT-IR (KBr, *ν*, cm^{-1}): 3010 (Csp^2-H, aromatic), 2968 (CH_3 (sp^3 -H), 2924 (CH_3 (Csp^3-H), 1697 (C=O), 1645 (-C=C- stretching), 1497 and 1453 (aromatic -C=C- stretching), 1278 (-CH_2-*N*-), 1213 (-CH_2-*C-O*-stretching). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.18-7.45 (m, 4H, C_6H_5), 7.33 (d, *J* = 25.6 Hz, 1H, C_6H_5), 6.04 (s, 1H, C=CH(CO)), 5.91 (s, 1H, C(Me)=CH), 5.15 (d, *J* =28.8 Hz, 2H, Ph-C*H*$_2$-O-), 4.42 (d, *J* = 3.2 Hz, 1H, *N*-C*H*$_2$), 4.41 (d, *J* =12.8 Hz, 1H, *N*-C*H*$_2$-), 2.97 (s, 1H, CH), 2.18 (dd, *J* = 10.8 and 42 Hz, 1H, one of the allylic methylene protons, C=C-C*H*$_2$), 2.17 (dd, *J* = 3.6 and 53.6 Hz, 1H, the other allylic methylene proton, C=C-C*H*$_2$), 2.07 (d, *J* = 18.0 Hz, 2H, C(O)-C*H*$_2$), 1.73 (dd, *J* = 3.6 and 26 Hz, 1H, one of the methylene protons, CH_2), 1.64 (dd, *J* = 6.0 and 36.8 Hz, 1H, the other methylene proton, CH_2),1.59 (d, *J* =10 Hz, 1H, one of the methylene protons, *CH*$_2$), 1.22 (s, 3H, CH_3), 0.90 (dd, *J*= 2.4 and 33.6 Hz, 1H, the other methylene proton, C*H*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 213.4, 171.5, 152.6, 142.2, 136.6, 128.7, 128.6, 128.4, 128.3, 128.1, 127.0, 123.7, 67.4, 54.7, 49.1, 47.0, 31.1, 29.8, 27.6, 22.3, 21.2. HRMS-ESI, $C_{21}H_{24}NO_3$, $[M+H]^+$ Calculated mass; 338.1756, Found mass; 338.1784.

3. Results and discussion

Initially, homoallyl imines (**1a**, **1b**) were transformed into corresponding *N*-anchored diene scaffolds **2a** and **2b** by Grignard type reactions in the presence of Mg and allyl bromide 70 and 75 % chemical yield, respectively. The subsequent RCM reaction afforded azaspirodecadiene (**3a**) and azaspiroundecadiene (**3b**) [18] with 78 and 82% chemical yields, respectively (Scheme 3). Then the most important part of the report is the enzymatic kinetic resolution reaction of the corresponding spirocyclic amines; *rac*- **3a**-**3b** were achieved. First, optimization reactions were performed by using various hydrolase type enzymes; i.e. CAL-A, CAL-B, CRL, Amano PS-C II, CAL-A-*CLEA*, CAL-B recombinant from *Aspergillus oryzae* with substrate: enzyme ratio (w/w) 1:0.5 at the screening temperature of 25 °C to 42 °C in various *co*-solvents *i.e.* THF, TBME and DIPE, isopropenyl acetate and vinyl acetate as an acyl donor.



Scheme 9. Synthesis of **6a-b** by ring closing metatesis.



Scheme 10. Synthesis of compounds **11b-13b** by the Pauson-Khand reaction.

The CAL-B recombinant from *Aspergillus oryzae* had the most promising results among the lipases screened in terms of the reaction duration and enantioselectivity in the resolution of (±)-2-methyl-6-azaspiro[4,5]deca-1,8-diene (*rac*-**3a**) and (±)-8-methyl-1-azaspiro[5,5]undeca-3,7-diene (*rac*-**3b**). In the enzymatic kinetic resolution of *rac*-**3a** when the acyl donor changed to more bulky group, vinyl acetate to octyl acetate, the enantioselectivity of (-)-1-(2-methyl-6-azaspiro[4,5]deca-1,8-dien-6-yl)ethanone (-) (**4a**) decreased from 75 to 52 %, whereas it increased the enantioselectivity of (+)-2-methyl-6-azaspiro[4,5]deca-1,8-diene (+) (**3a**) from 60 to 77 % according to the lock and key mechanism of enzyme:substrate was fitted in TBME as *co*-solvent at 40 °C by shaking for 78 h. Furthermore, the CAL-B recombinant from *Aspergillus oryzae* has better enzyme-substrate unity when the substrate was *rac*-**3a** with (-)-1-(2-methyl-6-azaspiro[4,5]deca-1,8-dien-6-yl) ethanone (-) (**4a**), (+)-2-methyl-6-azaspiro[4,5]deca-1,8-diene (+) (**3a**) by 75% ee and 60% ee, respectively.

In the case of the enzymatic kinetic resoluton of (±)-8-methyl-1-azaspiro[5,5]undeca-3,7-diene (*rac*-**3b**) CAL-B recombinant from *Aspergillus oryzae* has better enzyme-substrate rhythm than CAL-A-*CLEA*; (-)-1-(8-methyl-1-azaspiro [5,5]undeca-3,7-dien-1-yl)ethan-1-one (-) (**4b**) 55 % ee and (+)- 1-(8-methyl-1-azaspiro[5,5]undeca-3,7-dien-1-yl)ethan-1-one (+) (**4b**) 30% ee at the end of 85 hour shaking with cosolvent TBME, octyl acetate as acyl donor. Furthermore, (+) -8-methyl-1-azaspiro [5,5]undeca-3,7-diene (+) (**3b**) 20% ee and (-)-8-methyl-1-azaspiro[5,5]undeca-3,7-diene (-) (**3b**) 2% ee nearly racemic, respectively. *Candida Rugosa Lipase* was also tried but did not work properly with (+)-1-(8-methyl-1-azaspiro[5,5]undeca-3,7-dien-1-il)ethan-1-one (+) (**3b**) 30% and (-)-8-methyl-1-azaspiro[5,5]undeca-3,7-diene (-) (**4b**) 5% ee, respectively at the end of 85 hour shaking in TBME as *cosolvent* and isopropenyl acetate as acyl donor as summarized in Table S1 in the supporting information part.

The second acyclic unsaturated unit was tailored by *N*-protection with benzylchloroformate, followed by a Grignard type reaction with vinylmagnesium bromide in THF (Scheme 9). Subsequently, diene scaffolds (**5a** and **5b**) were subjected to RCM with Grubbs' second-generation catalyst in DCM to allow azaspirodienecarboxylates (**6a** and **6b**) to produce 65 and 70% chemical yields, respectively.

The applicability of intramolecular PKR was also investigated to build cyclopentenone[*c*]-pyrrole and cyclopentenone[c]-pyridine fused ring systems with spirocyclic enyne motifs having *N*- homopropargylic backbones in the order of compounds **7a**, **7b**, **9b** and **12b**. Initial efforts have been made to ensure the availability of intramolecular PKR by constructing enynes tethered to cyclopentene and cyclohexene rings via (**7a, 7b**), *N*-protection of compounds **1c** and **2c** with benzyl chloroformate in THF, followed by Grignard addition of vinylmagnesium bromide (1M in THF) and via compound **10b** constructed Grignard addition of allylmagnesium bromide (**2c**) followed by *N*-protection of compound **9b** with benzylchloroformate. Enynes (**7a, 7b, 10b**) isolated in the order of 65, 75 and 78 % chemical yield with 83% chemical yield of compound **9b.**

Enyne (**10b**) leading to the tetrahydropyridine fused cyclopentenone framework enabled a single diastereomer (**11b**) (70 % chemical yield), while enynes (**7a, 7b**) leading to tetrahydropyrrole fused cyclopentenone derivative resulted in diastereomeric mixtures (**8a**, **8b**) with a 4.12:1, 1.51:1 ratio established by ^{1}H-NMR spectroscopy in 60 % and in turn 65% chemical yield. (Schemes 8 and 10). The lack of diastereoselectivity in pyrrole; furan analog fused cyclopentenone derivative was presumably due to the less conformational effect of the pyrrole ring; furan analog on the diastereoselectivity was compared with the most favored chair conformation of the pyridine ring; pyran analog as indicated in our previous studies [41-43].

Furthermore, cyclohexene tethered enyne (**12b**) was also subjected to intramolecular PKR with the same protocol, cobalt: alkyne complexes were prepared using enyne:dicobalt octacarbonyl in a molar ratio of 1.0:1.7 in DCM and then, *N*-methylmorpholine *N*-oxide monohydrate (NMO) was added as a promoter. All reactions were monitored by thin layer chromatography (TLC). Enyne **12b** leads to cyclopentenone [c]-pyridine; pyran analog framework provided a single diastereomer (**13b**) (65% chemical yield) as expected (Scheme 10).

Finally, the ring closing enyne metathesis (RCEM) reaction tested to afford vinil azaspiro- decadiene (**14b**) (Scheme 7). In contrast to olefin metathesis, all carbon atoms of the starting material are retained in the product, and it contains a synthetically useful 1,3 diene moiety that can be investigated in detail, particularly through the Diels-Alder reaction or other transformations [44].

Enyne metathesis reactions generally require special reaction conditions [22], such as an ethylene atmosphere, to obtain the target product with a high yield, depending on the structure of substrate as we applied in our case which led to the predicted conjugated diene (**14b**) As mentioned earlier, the structure of the substrate is important in RCEM reaction; since cyclopentene based *N*-propargyl anchored enyne skeleton;

benzyl(3-methyl-1-vinylcyclopent-2-en-1-yl)(prop-2-yn-1-yl)carbamate (**7a**) does not undergo enyne metathesis efficiently like cyclohexene based enyne subunits; benzyl(3-methyl-1-vinylcyclohex-2-en-1-yl)(prop-2-yn-1-yl)carbamate (**7b**) yield is lower. Corresponding RCEM product, Diels Alder precursor; benzyl 7-methyl-3-vinyl-1-azaspiro [4,5] deca-3,6-diene-1-carboxylate (14b) can be a key product that has a potential stereogenic center created as a result of Diels-Alder cyclization on the pyrrole ring, stereochemistry will be under investigation in the near future as there are a few studies in the literature related to this concept [45,46].

4. Conclusions

In this report, we have demonstrated the enzyme-catalyzed kinetic resolution of secondary amines; azaspirodecadiene (rac-3a) and azaspiroundecadiene (*rac*-**3b**) for the first time. According to the results obtained, the CAL-B recombinant from *Aspergillus oryzae* gave the most promising results among the lipases screened in terms of reaction duration and enantioselectivity in the resolution of (+)-2-methyl-6-azaspiro[4,5]deca-1,8-diene (+) (**3a**) in 60 % ee with the corresponding ester (-)-1-(2-methyl-6-azaspiro[4,5]deca-1,8-dien-6-yl)ethan-1-one (-) (**4a**) with 75 % ee; as well as (+)-8-methyl-1-azaspiro[5,5]undeca-3,7-diene (+) (**3b**) in 20 % ee with (-)-1-(8-methyl-1-azaspiro[5,5]undeca-3,7-dien-1-yl)ethan-1-one(-) (**4b**) in 55 % ee, respectively. Furthermore, CAL-B recombinant from *Aspergillus oryzae* and CAL-A-*CLEA* provided reverse enantiomeric separation of both (±)-2-methyl-6-azaspiro[4,5]deca-1,8-diene (*rac*-**3a**) and (±)-8-methyl-1-azaspiro[5,5]undeca-3,7-diene, (*rac*-**3b**) being the first time.

The unsaturated portion of the synthesized azaspirocyclic intermediates makes them valuable building blocks for the target azaspirocyclic compounds. Both Ring Closing Metatesis and Enyne Metatesis reactions as well as Pauson-Khand reaction are useful methods to build up corresponding azaspirocyclic targets. From this point of view, the applicability of RCM has initially been tested in diene systems anchored to allylic secondary amine backbones (**5a** and **5b**) to obtain spirocyclic dihydropyrrole compounds **6a** and **6b** with acceptable chemical yields of 65 % and 70 %, respectively. Subsequent application of RCM with dienes (**2a, 2b**) tethered to *N*-templates afforded spirocyclic tetrahydropyridine compounds *rac*-**3a** and *rac*-**3b**, with 78 % and 82 % chemical yields, respectively. Then, intramolecular PKR was applied to enynes constructed on *N*-homopropargylic templates by anchoring allyl and vinyl units, respectively. Cycloopentenone pyrrole; furan analog with spirocyclic motifs **8a**, **8b** were isolated as diastereomeric mixture, whereas cyclopentanone-pyridines; pyran analogs; **11b, 13b** were isolated as single diastereomers due to the most favored chair conformation of the pyridine; pyran analog ring. Using this testing background, *N*-anchored homopropargylic templates (**2c** and **3c**) were used to build the corresponding homoallylic enynes **10b** and **12b** in the order of 78 and 72% chemical yield with allylic enynes (**7a, 7b**) in 65%, 75% chemical yields, in turn. Finally, enynes tethered to homopropargyl amine backbones (**7a** and **7b**) subjected to the enyne metathesis reaction. However, as stated above, the structure of substrate is conjuncture; in this regard, the cyclopentene based *N*-propargyl anchored enyne skeleton; **7a** did not react appropriately as cyclohexene-based analog; (**7b**) resulting dihdyropyrrole ring possesses a conjugated diene unit (**14b**), which is a valuable candidate in Diels Alder reactions and it is used to construct bicyclic ring systems.

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Supporting information

Electronic supplementary information (ESI) available: Full experimental, characterization, experimental procedures, characterization and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Structure determination from powder data without prior indexing. Experimental results and NMR data. Experimental procedures on prepared compounds and their characterization. Experimental details, NMR spectra, and competition studies. Experimental procedures, product characterizations, NMR spectra, compound preparation procedures, screening tests, and photophysical and electrochemical data. Full experimental procedures, mass spectrometry. Experimental details, spectroscopic data, device details, and copies of ^{1}H and ^{13}C NMR spectra. The online version of this article contains supplementary material, which is available to authorized users.

Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered to.
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CRediT authorship contribution statement

Methodology: Devrim Özdemirhan; Formal Analysis: Devrim Özdemirhan, Shafeek Buhlak and Durukan Koç; Investigation: Devrim Özdemirhan, Shafeek Buhlak and Durukan Koç; Resources: Devrim Özdemirhan; Data Curation: Devrim Özdemirhan, Shafeek Buhlak and Durukan Koç; Writing-Original Draft: Devrim Özdemirhan; Writing-Review and Editing: Devrim Özdemirhan Visualization: Devrim Özdemirhan; Funding Acquisition: Devrim Özdemirhan Project Administration: Devrim Özdemirhan.

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