ACTIVATION OF CARBONYL β-CARBONS FOR CHEMICAL TRANSFORMATIONS

FIELD OF THE INVENTION

[001] The present invention relates to the fields of organocatalytic activation of carbonyl β-carbons to synthesize β-carbon nucleophiles. The present invention is further directed to the organocatalysts used herein and their respective uses.

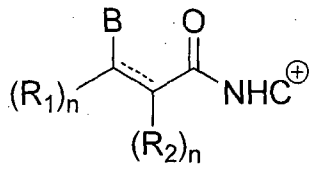
BACKGROUND

[002] Carbonyl compounds, such as esters, ketones, and aldehydes are essential building blocks in organic chemistry, particularly in the field of pharmaceuticals, fine chemicals, and materials. Therefore, carbonyl compounds are involved in different multistage chemical synthesis. The activation of the α-carbons of carbonyl compounds in order to generate enolate equivalents as nucleophiles is one of the most powerful strategies and commonly used synthesis in organic chemistry including aldol reactions and Mannich reactions. The functionalization of these α-carbons is well known and can be realized via metal-based or organic catalysts or reagents. The most relevant method is directing group-assisted metal insertion and C-H bond activation involving the ester β-carbons using palladium-based transition metal catalysts. As starting material, typically the corresponding α,β-unsaturated carbonyl compounds are used. In contrast herein, the β-carbon of saturated carbonyl compounds is considered to be rather inert. Despite of the fundamental and practical values, direct transformation of β-carbons of saturated carbonyl compounds to nucleophiles is still challenging.

[003] Hence, there is a need in the art for direct activation of carbonyl β-carbons for chemical transformations.

SUMMARY OF THE INVENTION

[004] The present invention provides a method for synthesizing a compound of Formula (I)



(I)

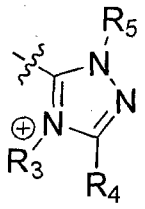
wherein

------ is a single or a double bond, wherein if it is a double bond n is 1 and if it is a single bond n is 2;

each R_1 and R_2 is independently selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety;

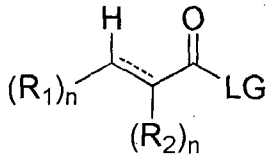
B is an electrophilic group; and

NHC^+ is



comprising:

(i) activating a compound of Formula (II)

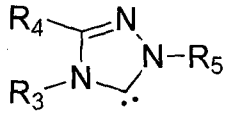


(II)

wherein

LG is a leaving group;

by reacting said compound of Formula (II) with a compound of Formula (III) in the presence of a base

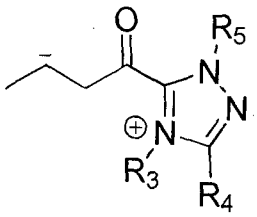


(III)

wherein

R_3, R_4, and R_5 are independently from each other selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety;

to obtain a compound of Formula (IV)

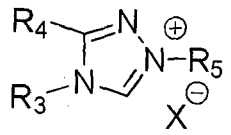


(IV)

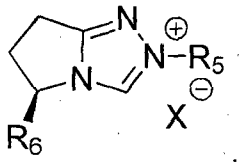
and

(ii) reacting the compound of Formula (IV) with an electrophile to obtain the compound of Formula (I).

[005] In another aspect the present invention is directed to compounds of Formulae (VI) and (VII)



(VI)



(VII)

wherein R_3, R_4, R_5, and R_6 are independently from each other selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety.

[006] In a still further aspect the present invention relates to the use of compounds of Formulae (VI) and (VII) for activating a compound of Formula (II).

DETAILED DESCRIPTION OF THE PRESENT INVENTION

[007] The present invention is based on the inventors' surprising finding that the β-carbon of a compound of Formula (II) can be activated to transform the compound into a nucleophilic compound of Formula (IV) by organocatalytic activation with a triazol carbene compound of Formula (III) and deprotonation with a base. Without wishing to be bound to any particular theory, it is believed that due to the electron-withdrawing ability of the NHC^+ moiety of Formula (III) and the conjugated nature of the compound of formula (IV), the proton(s) attached to the β-carbon become acidic. The obtained nucleophilic compound of Formula (IV) can then further be reacted with an electrophile in order to synthesize a compound of Formula (I).

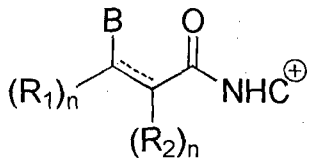
[008] To obtain β-carbon functionalization, typically the corresponding α,β-unsaturated carbonyl compound is used which is subsequently transformed into the desired nucleophile by, e.g., directing group-assisted transition metal insertion using palladium and C-H bond activation involving the β-carbons. When the saturated compound is the starting material, a further synthetic step is required for converting the saturated carbonyl compound into the

corresponding α,β-unsaturated compound. Thus, to functionalize the β-carbon additional synthetic steps involving additional chemicals are necessary and, as a result, complexity of the synthesis procedure and costs are increased.

[009] In contrast to the existing approaches, the present invention provides a cost-effective and less complex strategy for the direct activation of β-carbons of carbonyl compounds without the need for additional synthetic steps and chemicals. The subsequent reaction of the compound of Formula (IV) with an electrophile of interest to yield the desired compound of Formula (I) advantageously provides for high product yields and high selectivity, in particular with respect to enantiomeric ratios.

[010] The inventive synthesis can be conducted at ambient conditions and as a simple *one-pot* synthesis without purification steps between the synthesis of the compound of Formula (IV) and the subsequent synthesis of the compound of Formula (I).

[011] Based on this finding, in a first aspect the present invention thus relates to a method for synthesizing a compound of Formula (I)



(I)

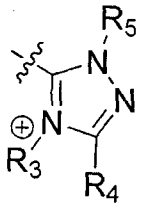
wherein

------ is a single or a double bond, wherein if it is a double bond n is 1 and if it is a single bond n is 2;

each R_1 and R_2 is independently selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety;

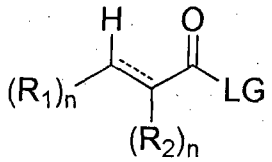
B is an electrophilic group; and

NHC^+ is



comprising:

(i) activating a compound of Formula (II)

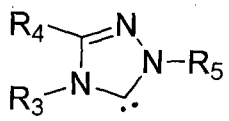


(II)

wherein

LG is a leaving group;

by reacting said compound of Formula (II) with a compound of Formula (III) in the presence of a base

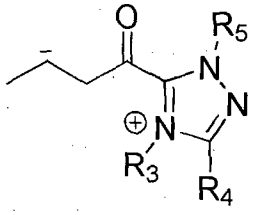


(III)

wherein

R_3, R_4, and R_5 are independently from each other hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety;

to obtain a compound of Formula (IV)



(IV)

and

(ii) reacting the compound of Formula (IV) with an electrophile to obtain the compound of Formula (I).

[012] In a preferred embodiment, the compound of Formula (I) can be a saturated carbonyl compound or its corresponding α,β-unsaturated compound. Preferably, the compound of Formula (I) is a saturated carbonyl compound meaning that the bond between the carbon atoms to which R_1 and R_2 are attached to is a single bond and n is 2. Consequently, the α- and β-carbon atom bear two R_1 and R_2 moieties, respectively. The two R_1 moieties can be selected independently from each other. In other words, the first R_1 moiety can be different from the second R_1 moiety. The same applies for the R_2 moiety.

[013] The term "any organic moiety" as used herein refers to carbon-containing moieties. These moieties can be linear or branched, substituted or unsubstituted, and are preferably derived from hydrocarbons, typically by substitution of one or more hydrogen or carbon atoms by other atoms, such as oxygen, nitrogen, sulfur, phosphorous, or functional groups that contain oxygen, nitrogen, sulfur, phosphorous. The organic moiety can comprise any number of carbon atoms, for example up to up to 5000 or more (typically in case of polymeric moieties), but

preferably it is a low molecular weight organic moiety with up to 100, or more preferably up to 40 carbon atoms and, optionally, a molecular weight Mw of 1000 or less. It is preferred that the organic moiety is compatible with the activation reaction described herein and does not adversely affect the described reaction mechanism. Suitable groups and moieties are well known to those skilled in the art or can be readily identified by routine experimentation.

[014] In a preferred embodiment, the organic moiety can be a linear or branched, substituted or unsubstituted alkyl with 1 to x carbon atoms; linear or branched, substituted or unsubstituted alkenyl with 2 to x carbon atoms; linear or branched, substituted or unsubstituted alkinyl with 2 to x carbon atoms; linear or branched, substituted or unsubstituted alkoxy with 1 to x carbon atoms; substituted or unsubstituted cycloalkyl with 3 to x carbon atoms; substituted or unsubstituted cycloalkenyl with 3 to x carbon atoms; substituted or unsubstituted aryl with 6 to x carbon atoms; and substituted or unsubstituted heteroaryl with 3 to x carbon atoms; with x being any integer of 2 or more, preferably up to 50, more preferably up to 30.

[015] In a further embodiment of the present invention, the organic moiety can be a linear or branched, substituted or unsubstituted alkyl with 1 to 40 carbon atoms; linear or branched, substituted or unsubstituted alkenyl with 3 to 40 carbon atoms; linear or branched, substituted or unsubstituted alkoxy with 1 to 40 carbon atoms, substituted or unsubstituted cycloalkyl with 5 to 40 carbon atoms; substituted or unsubstituted cycloalkenyl with 5 to 40 carbon atoms; substituted or unsubstituted aryl with 5 to 40 carbon atoms; and substituted or unsubstituted heteroaryl with 5 to 40 carbon atoms.

[016] In another embodiment, the organic moiety can be a linear or branched, substituted or unsubstituted alkyl with 1 to 20 carbon atoms; linear or branched, substituted or unsubstituted alkenyl with 3 to 20 carbon atoms; linear or branched, substituted or unsubstituted alkoxy with 1 to 20 carbon atoms, substituted or unsubstituted cycloalkyl with 5 to 20 carbon atoms; substituted or unsubstituted cycloalkenyl with 5 to 20 carbon atoms; substituted or unsubstituted aryl with 5 to 14 carbon atoms; and substituted or unsubstituted heteroaryl with 5 to 14 carbon atoms.

[017] The organic moiety can also be a combination of any of the above-defined groups, including but not limited to alkylaryl, arylalkyl, alkylheteroaryl and the like, to name only a few, all of which may be substituted or unsubstituted.

[018] The term "substituted" as used herein in relation to the above moieties refers to a substituent other than hydrogen. Such a substitutent is preferably selected from the group consisting of halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH -OR, -NRR', -C(O)R, -C(O)OR, -(CO)NRR', -NR'C(O)R, -OC(O)R, aryl with 5 to 20 carbon atoms, cycloalk(en)yl with 3 to 20

carbon atoms, 3- to 8-membered heterocycloalk(en)yl, and 5- to 20-membered heteroaryl, wherein R and R' are independently selected from hydrogen, alkyl with 1 to 10 carbon atoms, alkenyl with 2 to 10 carbon atoms, alkynyl with 2 to 10 carbon atoms, aryl with 5 to 14 carbon atoms, cycloalk(en)yl with 3 to 20 carbon atoms, 5- to 14- membered heteroaryl, comprising 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur, and 5- to 14- membered heterocycloalk(en)yl, comprising 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur. Any of these substituents may again be substituted, it is however preferred that these substituents are unsubstituted.

[019] Alkyl refers to a saturated hydrocarbon moiety, such as methyl, ethyl, and the like.

[020] Alkenyl and Alkynyl comprise at least one carbon-carbon double bonds or triple bonds, respectively, and are otherwise defined as alkyl above.

[021] Cycloalkyl refers to a non-aromatic carbocyclic moiety, such as cyclopentanyl, cyclohexanyl, and the like.

[022] Cycloalkenyl refers to non-aromatic carbocyclic compounds that comprise at least one C-C double bond.

[023] Similarly, heterocycloalk(en)yl relates to cycloalk(en)yl groups wherein 1 or more ring carbon atoms are replaced by heteroatoms, preferably selected from nitrogen, oxygen, and sulfur.

[024] Aryl relates to an aromatic ring that is preferably monocyclic or consists of condensed aromatic rings. Preferred aryl substituents are moieties with 6 to 14 carbon atoms, such as phenyl, naphthyl, anthracenyl, and phenanthrenyl.

[025] Heteroaryl refers to aromatic moieties that correspond to the respective aryl moiety wherein one or more ring carbon atoms have been replaced by heteroatoms, such as nitrogen, oxygen, and sulfur.

[026] All of the afore-mentioned groups can be substituted or unsubstituted. When substituted the substituent can be selected from the above list of substituents.

[027] The term "at least one" as used herein relates to one or more, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or more of the referenced species.

[028] Halogen as used herein refers to F, Cl, Br, and I.

[029] In various embodiments of the present invention, the compound of formula (I) is an α,β-saturated compound, i.e. there is a single bond connecting the α- and β-carbon atom.

[030] In various embodiments of the invention, moiety R_1 of Formula (I) and (II) is an alkyl with 1 to 5, preferably 3 carbon atoms.

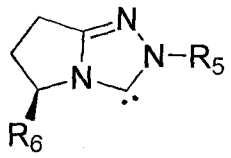
[031] In various other embodiments, moiety R_1 of Formula (I) and (II) is an aryl, selected from the group consisting of phenyl, furane, and naphthalene, which optionally can be substituted, preferably by halogen, alkyl with 1 to 5 carbon atoms, and/or alkoxy with 1 to 5 carbon atoms.

[032] In a further embodiment of the present invention, the compound of Formula (II) is selected from the group consisting of 4-Nitrophenyl 3-(*para*-tolyl)propanoate, 4-Nitrophenyl 3-(4-methoxyphenyl)propanoate, 4-Nitrophenyl 3-(4-fluorophenyl)propanoate, 4-Nitrophenyl 3-(4-chlorophenyl)propanoate, 4-Nitrophenyl 3-(4-bromophenyl)propanoate, 4-Nitrophenyl 3-(naphthalen-1-yl)propanoate, 4-Nitrophenyl 3-(furan-2-yl)propanoate, 4-Nitrophenyl hexanoate, 4-nitrophenyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)propanoate, 4-nitrophenyl butyrate, 4-nitrophenyl propionate, and cinammaldehyde.

[033] The term "electrophilic group" as used herein refers to a group that results from the reaction of an electrophile, as described below, with the compound of Formula (IV).

[034] In a preferred embodiment of the present invention, the moieties R_3 and R_4 of the compound of Formula (III) combine to form together with the carbon atoms to which they are attached a substituted or unsubstituted 5- to 40-membered cycloalkyl, cycloalkenyl, heteroalicyclic, aryl, or heteroaryl ring.

[035] In various embodiments, the compound of Formula (III) is a compound of Formula (V)



(V)

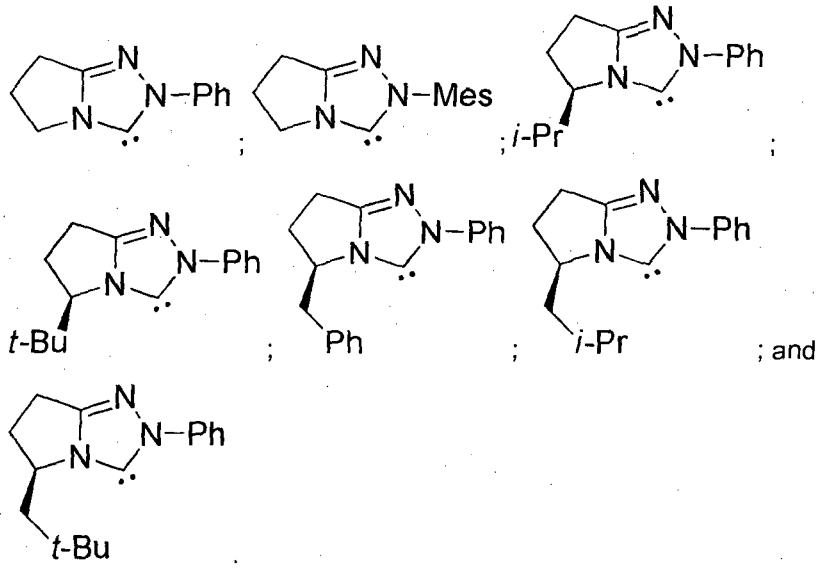
wherein R_5 is as defined above and R_6 is selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety.

[036] R_6 can be selected from the group consisting of substituted or unsubstituted, linear or branched alkyl with 1-20 carbon atoms; substituted or unsubstituted, linear or branched alkenyl with 1-20 carbon atoms; substituted or unsubstituted cycloalkyl with 5 to 20 carbon atoms; substituted or unsubstituted cycloalkenyl with 5 to 20 carbon atoms; substituted or unsubstituted aryl with 5-14 carbon atoms; and substituted or unsubstituted heteroaryl with 5-14 carbon atoms. Preferably, R_6 is selected from the group consisting of -*iso*-Pr, -*tert*-Bu, $-CH_2Ph$, $-CH_2-$

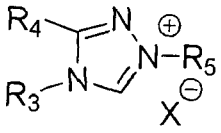
iso-Pr, and -CH_2-*tert*-Bu. More preferably, R_6 is selected from the group consisting of -CH_2-*tert*-Bu and -CH_2-*iso*-Pr.

[037] In one embodiment of the compound of Formula (V), R_5 is aryl. Preferably R_5 is selected from the group consisting of phenyl and mesitylene, more preferably R_5 is phenyl.

[038] In a preferred embodiment, the compound of Formula (V) is selected from the group consisting of



[039] In various embodiments, the compound of Formula (III) or (V) is synthesized from a compound of Formula (VI)

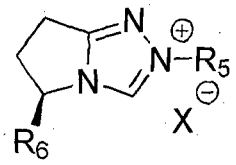


(VI)

wherein X is any anion and R_3-R_5 are as defined above.

[040] In various embodiments of the present invention, X can be selected from the group consisting of F^-, Cl^-, Br^-, I^-, OH^-, HSO_3^-, SO_3^{2-}, SO_4^{2-}, NO_2^-, NO_3^-, PO_4^{3-}, BF_4^-, PF_6^-, ClO_4^-, OTf^-, acetate, citrate, formiate, glutarate, lactate, malate, malonate, oxalate, pyruvate, and tartrate. In a preferred embodiment of the present invention, X is selected from the group consisting of F^-, Cl^-, Br^-, I^-, BF_4^-, OTf^-, and acetate.

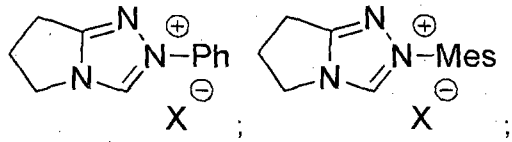
[041] In another embodiment, the compound of Formula (VI) is a compound of Formula (VII)



(VII)

wherein R_5 and R_6 are as defined above.

[042] In still another embodiment of the present invention, the compound of Formula (VII) is selected from the group consisting of



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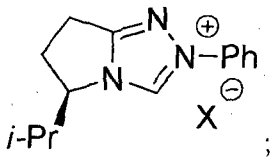
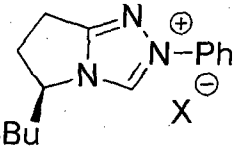


; *t*-Bu



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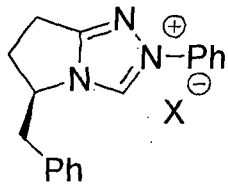
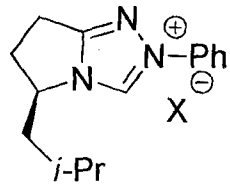


; *i*-Pr



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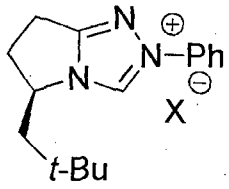

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[043] In a preferred embodiment, the compound of Formula (III) or (V) is generated *in situ* from a compound of Formula (VI) or (VII).

[044] The term "*in situ*" as used herein means in the reaction mixture. Specifically, this means that the respective compound is synthesized in the reaction mixture.

[045] The term "leaving group" as used herein refers to a moiety that is released from a molecule it was covalently bound to by keeping the pair of electrons previously forming the bond. A leaving group can be a single atom, a molecule, or a functional group. These groups can be an anion or a neutral molecule. The leaving group may have a –I effect. The leaving group of the present invention can be any leaving group which is suitable for the described reaction. In various embodiments, the leaving group can be selected from the group of hydrogen, halogen, $-N_2^+$, $-OR_2^+$, $-OSO_2C_4F_9$, $-OSO_2CF_3$, $-OSO_2F$, -OTs, -OMs, $-OH_2^+$, $-OHR^+$, $-ONO_2$, $-OPO(OH)_2$, $-SR_2$, $-NR_3$, -OCOR, $-NH_3^+$, and $-O-C_6H_4$-*para*-NO_2, and R can be any organic residue or moiety. In a preferred embodiment, the leaving group is $-O-C_6H_4$-*para*-NO_2.

[046] The reactions can be carried out in an organic solvent. The organic solvent used in the present invention can be any organic solvent which is suitable. In a preferred embodiment, the

organic solvent is selected from the group consisting of *tert*-Butanol, toluene, THF, CH_3CN, CH_2Cl_2, dioxane, ethyl acetate, and mixtures thereof. For the different steps of (i), i.e. activating a compound of Formula (I), and (ii), i.e. reacting the compound of Formula (IV) with an electrophile, different or the same organic solvents can be used.

[047] In various embodiments, both steps (i) and (ii) are conducted in a *one-pot* synthesis.

[048] The term "*one-pot* synthesis" as used herein means that the reactions (i) and (ii) according to the present invention are carried out in the same reaction vessel without any purification step of an intermediate.

[049] In various embodiments, the base in the reaction mixture is present in an amount of 100 to 300 mol-%, preferably 115 to 250 mol-%, more preferably 130 to 200 mol-%, most preferably about 150 mol-%, based on the total amount of the compound of Formula (I).

[050] "About", as used herein, refers to the numerical value it relates to ±10%.

[051] In various embodiments of the present invention, the electrophile can be any suitable electrophile. "Electrophile", as used herein, generally relates to any reagent, such as atom or molecule, that is attracted to electrons and participates in the chemical reaction by accepting an electron pair in order to bind to the nucleophile. In various embodiments, the electrophile may be a Lewis acid. In preferred embodiments, the electrophile is selected from the group consisting of F_2, Cl_2, Br_2, I_2, alkyl-LG, alkenyl-LG, alkoxy-LG, acyl-LG, aryl-LG, heteroaryl-LG, hydrazone, and a carbonyl compound. "LG" is a leaving group and is defined as above. The electrophile can also be any Michael acceptor.

[052] In specific embodiments, the electrophile is selected from the group of optionally α,β-unsaturated, linear or branched, substituted or unsubstituted ketone; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted aldehyde; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted esters; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted trifluoroketone; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted carboxamide; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted amide; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted nitrile; optionally linear or branched, substituted or unsubstituted imine; linear or branched, substituted or unsubstituted nitrone; linear or branched, substituted or unsubstituted diazene, and optionally α,β-unsaturated, linear or branched, substituted or unsubstituted hydrazone. More preferably, the electrophile is selected from the group consisting of α,β-unsaturated, linear or branched, substituted or unsubstituted ketone, trifluoroketone, and hydrazone.

[053] In various embodiments, the base used in accordance with the present invention contains one or more nitrogen atom(s). The base used can be any suitable base and may, for example, be selected from the group consisting of pyrrolidine; $N(CH_3)_3$; $N(CH_2CH_3)_3$; (*iso*-Propyl)$_2$NH; 2,2,6,6-Tetramethyl-1-piperidin; LDA (Lithium di*iso*propylamid); LHMDS (Lithium bis(trimethylsilyl)amide); LTMP (Lithium tetramethylpiperidide); and 4-aminopyridine.

[054] In a preferred embodiment, the base is an amidine. The amidine can be selected from the group consisting of DBU (1,8-Diazabicyclo[5.4.0]undec-7-en); DBN (1,5-Diazobicyclo[3.4.0]non-5-ene); and DABCO (1,4-Diazobicyclo[2.2.2]octan).

[055] In another embodiment of the present invention, the base is a phosphazine. The phosphazine can be selected from the group consisting of P_1-*tert*-Bu-tris(tetramethylene); 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; and 1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene).

[056] In various embodiments, the reaction temperature used in steps (i) and (ii) of the method disclosed herein ranges from 0 °C to 85 °C. The reaction temperature of these steps can also be from 15 °C to 55 °C. Preferably, the reaction temperature used in steps (i) and (ii) is about 20 to 30 °C, more preferably about 25°C.

[057] The reaction temperatures of steps (i) and (ii) may be selected independently from each other, for instance the reaction temperature of step (i) may be 25 °C whereas the reaction temperature of step (ii) may be 40 °C.

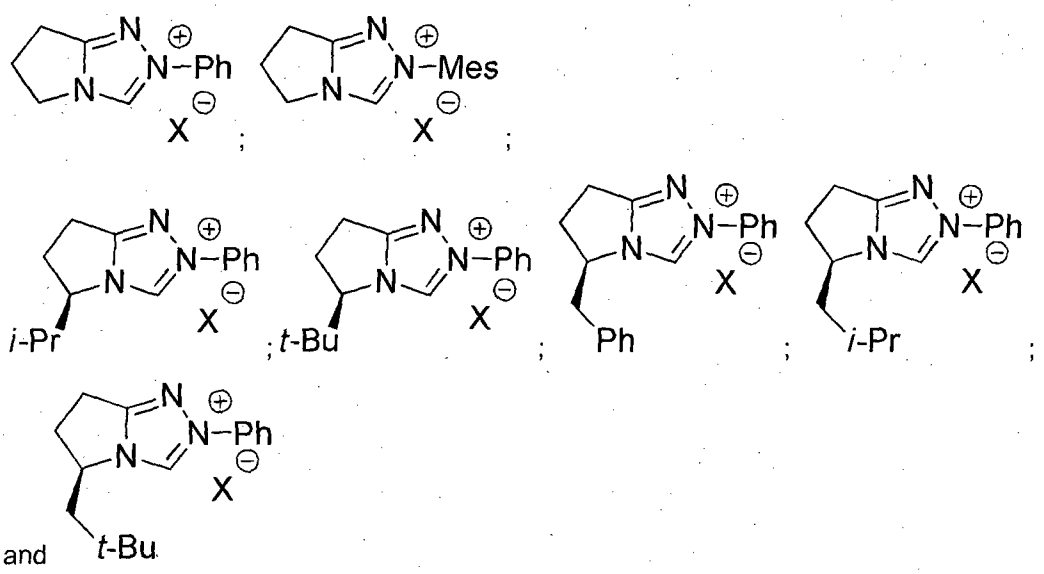
[058] In various embodiments of the invention, the reaction time is from 0.1 hours to 72 hours. The reaction time can also be from 1 hour to 48 hours. In still another embodiment, the reaction time is from 5 hours to 36 hours, preferably about 24 hours.

[059] In various embodiments of the present invention, a molecular sieve is present in the reaction mixture, preferably with apertures of a size of approximately 4 Å.

[060] The method disclosed herein may comprise additional reaction steps which may be carried out after or between the reaction steps (i) and (ii) according to the present invention. Such additional steps may include steps for catalyst regeneration, Michael reactions, aldol reactions, lactonization, and/or decarboxylation.

[061] The present invention also encompasses a compound of Formula (VI) or (VII).

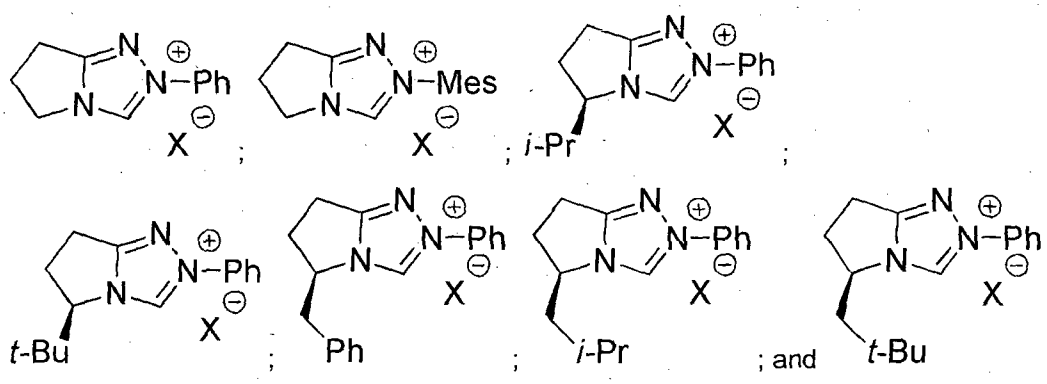
[062] In various embodiments, the compound of Formula (VI) or (VII) may be selected from the group consisting of



wherein X is defined as above.

[063] Also encompassed by the present invention is the use of a compound of Formula (VI) or (VII) for activating a compound of Formula (II), wherein said compounds are as defined above.

[064] In various embodiments, for this use the compound of Formula (VI) or (VII) is selected from the group consisting of



wherein X is defined as above.

[065] By "comprising", as used herein, is meant including, but not limited to, whatever follows the word "comprising". Thus, use of the term "comprising" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present.

[066] The following examples are provided to better illustrate the claimed invention and are not be interpreted in any way as limiting the scope of the invention. All specific compounds, materials, and methods described below, in whole or in part, fall within the scope of the invention. These specific compounds, materials, and methods are not intended to limit the

invention, but merely to illustrate specific embodiments falling within the scope of the invention. One skilled in the art may develop equivalent compounds, materials, and use without the exercise of inventive capacity and without departing from the scope of the invention. It is the intention of the inventors that such variations are included in the scope of the present invention.

[067] All references cited herein are incorporated by reference in their entirety.

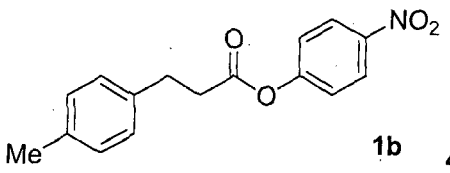
EXAMPLES

General information

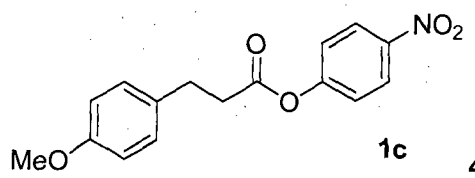
[068] Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. HPLC grade CH_3CN (purchased from TEDIA) was dried over 4Å molecular sieve prior use. Toluene and DCM was dried over Pure Solv solvent purification system. THF was distilled over sodium. Other solvents were dried over 4Å molecular sieve prior use. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ=0.00) or chloroform (δ=7.26, singlet). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of enantiomeric excess was performed *via* chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]^{rt}_D$ (c is in gm per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp or potassium permanganate stain.

Substrate preparation

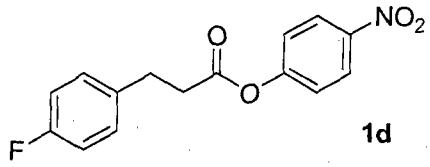
[069] The synthesis of 4-nitrophenyl esters (**1b-i**) was performed by adopting known procedures.[1]



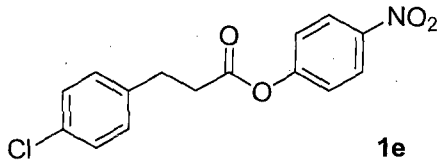
1b **4-Nitrophenyl 3-(*para*-tolyl)propanoate:** White solid; 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.34 (s, 3H), 2.91 (t, J = 7.6 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 7.12–7.25 (m, 6H), 8.22–8.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.5, 155.4, 145.3, 136.6, 136.2, 129.4, 128.3, 125.2, 122.5, 36.1, 30.4, 21.1; HRMS(ESI) calcd for $C_{16}H_{16}NO_4$ $(M+H)^+$: 286.1079, Found: 286.1088.



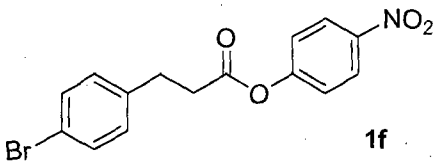
1c **4-Nitrophenyl 3-(4-methoxyphenyl)propanoate:** White solid; 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.90 (t, J = 7.2 Hz, 2H), 3.02 (t, J = 7.2 Hz, 2H), 3.80 (s, 3H), 6.87 (d, J = 8.8 Hz, 2H), 7.18–7.26 (m, 4H), 8.24 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.5, 158.4, 155.4, 145.3, 131.7, 129.4, 125.2, 122.5, 114.1, 55.3, 36.2, 30.0; HRMS(ESI) calcd for $C_{16}H_{16}NO_5(M+H)^+$: 302.1028, Found: 302.1032.



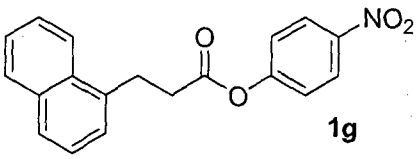
1d **4-Nitrophenyl 3-(4-fluorophenyl)propanoate:** White solid; 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.89–2.93 (m, 2H), 3.06 (t, J = 7.2 Hz, 2H), 6.99–7.04 (m, 2H), 7.17–7.24 (m, 4H), 8.23–8.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.3, 162.9, 160.5, 155.3, 145.4, 135.4, 135.3, 129.9, 129.8, 125.2, 122.4, 115.6, 115.4, 36.0, 30.0; HRMS(ESI) calcd for $C_{15}H_{13}FNO_4(M+H)^+$: 290.0829, Found: 290.0841.



1e **4-Nitrophenyl 3-(4-chlorophenyl)propanoate:** White solid; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.90–2.94 (m, 2H), 3.05 (t, J = 7.2 Hz, 2H), 7.18–7.31 (m, 6H), 8.25 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.2, 155.3, 145.4, 138.1, 132.5, 129.8, 128.8, 125.2, 122.4, 35.7, 30.1; HRMS(ESI) calcd for $C_{15}H_{13}ClNO_4$ $(M+H)^+$: 306.0533, Found: 306.0542.

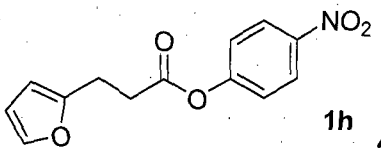


1f **4-Nitrophenyl 3-(4-bromophenyl)propanoate:** White solid; 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.90–2.94 (m, 2H), 3.03 (t, J = 7.2 Hz, 2H), 7.13–7.22 (m, 4H), 7.45 (d, J = 7.2 Hz, 2H), 8.23–8.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.2, 155.3, 145.4, 138.7, 131.8, 130.2, 125.2, 122.4, 120.5, 35.7, 30.1; HRMS(ESI) calcd for $C_{15}H_{13}BrNO_4Na$ $(M+Na)^+$: 371.9847, Found: 371.9846.

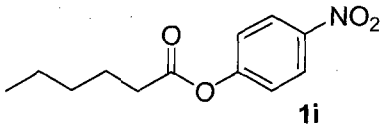


1g **4-Nitrophenyl 3-(naphthalen-1-yl)propanoate:** White

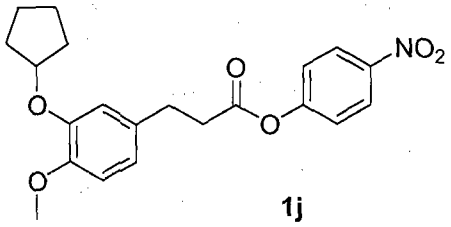
solid; 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.06 (t, J = 7.6 Hz, 2H), 3.54 (t, J = 7.6 Hz, 2H), 7.15–7.19 (m, 2H), 7.40–7.58 (m, 4H), 7.77 (dd, J = 7.2, 2.4 Hz, 1H), 7.88–7.90 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H), 8.20–8.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 155.4, 145.4, 135.7, 134.0, 131.6, 129.1, 127.6, 126.4, 126.3, 125.8, 125.6, 125.2, 123.2, 122.4, 35.3, 28.0; HRMS(ESI) calcd for $C_{19}H_{16}NO_4(M+H)^+$: 322.1079, Found: 322.1093.



1h **4-Nitrophenyl 3-(furan-2-yl)propanoate:** White solid; 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.94–2.97 (m, 2H), 3.11 (t, J = 7.2 Hz, 2H), 6.10 (dd, J = 3.2, 0.4 Hz, 1H), 6.32 (dd, J = 3.2, 1.6 Hz, 1H), 7.23–7.27 (m, 2H), 7.35 (d, J = 1.2 Hz, 1H), 8.24–8.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.1, 155.4, 153.3, 145.4, 141.6, 125.2, 122.4, 110.4, 105.9, 33.0, 23.4; HRMS(ESI) calcd for $C_{13}H_{12}NO_5$ $(M+H)^+$: 262.0715, Found: 262.0710.



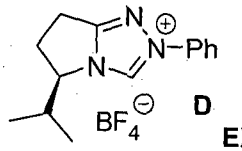
1i **4-Nitrophenyl hexanoate:** colorless liquid; 95% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.94 (t, J = 7.2 Hz, 3H), 1.36–1.43 (m, 4H), 1.76 (q, J = 7.6 Hz, 2H), 2.60 (t, J = 7.2 Hz, 2H), 7.27–7.29 (m, 2H), 7.26 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.3, 155.6, 145.3, 125.2, 122.4, 34.3, 31.2, 24.4, 22.3, 13.9; HRMS(ESI) calcd for $C_{12}H_{16}NO_4$ $(M+H)^+$: 238.1079, Found: 238.1079.



1j **4-nitrophenyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)propanoate**: yellow oil; 90% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.55–1.62 (m, 2H), 1.84–1.91 (m, 6H), 2.90 (t, J = 7.2 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 3.84 (s, 3H), 4.73–4.76 (m, 1H), 6.76–6.84 (m, 3H), 7.19 (d, J = 8.8 Hz, 2H), 8.25 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.5, 155.4, 148.9, 147.8, 145.3, 132.1, 125.2, 122.4, 120.3, 115.6, 112.2, 80.5, 56.2, 36.2, 32.8, 30.4, 24.0; HRMS(ESI) calcd for $C_{21}H_{24}NO_6(M+H)^+$: 386.1604, Found: 386.1603.

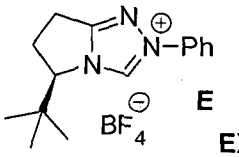
Catalytic preparation

[070] The triazolium-based compound of Formulae (III) and (V) (**A-H**) were prepared by adopting known procedures.[2]



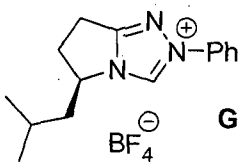
D

EXAMPLE 1: (*R*)-5-Isopropyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate: White solid; $[\alpha]_D^{23}$ (c 2.0, CH_3CN) = + 49.6°; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 2.42–2.59 (m, 2H), 2.88–2.98 (m, 1H), 3.09–3.18 (m, 1H), 3.22–3.30 (m, 1H), 4.89–4.94 (m, 1H), 7.48–7.54 (m, 3H), 7.86 (d, J = 6.8 Hz, 2H), 10.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 136.9, 135.6, 130.7, 130.1, 120.8, 66.2, 31.1, 28.4, 21.7, 18.4, 16.2; HRMS(ESI) calcd for $C_{14}H_{18}N_3(M)^+$: 228.1501, Found: 228.1496.



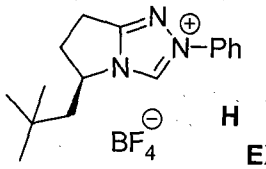
E

EXAMPLE 2: (*R*)-5-(Tert-butyl)-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate: White solid; $[\alpha]_D^{23}$ (c 2.0, CH_3CN) = + 45.4°; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H), 2.58–2.65 (m, 1H), 2.94–3.22 (m, 3H), 4.75–4.77 (m, 1H), 7.49–7.55 (m, 3H), 7.88 (d, J = 7.2 Hz, 2H), 10.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 137.5, 135.5, 130.7, 130.1, 121.0, 70.5, 34.6, 29.0, 25.6, 21.7; HRMS(ESI) calcd for $C_{15}H_{20}N_3(M)^+$: 242.1657, Found: 242.1655.



G

EXAMPLE 3: (*R*)-5-Isobutyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate: White solid; $[\alpha]_D^{23}$ (c 2.0, CH_3CN) = + 40.7°; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97–1.00 (m, 6H), 1.59–1.75 (m, 2H), 2.14–2.20 (m, 1H), 2.42–2.47 (m, 1H), 3.02–3.07 (m, 1H), 3.19–3.29 (m, 2H), 4.99–5.03 (m, 1H), 7.47–7.52 (m, 3H), 7.81–7.84 (m, 2H), 10.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 136.6, 135.6, 130.6, 130.1, 120.8, 60.2, 42.9, 33.3, 25.2, 22.9, 21.6, 21.3; HRMS(ESI) calcd for $C_{15}H_{20}N_3(M)^+$: 242.1657, Found: 242.1657.



H

EXAMPLE 4: (*R*)-5-Neopentyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate: White solid; $[\alpha]_D^{23}$ (c 2.0, CH_3CN) = + 48.2°; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.67 (dd, J = 13.6, 11.2 Hz, 1H), 2.36 (dd, J = 12.8, 2.0 Hz, 1H), 2.45–2.51 (m, 1H), 3.08–3.22 (m, 2H), 3.27–3.36 (m, 1H), 4.98–5.01 (m, 1H), 7.45–7.51 (m, 3H), 7.81–7.83 (m, 2H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 136.5, 135.6, 130.5, 130.1, 120.8, 59.8, 48.2, 35.8, 30.4, 29.7, 22.1; HRMS(ESI) calcd for $C_{16}H_{22}N_3(M)^+$: 256.1814, Found: 256.1812.

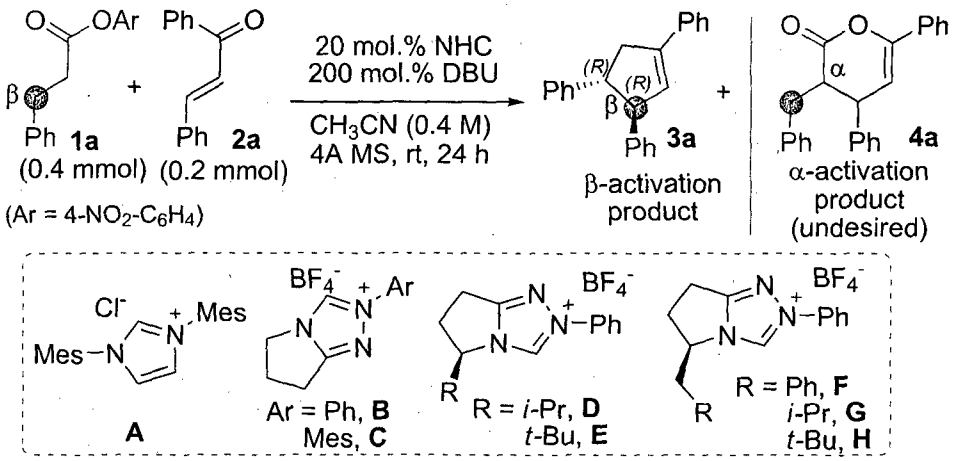
General procedure of the catalytic reactions

[071] EXAMPLE 5: Reaction of esters and enones to synthesize 3 (3a as an example): A dry 10 mL Schlenk tube equipped with a magnetic stirring bar was successively charged with ester **1a** (109 mg, 0.40 mmol), chalcone **2a** (42 mg, 0.20 mmol), NHC pre-catalyst **H** (13.8 mg, 0.04 mmol) and 4Å Molecular Sieve (200 mg). The tube was closed with a septum, evacuated, and refilled with nitrogen. To this mixture was added dry CH_3CN (0.5 mL), followed by the addition of DBU (46 μL, 0.30 mmol) *via* a micro syringe. After stirred for 24 hours at room temperature, the reaction mixture was analyzed by ^1H NMR analysis (to determine *d.r.*), and then directly applied to silica gel column chromatography (1% v/v ethyl acetate in hexane) to afford **3a** as a colorless oil in 66% yield, 7:1 *d.r.* and 95:5 *e.r.*.

[072] EXAMPLE 6: The synthesis of γ-lactone 5a from ester 1a and trifluoroketone 4a was performed using a procedure similar to that used in the catalytic synthesis of **3a**: A dry 10 mL Schlenk tube equipped with a magnetic stirring bar was successively charged with ester **1a** (109 mg, 0.40 mmol), 2,2,2-trifluoro-1-phenylethanone **4a** (28 μL, 0.20 mmol), NHC pre-catalyst **H** (13.8 mg, 0.04 mmol) and 4Å Molecular Sieve (200 mg). The tube was closed with a septum, evacuated, and refilled with nitrogen. To this mixture was added dry toluene (1.0 mL), followed by the addition of DBU (46 μL, 0.30 mmol) *via* a micro syringe. After stirred for 48 hours at 0 °C, the reaction mixture was concentrated under reduced pressure. The crude residue was analyzed by ^1H NMR analysis (to determine *d.r.*), and then directly applied to silica gel column chromatography (2:1 v/v hexanes/dichloromethane) to afford γ-lactone products-a mixture of diastereomers (**5a**, and **5a'**) as a colorless oil in 54% yield with 1.3:1 *d.r.*, 91:9 and 94:6 *e.r.* for the major and minor diastereomer respectively. For the *trans*- and *cis*-isomers, (*4S*, *5S*)-**5a** and (*4S*, *5R*)- **5a'** were obtained as the major enantiomers respectively. The relative and absolute chemistry were determined by comparing the chiral phase HPLC trace with authentic samples prepared using literature methods.[3] HPLC (Chiralcel OD, 99:1 hexanes/*i*-PrOH, 0.7 mL/min), t_r

(**5a**-major) = 22.6 min, t_r (**5a**-minor) = 42.3 min, t_r (**5a'**-major) = 20.0 min, t_r (**5a'**-minor) = 68.7 min.

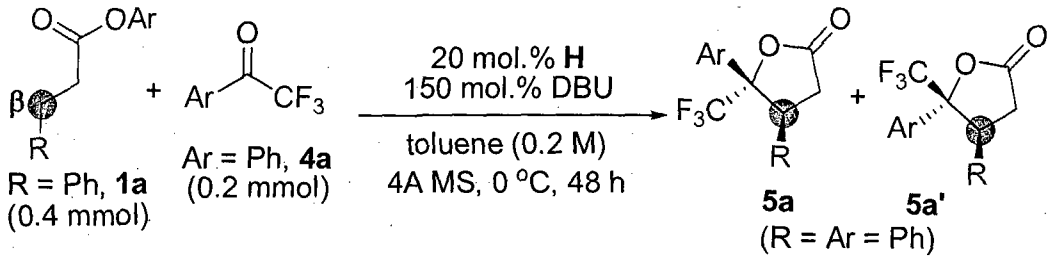
Table S1. Organocatalytic approach to activate saturated ester *β*-carbon as nucleophile for asymmetric reaction.



Entry	Compound of Formula (VI)	**3a**:**4a**	**3a** yield	**3a** *d.r.*	**3a** *e.r.*
1	**A**	n.d.	< 5	n.d	-
2	**B**	> 20:1	85	14:1	-
3	**C**	5:1	79	7:1	-
4	**D**	> 20:1	69	11:1	87:13
5	**E**	> 20:1	30	8:1	95:5
6	**F**	8:1	54	16:1	87:13
7	**G**	> 20:1	71	12:1	91:9
8*	**G**	> 20:1	74	14:1	91:9
9*	**H**	> 20:1	70(66)	7:1	95.5:4.5

Unpurified reaction mixture. The enantiomeric ratio (*e.r.*) of **3a** (major diastereomer) was determined *via* chiral phase HPLC analysis, absolute configuration of **3a** was determined *via* X-ray structure of **3y**. Structure of *α*-activation product **4a** was confirmed *via* ^{1}H NMR analysis. *Reactions run with 150 mol.% DBU, yield for **3a** in parentheses (entry 9) was isolated yield. NHC, N-heterocyclic carbene. DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene. MS, molecular sieve. Mes, 1,3,5-trimethylbenzene. *i*-Pr, *iso*-propyl. *t*-Bu, *tert*-butyl.

Table S2. Condition optimization for synthesis of γ-lactone **5a** and **5a'** from ester **1a** and triflouroketone **4a**



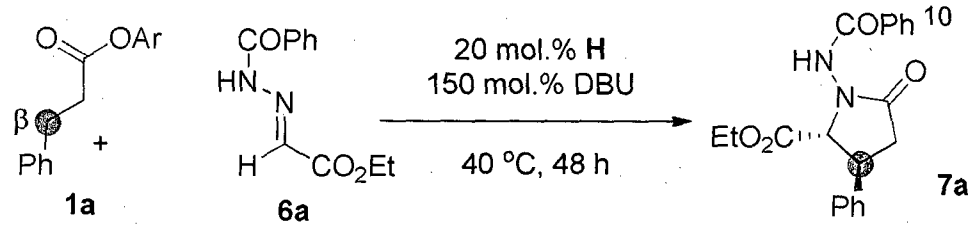
Entry	Solvent	Temperature	Time (h)	Yield (**5a+5a'**) (%)[a]	*d.r.* (**5a:5a'**)[b]	*e.r.* [c]
1	CH_2Cl_2	RT	24	61	2.1:1	77:23/79:22
2	Toluene	RT	24	56	1.3:1	89:11/92:8
3	CH_3CN	RT	24	58	1.8:1	75:25/79:22
4	Ethyl Acetate	RT	24	58	1.4:1	86:14/91:9
5	THF	RT	24	57	1.3:1	86:14/91:9
6	t-BuOH	RT	24	73	3.0:1	72:28/75:25
7	Dioxane	RT	24	49	1.4:1	87:13/90:10
8	Toluene.	0 °C	24	45	1.3:1	91:9/94:6
9	Toluene.	0 °C	48	54	1.3:1	91:9/94:6

[a] Isolated yield. [b] Diastereomeric ratio, estimated *via* ^{1}H NMR analysis of crude reaction mixture. [c] Enatiomeric ratio of **5a** and **5a'** respectively, estimated *via* chiral phase HPLC analysis. RT, room temperature, which is 25 °C.

[073] EXAMPLE 7: The synthesis of γ-lactam 7a and 7a' from ester 1a and hydrazone 6a was performed using a similar procedure to that for the preparation of **5a** above: A dry 10 mL Schlenk tube equipped with a magnetic stir bar was successively charged with ester **1a** (55 mg, 0.2 mmol), hydrazone **6a** (22 mg, 0.10 mmol), NHC pre-catalyst **H** (6.9 mg, 0.02 mmol) and 4Å Molecular Sieve (200 mg). The tube was closed with a septum, evacuated, and refilled with nitrogen. To this mixture was added dry EA (0.5 mL), followed by the addition of DBU (23 μL, 0.15 mmol) *via* a micro syringe. After being stirred for 48 hours at 40 °C, the reaction mixture was concentrated under reduced pressure. The crude residue was analyzed by ^{1}H NMR analysis (to determine *d.r.*), and then was diluted with CH_2Cl_2 (15 mL) and washed with a 1:1 mixture of saturated aqueous NH_4Cl and water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The oily residue was applied to silica gel column chromatography (3:1 v/v hexanes/ethyl acetate) to afford γ-lactam products-a mixture of diastereomers as a

colorless oil in 74% yield with 6 : 1 *d.r.*, 97:3/90:10 *e.r.* for the major and minor diastereomers respectively. The two diastereomers could also be separated for HPLC, NMR, and optical rotation analysis. The relative stereo-configurations of both diastereomers were determined by comparison with literature samples,[4] and the absolute configuration of the *trans*-isomer (**7a**) was determined via x-ray structure analysis. HPLC [Chiralcel IA, 75:20:5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 75:20:5)/*i*-PrOH, 0.7 mL/min], t_r(**7a**-major) = 88.3 min, t_r(**7a**-minor) = 110.2 min, t_r (major enantiomer of the minor diastereomer) = 66.7 min, t_r (minor enantiomer of the minor diastereomer) = 72.9 min. Optical rotation: **7a**, $[\alpha]_D^{23}$ (c 0.94, CH_2Cl_2) = - 39.1°.

Table S3. Condition optimization for synthesis of γ-lactam **7a** from ester **1a** and hydrazone **6a**



1a (0.2 mmol) **6a** (0.1 mmol)

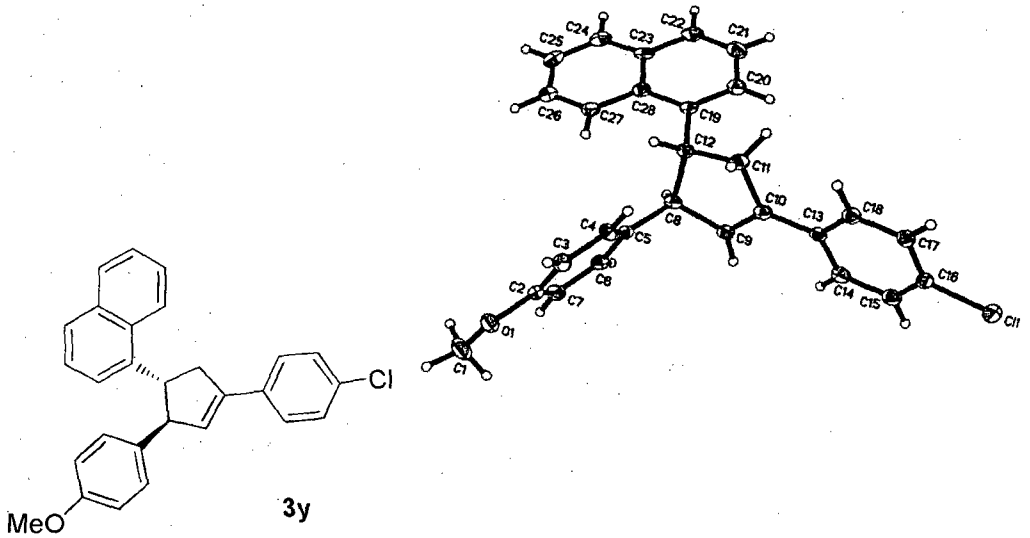
Entry[a]	Solvent	Yield (%)[b]	*d.r.*[c]	*e. r.* [d]
1	CH_3CN	26	3.3:1	98:2/91:9
2	Toluene	72	5.8:1	97:3/89:11
3	Dioxane	95	3.6:1	97:3/90:10
4	**Ethyl Acetate**	**82(74)[e]**	**6.0:1**	**97:3/90:10**
5	THF	78	5.3:1	97:3/92:8
6	CH_2Cl_2	71	4.0:1	97:3/92:8
7	t-BuOH	74	2.4:1	96:4/89:11
8[f]	Ethyl Acetate	79	6.0:1	97:3/90:10

[a] Reaction was carried out at 0.2 M concentration of **6a**, with the presence of 200 mg 4Å Molecular Sieve. [b] Yields were estimated via ^{1}H NMR yield. [c] Diastereomeric ratio, estimated *via* ^{1}H NMR analysis of crude reaction mixture. [d] Enantiomeric ratio of the **7a** and and its diastereomer respectively, estimated *via* chiral phase HPLC analysis. [e] Isolated yield. [f] 20 mmol% $Mg(Ot\text{-}Bu)_2$.

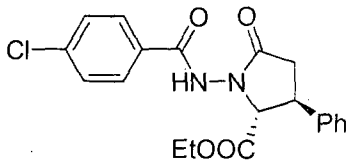
Note: The corresponding racemic products (for the above three type of reactions) for chiral phase HPLC method development were prepared using similar procedrues in presence of achiral catalyst **B** or **C**.

EXAMPLE 8: Stereochemistry determination (3y & 7j) *via* X-ray crystillographic analysis. Good quality crystal of **3y** (colorless flaky crystal) was obtained by vaporization of a hexane solution of compound **3y**. CCDC 900975 contains the supplementary crystallographic data that

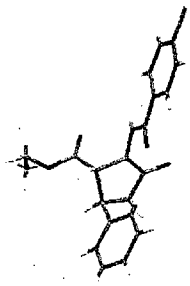
can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data request/cif.



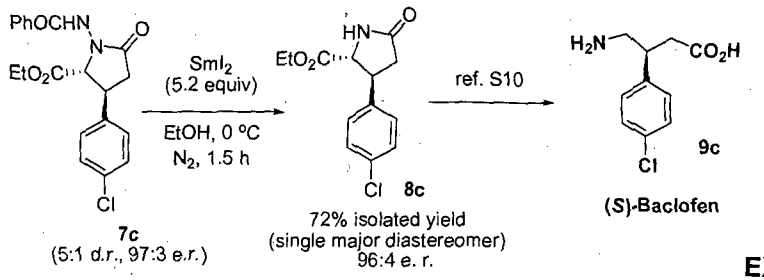
Product **7j** was crystallized as a colorless crystal *via* vaporization of a hexane/ethyl acetate solution, and its absolute configuration was determined by x-ray structure analaysis. CCDC 910100 contains the supplementary crystallographic data that can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data request/cif.



7j



Synthetic utilities: transformation of catalytic reaction products to bioactive compounds



[074] **EXAMPLE 9: Synthesis of (S)-baclefon 9c:** A dry 10 mL Schlenk tube equipped with a magnetic stir bar was successively charged with γ-lactam **7c** (5:1 *d.r.*, 97:3 *e.r.*, 0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. To this mixture was added a 0.1 M solution of SmI_2 (5.2 equiv) in THF at 0 °C, followed by the addition of EtOH (0.5 mL) *via* a syringe. After stirring for 1.5 hours at 0 °C, the reaction mixture was concentrated under reduced pressure. The crude residue was diluted with ethyl acetate (15 mL) and washed with water. The aqueous layer was extracted with ethyl acetate (2 x 15 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The oily residue was applied to silica gel column chromatography (1:100 v/v methanol/DCM) to afford *trans* γ-lactam **8c** as a colorless oil in 72 % isolated yield, 96:4 *e.r.*, and *cis* γ-lactam with 13% isolated yield. Compound **8c** can be converted to (S)-Baclofen **9c** by adopting a literature procedure.[5]

EXAMPLE 10: Synthesis of (S)-rolipram 9i: Compound **7i-2** was prepared using a procedure similar to that for the synthesis of **8c** above. Compound **7i-2** (50 mg, 0.14 mmol) was dissolved in 5 mL THF and $LiBH_4$ (8 mg, 0.36 mmol) was added in portions. After stirring at room temperature for 4 h, the reaction was quenched with 2 N HCl in an ice bath. The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silicon gel column chromatography gave the product **7i-3** as colorless oil (43 mg, 98% yield).

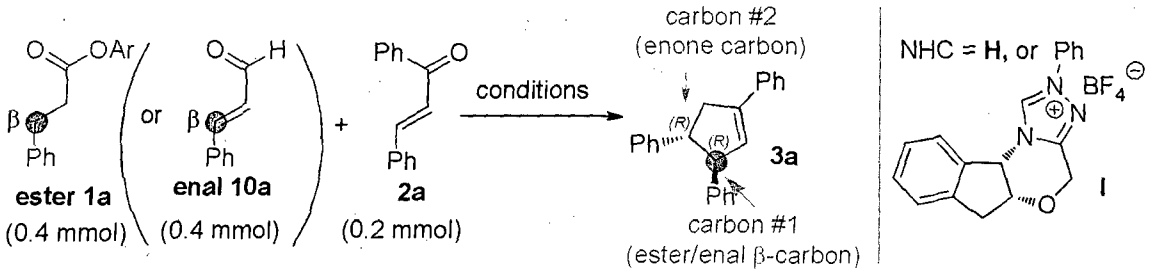
Compound **7i-3** (30.5 mg, 0.1 mmol) was dissolved in 3 mL anhydrous CH_2Cl_2, and TBSCl (16.5 mg, 0.11 mmol) and DMAP (14.4 mg, 0.12 mmol) was added. After stirring at room temperature for 3h, the reaction was quenched with 1N HCl The mixture was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in 3 mL anhydrous CH_2Cl_2, and Boc_2O (24.0 mg, 0.11 mmol) and DMAP (14.4 mg, 0.12 mmol) was added. After stirring at room temperature overnight, the reaction was quenched with 1N HCl, extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue was dissolved in 3 mL anhydrous THF and AcOH (6 μL, 0.1 mmol). TBAF (1 M in THF, 0.2 mL, 0.2 mmol) was added. The reaction was stirred at room temperature and monitored by TLC for completion. The mixture was extracted with ethyl acetate, washed with brine and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on silicon gel gave the product **8i** as colorless oil (27 mg, 67% yield, 96:4 *e.r.*).

Compound **8i** can be converted to (S)-Rolipram **9i** according to literature procedure.[6]

Comparison of our ester reactions with α,β-unsaturated aldehyde (enal) reactions:

[075] NHC-catalyzed reactions of ester 1a (OR ENAL 10a) with chalcone 2a (Table S4): The four enantiomers (from two diastereomers) of product **3a** and their ratios were assigned via chiral phase HPLC analsyis. The *R*/*S* ratios of each chiral center were then calculated. The results summerized in Table S3 showed that reactions with enone **2a** of from ester **1a** or the corresponding enal **10a** gave very different results. Several observations are given below:

Table S4: Comparison of enal reactions and our ester β-activation reactions (chalcone as electrophile)



Entry	Conditions	Reaction	**3a**	Carbon #1 (*R/S*)	Carbon #2 (*R/S*)
1	20 mol% **H**, 150 mol% DBU,CH_3CN (as Table 1, entry 9)	ester (**1a**)	66% yield, 7:1 *d.r.* 96:4 *e.r.(trans-***3a**) 81:19 *e.r.* (*cis-***3a**)	87:13	94:6
2	as entry 1 above	enal (**10a**)	51% yield, 1.8:1 *d.r.* 57:43 *e.r.(trans-***3a**) 88:12 *e.r.* (*cis-***3a**)	44:56	66:34
3	as entry 2 above except with 2.3 eq DBU and 2.0 eq 4-NO_2PHOH	enal (**10a**)	43% yield, 1.2:1 *d.r.* 57:43 *e.r.(trans-***3a**) 90:10 *e.r.* (*cis-***3a**)	41:59	68:32
4	as entry 1 above except NHC = **I**	ester (**1a**)	25% yield, 16:1 *d.r.* 85:15 *e.r.(trans-***3a**) 26:74 *e.r.* (*cis-***3a**)	84:16	81:19
5	as entry 4 above	enal (**10a**)	24% yield, 1.8:1 *d.r.* 36:64 *e.r.(trans-***3a**) 92:8 *e.r.* (*cis-***3a**)	28:72	52:48

(a) A comparsion of entry 1 and 2 showed that the ester reaction gave much better *d.r.* and *e.r.*. More remarkably, the enal reaction gave **3a** with a much lower and even opposite *e.r.* For example, for carbon #1 of product **3a**, the ester reaction (entry 1) favored *R*-configuration (87:13 *R/S*), while the enal reaction (entry 2) favored *S*-configuration (44:56 *R/S*).

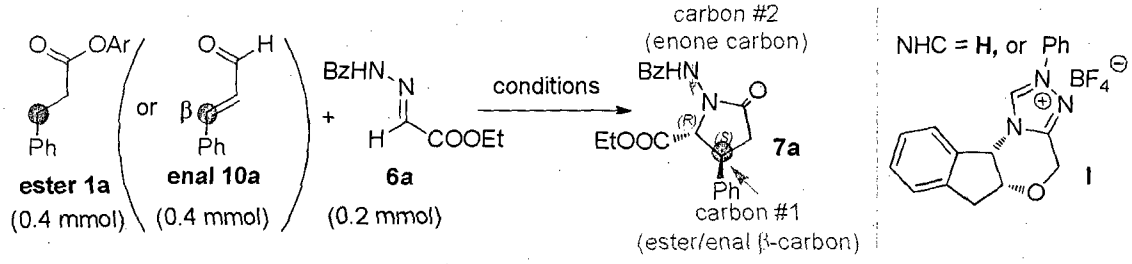
(b) Since the ester reaction (entry 1) released 4-NO2-PhOH in the catalytic reaction; we wondered if the difference in e.r. and d.r was caused by the phenol side proeuct. We therefore added 2.0 equivaletns of 4-NO2-PhOH as an additive to the enal reaction (entry 3). To maintain a basic medium for effective reaction, 2.3 eq DBU was also added. A comparson of entry 3 and 2 showed that the additive had only very little influence on the stereo-selectivities. The R/S ratios for each chiral carbon center remained nearly the same (e.g., for carbon #1, 44:56 *R/S* in entry 2, as compared to 41:59 R/S in entry 3 when phenol additive was introduced)

(c) A comparison of entries 1-3 suggested that that the "similar" homoenolate intermediates obtained using the enal and our ester approaches showed different reactivities and selectivities. More specifically, the enal homoenolate intermediate comes from addition of NHC to the aldehyde group of enal to form a Breslow intermediate. In contrast, our ester "homoenolate" is obtained through β-carbon deprotonation of an "enolate intermediate". The ester "homoenolate" intermediate with a formal nucleophilic β-carbon may be stabilized in a different form. Additional mechanistic studies are in progress.

(d) Similar differences between ester and enal reactions were obaserved using other conditions and NHC catalysts. For example, with **I** as an NHC pre-catalsyt, the ester and enal reactions gave opposite enantioselectivities for both *trans*- and *cis*-**3a** and both carbon chiral centers of **3a** (entryies 4-5). Notabely, as observed by Bode previously,[7] the enal reaction gave cis-cyclopetene product with high e.r., (e.g., 92:8 *e.r.*, for *cis*-**3a**, entry 5), but *trans*-isomer with low *e.r.* (e.g., 36:64 e.*r.* for *trans*-**3a**, entry 5). These results again clearly demonstrate the practical utiltilties of our ester activation strategy in enantioselective synthesis.

Similar results were also observed when hydrazone (Table S5) or trifluoroketone (Table S6) were used the electrophiles:

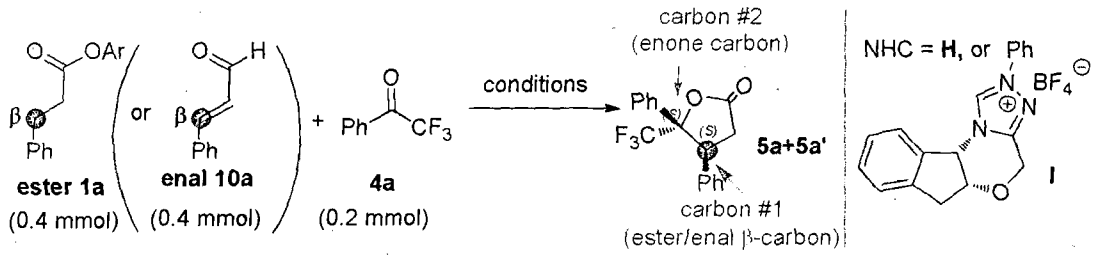
Table S5: Comparison of enal reactions and our ester β-activation reactions (hydrazone as electrophile)



Entry	Conditions	Reaction	7a	Carbon #1 (*R*/*S*)	Carbon #2 (*R*/*S*)
1	20 mol% **H**, 150 mol% DBU, EA(0.2M), 40°C, 48 h	ester (**1a**)	74% yield, 6:1 *d.r.* 97:3 *e.r.(trans-**7a**)* 90:10 *e.r.* (*cis-**7a**)*	13:87	97:3
2	as entry 1 above	enal (**10a**)	20% yield, 1:2.2 *d.r.* 40:60 *e.r.(trans-**7a**)* 3:97 *e.r.* (*cis-**7a**)*	10:90	7:93
3	as entry 2 above except with 2.3 eq DBU and 2.0 eq 4-NO_2PHOH	enal (**10a**)	20% yield, 1:1.4 *d.r.* 84:16 *e.r.(trans-**7a**)* 11:89 *e.r.* (*cis-**7a**)*	13:87	49:51
4	as entry 1 above except NHC = **I**	ester (**1a**)	44% yield, 3.8:1 *d.r.* 77:23 *e.r.(trans-**7a**)* 76:24 *e.r.* (*cis-**7a**)*	30:70	77:23

5	as entry 4 above	enal (**10a**)	5% yield, nd *d.r.* 35:65 *e.r.(trans-***7a**) 10:90 *e.r.* (*cis-***7a**)	28:72	17:83

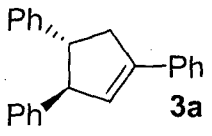
Table S6: Comparison of enal reactions and our ester β-activation reactions (trifluoroketone as electrophile)



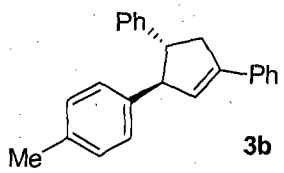
Entry	Conditions	Reaction	**5a+5a'**	Carbon #1 (*R/S*)	Carbon #2 (*R/S*)
1	20 mol% **H**, 150 mol% DBU, Tol. (0.2 M), 0℃, 48 h	ester (**1a**)	54% yield, 1.3:1 *d.r.* 91:9 *e.r.(**5a**)* 94:6 *e.r.* (*5a'*)	8:92	46:54
2	as entry 1 above	enal (**10a**)	38% yield, 1.4:1 *d.r.* 59:41 *e.r.(**5a**)* 80:20 *e.r.* (*5a'*)	34:66	54:46
3	as entry 2 above except with 2.3 eq DBU and 2.0 eq 4-NO_2PHOH	enal (**10a**)	62% yield, 1:1.1 d.r. 61:39 *e.r.(**5a**)* 64:36 *e.r.* (*5a'*)	36:64	53:47
4	as entry 1 above except NHC = **I**	ester (**1a**)	17% yield, 1.2:1 *d.r.* 65:35 *e.r.(**5a**)* 59:41 *e.r.* (*5a'*)	38:62	49:51
5	as entry 4 above	enal (**10a**)	19% yield, 1.5:1 *d.r.* 59:41 *e.r.* (***5a***) 49:51 *e.r.* (*5a'*)	45:55	44:56

CHARACTERIZATIONS OF PRODUCTS

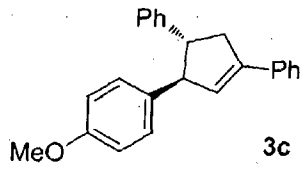
[076] ^{1}H NMR and ^{13}C NMR characterization of exemplary compounds is provided in the following.



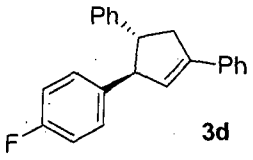
3a **EXAMPLE 11: (*1R,2R*)-Cyclopent-3-ene-1,2,4-triyltribenzene** : $[\alpha]_D^{23}$ (c 2.23, CH_2Cl_2) = -138.9°; 95:5 *e.r.* as determined by HPLC (Chiralcel OD, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 35.8 min, t_r(minor) = 46.9 min.



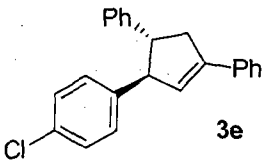
3b **EXAMPLE 12: ((*1R,5R*)-5-(*p*-Tolyl)cyclopent-3-ene-1,3-diyl)dibenzene:** $[\alpha]_D^{23}$ (c 1.85, CH_2Cl_2) = -133.8°; 97:3 *e.r.* as determined by HPLC (Chiralcel ADH, 99.9:0.1 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 39.1 min, t_r(minor) = 51.4 min.



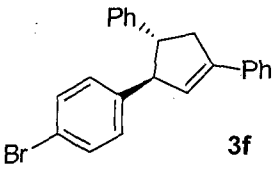
3c **EXAMPLE 13: ((*1R,5R*)-5-(4-Methoxyphenyl)cyclopent-3-ene-1,3-diyl)dibenzene:** $[\alpha]_D^{23}$ (c 2.83, CH_2Cl_2) = -116.5°; 95:5 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 45.4 min, t_r(minor) = 41.7 min.



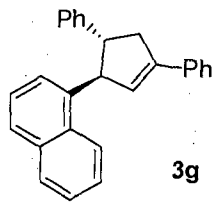
3d **EXAMPLE 14: ((*1R,5R*)-5-(4-Fluorophenyl)cyclopent-3-ene-1,3-diyl)dibenzene:** $[\alpha]_D^{23}$ (c 1.95, CH_2Cl_2) = -110.4°; 96:4 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 29.1 min, t_r(minor) = 23.4 min.



3e **EXAMPLE 15: ((*1R,5R*)-5-(4-Chlorophenyl)cyclopent-3-ene-1,3-diyl)dibenzene:** $[\alpha]_D^{23}$ (c 2.47, CH_2Cl_2) = -117.7°; 95:5 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 32.0 min, t_r(minor) = 25.8 min.

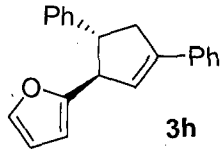


3f **EXAMPLE 16: ((*1R,5R*)-5-(4-Bromophenyl)cyclopent-3-ene-1,3-diyl)dibenzene:** $[\alpha]_D^{23}$ (c 2.46, CH_2Cl_2) = -127.0°; 95:5 *e.r.* as determined by HPLC (Chiralcel ODH, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 65.2 min, t_r(minor) = 97.6 min.



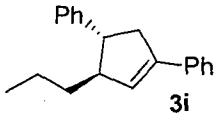
3g

EXAMPLE 17: 1-((*1R,5R*)-3,5-Diphenylcyclopent-2-en-1-yl)naphthalene: colorless gum; $[\alpha]_D^{23}$ (c 1.17, CH_2Cl_2) = +22.3°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.98–3.03 (m, 1H), 3.40–3.46 (m, 1H), 3.53–3.57 (m, 1H), 4.89 (dd, J = 4.4, 2.0 Hz, 1H), 6.42 (dd, J = 4.0, 1.6 Hz, 1H), 6.71–6.75 (m, 1H), 7.23–7.45 (m, 11H), 7.59–7.61 (m, 2H), 7.64–7.79 (m, 2H), 7.85 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.0, 142.9, 136.0, 134.1, 131.8, 128.7, 128.6, 128.5, 128.5, 128.1, 127.6, 127.1, 127.0, 126.4, 125.9, 125.8, 125.7, 125.6, 125.5, 124.2, 124.0, 56.6, 52.8, 42.0; HRMS(ESI) calcd for $C_{27}H_{23}(M+H)^+$: 347.1800, Found: 347.1797; 95:5 *e.r.* as determined by HPLC (Chiralcel ODH, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r (major) = 28.7 min, t_r(minor) = 27.4 min.



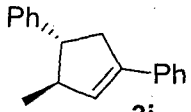
3h

EXAMPLE 18: 2-((*1R,5R*)-3,5-Diphenylcyclopent-2-en-1-yl)furan: $[\alpha]_D^{23}$ (c 2.54, CH_2Cl_2) = -78.7°; 91:9 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 28.0 min, t_r(minor) = 21.2 min.



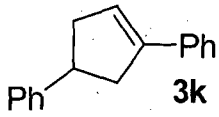
3i

EXAMPLE 19: ((*1R,5R*)-5-Propylcyclopent-3-ene-1,3-diyl)dibenzene: $[\alpha]_D^{23}$ (c 0.62, CH_2Cl_2) = -24.0°; 91:9 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 16.0 min, t_r(minor) = 13.7 min.

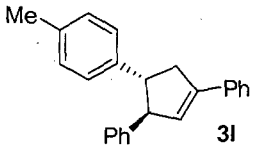


3j

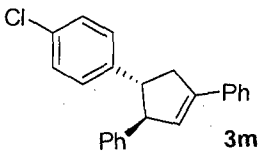
EXAMPLE 20: ((*1R,5R*)-5-Methylcyclopent-3-ene-1,3-diyl)dibenzene: colorless gum; $[\alpha]_D^{23}$ (c 0.63, CH_2Cl_2) = +48.2°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.17 (d, J = 6.4 Hz, 3H), 2.86–2.93 (m, 1H), 2.98–3.07 (m, 2H), 3.17–3.24 (m, 1H), 6.11–6.12 (m, 1H), 7.20–7.34 (m, 8H), 7.45–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.8, 140.0, 136.4, 130.8, 128.4, 128.3, 127.5, 127.1, 126.1, 125.6, 53.3, 49.4, 42.2, 19.9; HRMS(ESI) calcd for $C_{18}H_{19}(M+H)^+$: 235.1487, Found: 235.1500; 94:6 *e.r.* as determined by HPLC (Chiralcel IA, 99.9:0.1 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 15.9 min, t_r(minor) = 14.0 min.



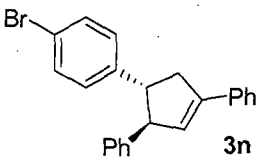
3k **EXAMPLE 21: Cyclopent-3-ene-1,3-diyldibenzene :** colorless gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.64–2.69 (m, 1H), 2.83–2.88 (m, 1H), 2.99–3.01 (m, 1H), 3.18 (ddd, J = 9.2, 2.4, 1.2 Hz, 1H), 3.62–3.67 (m, 1H), 6.22 (dd, J = 4.0, 2.0 Hz, 1H), 7.18–7.34 (m, 8H), 7.47 (dd, J = 4.0, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.2, 141.5, 136.4, 128.5, 128.4, 127.1, 127.0, 126.0, 125.6, 124.8, 43.5, 42.0, 41.8; HRMS(ESI) calcd for $C_{17}H_{17}(M+H)^+$: 221.1330, Found: 221.1342.



3l **EXAMPLE 22: ((*3R,4R*)-4-(*p*-Tolyl)cyclopent-1-ene-1,3-diyl)dibenzene:** colorless gum; $[\alpha]_D^{23}$ (c 1.13, CH_2Cl_2) = -147.4°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.33 (s, 3H), 2.96–3.02 (m, 1H), 3.29–3.44 (m, 2H), 4.09–4.12 (m, 1H), 6.25 (dd, J = 3.6, 2.0 Hz, 1H), 7.09–7.38 (m, 12H), 7.52–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.0, 142.4, 142.2, 136.1, 135.8, 129.2, 128.5, 128.4, 128.2, 127.5, 127.4, 127.2, 126.4, 125.8, 60.8, 54.2, 42.1, 21.1; HRMS(ESI) calcd for $C_{24}H_{23}(M+H)^+$: 311.1800, Found: 311.1798; 95:5 *e.r.* as determined by HPLC (Chiralcel OD, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r (major) = 29.9 min, t_r(minor) = 37.9 min.

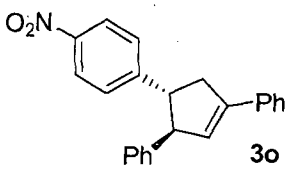


3m **EXAMPLE 23: ((*3R,4R*)-4-(4-Chlorophenyl)cyclopent-1-ene-1,3-diyl)dibenzene:** colorless gum; $[\alpha]_D^{23}$ (c 1.27, CH_2Cl_2) = -116.3°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.93–2.99 (m, 1H), 3.29–3.42 (m, 2H), 4.05–4.07 (m, 1H), 6.24 (dd, J = 3.6, 2.0 Hz, 1H), 7.11–7.39 (m, 12H), 7.51–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.5, 143.8, 142.1, 135.8, 132.0, 128.7, 128.6, 128.6, 128.5, 128.0, 127.7, 127.4, 126.6, 125.8, 60.9, 54.0, 41.9; HRMS(ESI) calcd for $C_{23}H_{19}Cl(M+Na)^+$: 353.1073, Found: 353.1060; 95:5 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r (major) = 31.8 min, t_r (minor) = 25.1 min.

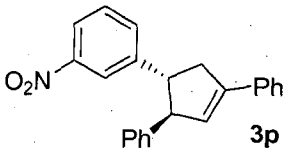


3n **EXAMPLE 24: ((*3R,4R*)-4-(4-Bromophenyl)cyclopent-1-ene-1,3-diyl)dibenzene:** colorless gum; $[\alpha]_D^{23}$ (c 2.42, CH_2Cl_2) = -117.1°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.96 (dd, J = 15.2, 7.2 Hz, 1H), 3.32–3.41 (m, 2H), 4.05–4.07 (m, 1H), 6.24 (dd, J = 3.6, 2.0 Hz, 1H), 7.10–7.42 (m, 12H), 7.52–7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.5, 144.4,

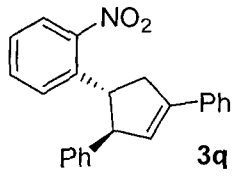
142.1, 135.8, 131.6, 129.1, 128.6, 128.5, 128.0, 127.7, 127.4, 126.6, 125.8, 120.0, 60.9, 54.1, 41.8; HRMS(ESI) calcd for $C_{23}H_{20}Br(M+H)^+$: 375.0748, Found: 375.0728; 95:5 *e.r.* as determined by HPLC (Chiralcel IA, 99.9:0.1 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 37.4 min, t_r(minor) = 27.6 min.



3o **EXAMPLE 25: ((*3R,4R*)-4-(4-Nitrophenyl)cyclopent-1-ene-1,3-diyl)dibenzene:** colorless gum; $[\alpha]_D^{23}$ (c 1.61, CH_2Cl_2) = -104.4°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.02 (dd, J = 16.0, 7.2 Hz, 1H), 3.37–3.44 (m, 1H), 3.53–3.57 (m, 1H), 4.10–4.12 (m, 1H), 6.27 (dd, J = 3.6, 2.0 Hz, 1H), 7.11–7.13 (m, 2H), 7.24–7.42 (m, 8H), 7.53–7.55 (m, 2H), 8.13–8.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.2, 146.7, 144.0, 142.1, 135.5, 128.7, 128.6, 128.2, 127.9, 127.8, 127.4, 126.9, 125.9, 123.9, 70.0, 54.4, 41.7; HRMS(ESI) calcd for $C_{23}H_{20}NO_2(M+H)^+$: 342.1494, Found: 342.1500; 95:5 *e.r.* as determined by HPLC (Chiralcel IA, 99:1 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 86.5 min, t_r(minor) = 46.4 min.

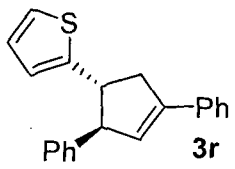


3p **EXAMPLE 26: ((*3R,4R*)-4-(3-Nitrophenyl)cyclopent-1-ene-1,3-diyl)dibenzene:** colorless gum; $[\alpha]_D^{23}$ (c 1.03, CH_2Cl_2) = -53.4°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.98–3.04 (m, 1H), 3.37–3.43 (m, 1H), 3.53–3.59 (m, 1H), 4.11–4.14 (m, 1H), 6.26 (d, J = 1.2 Hz, 1H), 7.12–7.45 (m, 9H), 7.53 (d, J = 7.6 Hz, 3H), 8.06–8.09 (m, 1H), 8.14 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.5, 147.4, 144.0, 142.0, 135.5, 133.8, 129.5, 128.8, 128.7, 128.6, 127.9, 127.4, 126.9, 125.9, 122.2, 121.6, 60.8, 54.2, 41.8; HRMS(ESI) calcd for $C_{23}H_{19}NO_2Na(M+Na)^+$: 364.1313, Found: 364.1298; 96:4 *e.r.* as determined by HPLC (Chiralcel ADH, 99:1 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 72.1 min, t_r(minor) = 48.4 min.

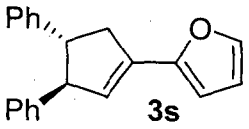


3q **EXAMPLE 27: ((*3R,4R*)-4-(2-Nitrophenyl)cyclopent-1-ene-1,3-diyl)dibenzene:** colorless gum; $[\alpha]_D^{23}$ (c 1.0, CH_2Cl_2) = -55.0°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.89–2.95 (m, 1H), 3.50–3.56 (m, 1H), 3.89–3.95 (m, 1H), 4.22 (dd, J = 5.6, 2.4 Hz, 1H), 6.30 (d, J = 2.0 Hz, 1H), 7.11–7.39 (m, 9H), 7.52–7.57 (m, 3H), 7.65–7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.1, 143.8, 142.1, 140.1, 135.5, 132.8, 128.7, 128.6, 128.5, 128.0, 127.9, 127.3, 127.1, 126.9, 125.9, 123.8, 60.4, 47.7, 42.4; HRMS(ESI) calcd for $C_{23}H_{19}NO_2Na(M+Na)^+$:

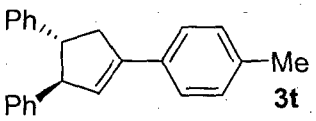
364.1313, Found: 364.1318; 96:4 *e.r.* as determined by HPLC (Chiralcel IA, 99.9:0.1 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 63.8 min, t_r(minor) = 56.3 min.



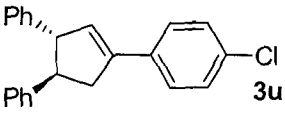
3r **EXAMPLE 28: 2-((*1R,2R*)-2,4-Diphenylcyclopent-3-en-1-yl)thiophene:** $[\alpha]_D^{23}$ (c 2.56, CH_2Cl_2) = -70.8°; 94:6 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 29.0 min, t_r(minor) = 25.5 min.



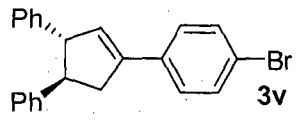
3s **EXAMPLE 29: 2-((*3R,4R*)-3,4-Diphenylcyclopent-1-en-1-yl)furan:** $[\alpha]_D^{23}$ (c 1.66, CH_2Cl_2) = -127.4°; 94:6 *e.r.* as determined by HPLC (Chiralcel OD, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 34.4 min, t_r(minor) = 49.9 min.



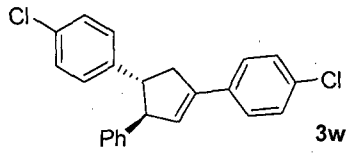
3t **EXAMPLE 30: ((*1R,2R*)-4-(*p*-Tolyl)cyclopent-3-ene-1,2-diyl)dibenzene:** colorless gum; $[\alpha]_D^{23}$ (c 1.00, CH_2Cl_2) = -112.4°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.37 (s, 3H), 2.96–3.02 (m, 1H), 3.29–3.46 (m, 2H), 4.10–4.13 (m, 1H), 6.20 (t, J = 1.6 Hz, 1H), 7.13–7.31 (m, 12H), 7.42–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.6, 145.1, 142.1, 137.4, 133.2, 129.2, 128.5, 128.4, 127.5, 127.3, 127.1, 126.4, 126.3, 125.7, 60.8, 54.5, 42.0, 21.3; HRMS(ESI) calcd for $C_{24}H_{23}$ $(M+H)^+$: 311.1800, Found: 311.1804; 95:5 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 26.1 min, t_r(minor) = 24.2 min.



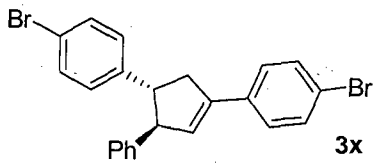
3u **EXAMPLE 31: ((*1R,2R*)-4-(4-Chlorophenyl)cyclopent-3-ene-1,2-diyl)dibenzene:** colorless gum; $[\alpha]_D^{23}$ (c 2.14, CH_2Cl_2) = -89.5°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.94–3.01 (m, 1H), 3.26–3.34 (m, 1H), 3.42–3.48 (m, 1H), 4.11–4.14 (m, 1H), 6.24 (dd, J = 3.6, 2.0 Hz, 1H), 7.12–7.34 (m, 12H), 7.43–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.1, 144.6, 141.1, 134.5, 133.2, 128.9, 128.6, 128.5, 128.5, 127.4, 127.3, 127.1, 126.5, 126.4, 60.8, 54.5, 42.0; HRMS(ESI) calcd for $C_{23}H_{20}Cl(M+H)^+$: 331.1254, Found: 331.1277; 95:5 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r(major) = 31.4 min, t_r(minor) = 29.3 min.



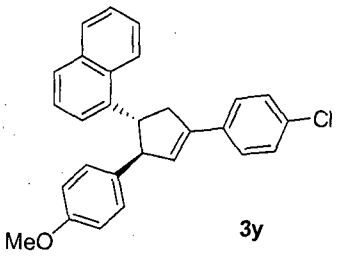
3v **EXAMPLE 32: ((*1R,2R*)-4-(4-Bromophenyl)cyclopent-3-ene-1,2-diyl)dibenzene:** $[\alpha]_D^{23}$ (c 2.78, CH_2Cl_2) = -87.5°; 96:4 *e.r.* (*1R*, *2R*)- isomer as determined by HPLC (Chiralcel IA, 99.9:0.1 hexanes/i-PrOH, 0.3 mL/min), t_r (major) = 35.2 min, t_r (minor) = 32.4 min.



3w **EXAMPLE 33: 4,4'-((*1R,5R*)-5-Phenylcyclopent-3-ene-1,3-diyl)bis(chlorobenzene):** $[\alpha]_D^{23}$ (c 2.5, CH_2Cl_2) = -94.4°; 95:5 *e.r.* isomer as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r (major) = 49.5 min, t_r (minor) = 38.1 min.

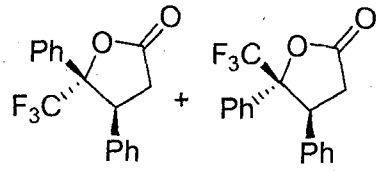


3x **EXAMPLE 34: 4,4'-((*1R,5R*)-5-Phenylcyclopent-3-ene-1,3-diyl)bis(bromobenzene):** colorless gum; $[\alpha]_D^{23}$ (c 3.45, CH_2Cl_2) = -68.8°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.89–2.96 (m, 1H), 3.25–3.27 (m, 1H), 3.30–3.43 (m, 1H), 4.03–4.05 (m, 1H), 6.23 (d, J = 1.6 Hz, 1H), 7.08–7.49 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.2, 144.0, 141.1, 134.7, 131.7, 131.6, 130.7, 129.1, 128.9, 128.6, 127.4, 126.7, 121.5, 120.1, 60.9, 54.1, 41.8; HRMS(ESI) calcd for $C_{23}H_{19}Br_2(M+H)^+$: 452.9854, Found: 452.9868; 95:5 *e.r.* as determined by HPLC (Chiralcel IA, 99.8:0.2 hexanes/i-PrOH, 0.3 mL/min), t_r (major) = 59.2 min, t_r (minor) = 46.3 min.



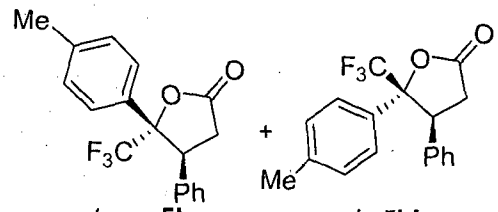
3y **EXAMPLE 35: 1-((*1R,2R*)-4-(4-Chlorophenyl)-2-(4-methoxyphenyl)cyclopent-3-en-1-yl)naphthalene:** $[\alpha]_D^{23}$ (c 3.0, CH_2Cl_2) = -124.4°; 97:3 *e.r.* as determined by HPLC (Chiralcel OD, 98:2 hexanes/i-PrOH, 0.3 mL/min), t_r (major) = 59.8 min, t_r (minor) = 38.4 min.

Note: For the products characterized as below, the two diastereomers (e.g., **5a** and **5a'**) were isolated as a mixture.



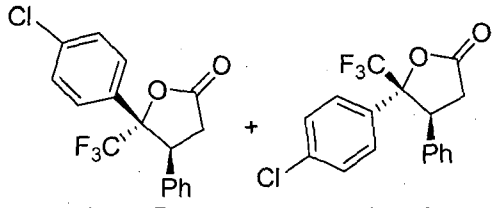
trans-**5a** *cis*-**5a'**

EXAMPLE 36: 4,5-Diphenyl-5-(trifluoromethyl)dihydrofuran-2(3H)-one: 91:9 *e.r.* (**5a**), 94:6 *e.r.* (**5a'**) as determined by HPLC (Chiralcel OD, 99:1 hexanes/i-PrOH, 0.7 mL/min), t_r(**5a**-major) = 23.1 min, t_r(**5a**-minor) = 44.0 min, t_r(**5a'**-major) = 19.8 min, t_r(**5a'**-minor) = 71.3 min.



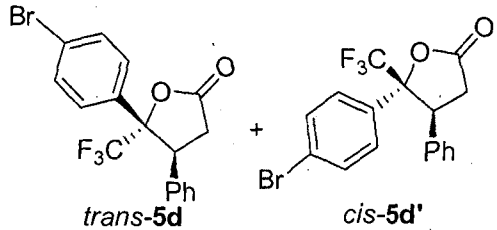
trans-**5b** *cis*-**5b'**

EXAMPLE 37: 4-phenyl-5-(p-tolyl)-5-(trifluoromethyl)dihydrofuran-2(3H)-one: 93:7 *e.r.* (**5b**), 95:5 *e.r.* (**5b'**) as determined by HPLC (Chiralcel OD, 99.8:0.2 hexanes/i-PrOH, 0.7 mL/min), t_r (**5b**-major) = 30.5 min, t_r (**5b**-minor) = 81.3 min, t_r(**5b'**-major) = 34.5 min, t_r(**5b'**-minor) = 106.5 min.



trans-**5c** *cis*-**5c'**

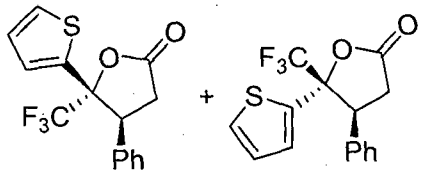
EXAMPLE 38: 5-(4-chlorophenyl)-4-phenyl-5-(trifluoromethyl)dihydrofuran-2(3H)-one: 94:6 *e.r.* (**5c**), 94:6 *e.r.* (**5c'**) as determined by HPLC (Chiralcel IA, 99:1 hexanes/i-PrOH, 0.7 mL/min), t_r(**5c**-major) = 18.2 min, t_r(**5c**-minor) = 38.5 min, t_r(**5c'**-major) = 19.4 min, t_r(**5c'**-minor) = 69.2 min.



trans-**5d** *cis*-**5d'**

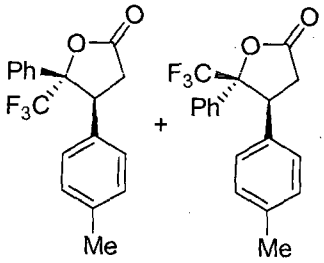
EXAMPLE 39: 5-(4-bromophenyl)-4-phenyl-5-(trifluoromethyl)dihydrofuran-2(3H)-one: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.74–2.81 (*trans*, m, 1H), 2.95–2.97 (*cis*, m, 1H), 3.17–3.32 (*cis*, m, 1H), 3.34–3.39 (*trans*, m, 1H),

3.93 (*cis*, t, J = 9.6 Hz, 1H), 4.26 (*trans*, dd, J = 9.6, 5.2 Hz, 1H), 6.84–6.87 (*trans*, m, 2H), 7.01 (*trans*, d, J = 8.4 Hz, 2H), 7.13–7.16 (*trans*, m, 3H), 7.27–7.33 (*trans*+cis, m, 4H), 7.39–7.42 (*cis*, m, 5H), 7.56–7.58 (*cis*, m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4(*trans*), 172.7(*cis*), 137.4(*trans*),134.5, 133.2, 132.0, 131.1, 130.5, 129.3, 129.0, 128.9, 128.9, 128.8, 128.7, 128.3, 128.1, 127.3, 127.3, 125.7, 124.1, 123.4, 122.9, 88.2 (q, J = 290 Hz)(*trans*), 87.3 (q, J = 260 Hz)(*cis*), 51.6(*cis*), 45.7(*trans*), 36.8(*trans*), 35.1(*cis*); HRMS(ESI) calcd for $C_{17}H_{13}O_2F_3Br(M+H)^+$: 385.0051, Found: 385.0055; 93:7 *e.r.* (**5d**), 94:6 *e.r.* (**5d'**) as determined by HPLC (Chiralcel IB, 98:2 hexanes/i-PrOH, 0.5 mL/min), t_r(**5d**-major) = 22.1 min, t_r(**5d**-minor) = 44.7 min, t_r(**5d'**-major) = 24.3 min, t_r(**5d'**-minor) = 74.6 min.



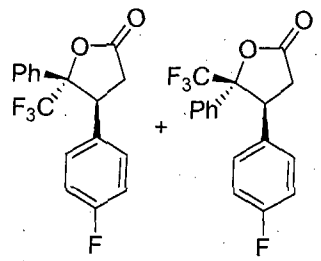
trans-**5e** *cis*-**5e'**

EXAMPLE 40: 4-phenyl-5-(thiophen-2-yl)-5-(trifluoromethyl)dihydrofuran-2(3H)-one: 90:10 *e.r.* (**5e**), 91:9 *e.r.* (**5e'**) as determined by HPLC (Chiralcel OD, 99:1 hexanes/i-PrOH, 0.7 mL/min), t_r(**5e**-major) = 41.6 min, t_r(**5e**-minor) = 70.5 min, t_r(**5e'**-major) = 26.6 min, t_r(**5e'**-minor) = 87.1 min.



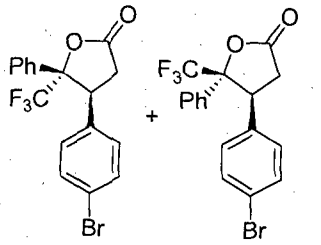
trans-**5f** *cis*-**5f'**

EXAMPLE 41: 5-phenyl-4-(p-tolyl)-5-(trifluoromethyl)dihydrofuran-2(3H)-one: colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 2.21 (*trans*, s, 3H), 2.39 (*cis*, s, 3H), 2.71–2.77 (*trans*, m, 1H), 2.90 (*cis*, q, J = 8.8 Hz, 1H), 3.14 (*cis*, dd, J = 18.0, 10.0 Hz, 1H),3.26–3.33 (*trans*, m, 1H), 3.97 (*cis*, t, J = 5.2 Hz, 1H), 4.25 (*trans*, dd, J = 9.2, 5.6 Hz, 1H), 6.71 (*trans*, d, J = 8.0 Hz, 2H), 6.91 (*trans*, d, J = 8.0 Hz, 2H), 7.12–7.22 (*trans*+*cis*, m, 10H), 7.44 (*trans*, dd, J = 6.4, 3.6 Hz, 2H), 7.53–7.54 (*cis*, m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.9(*trans*), 173.4(*cis*), 138.6(*cis*), 137.6(*trans*), 135.6(*cis*), 134.4(*trans*), 131.3(*trans*), 130.7(*cis*), 129.5, 129.4, 129.2, 128.8, 128.7, 128.3, 127.8, 127.0, 126.9, 126.0, 125.6, 125.3, 123.2, 122.5, 88.5 (q, J = 280 Hz)(*trans*), 87.4(q, J = 280 Hz)(*cis*), 51.2(*cis*), 45.5(*trans*), 36.8(*trans*), 35.3(*cis*), 21.1(*cis*), 21.0(*trans*); HRMS(ESI) calcd for $C_{18}H_{16}O_2F_3(M+H)^+$: 321.1102, Found: 321.1101; 92:8 *e.r.* (**5f**), 95:5 *e.r.* (**5f'**) as determined by HPLC (Chiralcel OD, 95:5 hexanes/i-PrOH, 0.7 mL/min), t_r(**5f**-major) = 19.5 min, t_r(**5f**-minor) = 34.7 min, t_r(**5f'**-major) = 14.8 min, t_r(**5f'**-minor) = 40.3 min.



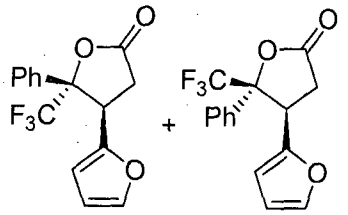
trans-**5g** *cis*-**5g'**

EXAMPLE 42: 4-(4-fluorophenyl)-5-phenyl-5-(trifluoromethyl)dihydrofuran-2(3H)-one: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.70–2.76 (m, 1H), 3.29–3.37 (m, 1H), 4.28 (dd, J = 9.6, 5.6 Hz, 1H), 4.03–4.05 (m, 1H), 6.80 (d, J = 6.8 Hz, 4H), 7.11–7.22 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5, 163.3, 160.8, 133.4, 133.3, 131.1, 130.1, 130.0, 129.0, 128.0, 126.8, 115.6, 115.4, 88.4 (q, J = 290 Hz), 45.2, 36.8; HRMS(ESI) calcd for $C_{17}H_{13}O_2F_4(M+H)^+$: 325.0852, Found: 325.0852; 95:5 *e.r.* (**5g**), 92:8 *e.r.* (**5g'**) as determined by HPLC (Chiralcel OD, 99:1 hexanes/i-PrOH, 0.7 mL/min), t_r (**5g**-major) = 28.5 min, t_r (**5g**-minor) = 26.1 min, t_r (**5g'**-major) = 23.1 min, t_r (**5g'**-minor) = 39.8 min.



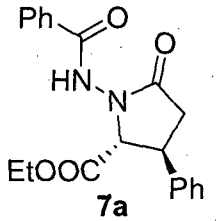
trans-**5h** *cis*-**5h'**

EXAMPLE 43: 4-(4-bromophenyl)-5-phenyl-5-(trifluoromethyl)dihydrofuran-2(3H)-one: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.67–2.74 (*trans*, m, 1H), 2.93–2.96 (*cis*, m, 1H), 3.06–3.09 (*cis*, m, 1H), 3.29–3.67 (*trans*, m, 1H), 3.97 (*cis*, t, J = 9.2 Hz, 1H), 4.25 (*trans*, dd, J = 9.6, 5.2 Hz, 1H), 6.71 (*trans*, d, J = 8.8 Hz, 2H), 7.12–7.26 (*trans*+*cis*, m, 10H), 7.44–7.46 (*trans*, m, 2H), 7.50–7.56 (*cis*, m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.3(*trans*), 172.8(*cis*), 136.7(*trans*), 135.2(*cis*), 133.0, 132.0, 131.7, 131.0, 130.9, 130.0, 129.7, 129.2, 128.9, 128.1, 126.8, 126.8, 125.9, 125.5, 123.0, 122.9, 121.9, 88.9 (q, J = 280 Hz)(*trans*), 87.6 (q, J = 280 Hz)(*cis*), 51.0(cis), 45.4(*trans*), 36.7(*trans*), 35.1(*cis*); HRMS(ESI) calcd for $C_{17}H_{12}O_2F_3BrNa(M+Na)^+$: 406.9870, Found: 406.9860; 94:6 *e.r.* (**5h**), 96:4 *e.r.* (**5h'**) as determined by HPLC (Chiralcel OD, 99:1 hexanes/i-PrOH, 0.7 mL/min), t_r (**5h**-major) = 52.9 min, t_r (**5h**-minor) = 114.9 min, t_r (**5h'**-major) = 41.4 min, t_r (**5h'**-minor) = 130.2 min.



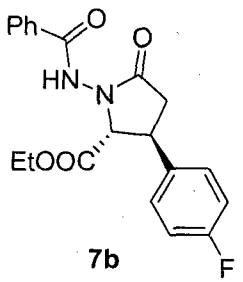
trans-**5i** *cis*-**5i'**

EXAMPLE 44: 4-(furan-2-yl)-5-phenyl-5-(trifluoromethyl)dihydrofuran-2(3H)-one: 84:16 *e.r.* (**5i**), 84:16 *e.r.* (**5i'**) as determined by HPLC (Chiralcel OJ-H, 95:5 hexanes/i-PrOH, 0.5 mL/min), t_r(**5i**-major) = 18.9 min, t_r(**5i**-minor) = 28.9 min, t_r(**5i'**-major) = 74.1 min, t_r(**5i'**-minor) = 62.6 min.



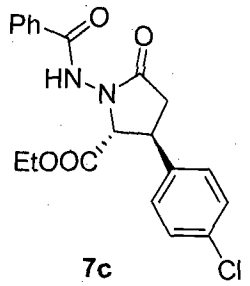
7a

EXAMPLE 45: (2R,3R)-ethyl 1-benzamido-5-oxo-3-phenylpyrrolidine-2-carboxylate: colorless oil; $[\alpha]_D^{23}$ (c 0.94, CH_2Cl_2) = - 39.1°. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (t, J = 7.2 Hz, 3H), 2.92 (d, J = 8.8 Hz, 2H), 3.64-3.72 (m, 1H), 3.77-3.85 (m, 1H), 4.10-4.17 (m, 1H), 4.96 (d, J = 8.8 Hz, 1H), 7.25-7.36 (m, 5H), 7.45 (t, J = 8.0 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 8.29 (s, 1H). HRMS(ESI) calcd for $C_{20}H_{20}N_2O_4(M+H)^+$: 353.1501, Found: 353.1496; 97:3 *e.r.* as determined by HPLC [Chiralcel IA, 75 : 20 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r (major) = 110.2 min, t_r (minor) = 88.3 min.



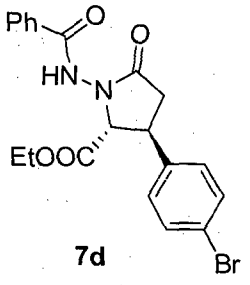
7b

EXAMPLE 46: (2R,3S)-ethyl1-benzamido-3-(4-fluorophenyl)-5-oxopyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 1.95, CH_2Cl_2) = - 44.9°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.23 (t, J = 7.2 Hz, 3H), 2.63 (dd, J = 17.6 Hz, 9.6 Hz, 1H), 3.04 (dd, J = 17.6 Hz, 9.6 Hz, 1H), 3.56–3.61 (m, 1H), 4.17–4.29 (m, 2H), 4.68 (d, J = 5.2 Hz, 1H), 7.09 (t, J = 8.4 Hz, 2H), 7.41–7.49 (m, 4H), 7.55 (t, J = 7.2 Hz, 1H), 7.85 (d, J = 7.2 Hz, 2H), 8.61 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.5, 170.8, 166.1, 163.5, 161.0, 137.3 (d, J = 3.0 Hz), 132.7, 131.2, 128.9 (d, J = 9.0 Hz), 128.7, 127.5, 116.0 (d, J = 21.0 Hz), 67.3, 62.0, 39.9, 36.8, 14.1; HRMS(ESI) calcd for $C_{20}H_{20}N_2O_4F(M+H)^+$: 371.1407, Found: 371.1410; 97:3 *e.r.* as determined by HPLC [Chiralcel IA, 75 : 20 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r(major) = 127.3 min, t_r(minor) = 105.4 min.



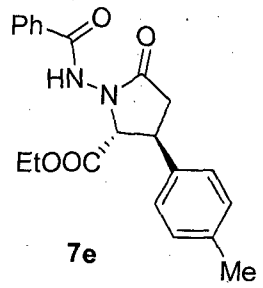
7c

EXAMPLE 47: (2R,3S)-ethyl1-benzamido-3-(4-chlorophenyl)-5-oxopyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 1.89, CH_2Cl_2) = - 67.2°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.23 (t, J = 7.2 Hz, 3H), 2.64 (dd, J = 17.6 Hz, 6.4 Hz, 1H), 3.06 (dd, J = 17.6 Hz, 9.6 Hz, 1H), 3.56–3.61 (m, 1H), 4.15–4.30 (m, 2H), 4.67 (d, J = 5.6 Hz, 1H), 7.37–7.45 (m, 6H), 7.52 (t, J = 7.6 Hz, 1H), 7.84 (d, J = 7.2 Hz, 2H), 8.83 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.7, 170.7, 166.1, 140.0, 133.6, 132.6, 131.1, 129.3, 128.7, 128.6, 127.6, 67.1, 62.0, 40.0, 36.7, 14.1; HRMS(ESI) calcd for $C_{20}H_{20}N_2O_4Cl$ $(M+H)^+$: 387.1112, Found: 387.1112; 97:3 *e.r.* as determined by HPLC [Chiralcel IA, 75 : 20 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r(major) = 136.0 min, t_r(minor) = 112.0 min.



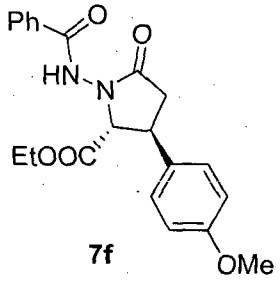
7d

EXAMPLE 48: (2R,3S)-ethyl1-benzamido-3-(4-bromophenyl)-5-oxopyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 2.49, CH_2Cl_2) = - 61.8°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.21 (t, J = 7.2 Hz, 3H), 2.64 (dd, J = 17.6 Hz, 6.4 Hz, 1H), 3.11 (dd, J = 17.6 Hz, 9.6 Hz, 1H), 3.56–3.61 (m, 1H), 4.15–4.26 (m, 2H), 4.68 (d, J = 5.6 Hz, 1H), 7.34–7.54 (m, 7H), 7.84 (d, J = 7.2 Hz, 2H), 9.49 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 170.7, 166.0, 140.4, 132.5, 132.2, 130.9, 129.0, 128.6, 127.6, 121.7, 67.1, 62.0, 40.1, 36.8, 14.1; HRMS(ESI) calcd for $C_{20}H_{20}N_2O_4Br^+$: 431.0606, Found: 431.0606; 97:3 *e.r.* as determined by HPLC [Chiralcel IA, 75 : 20 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r (major) = 142.7 min, t_r(minor) = 118.4 min.



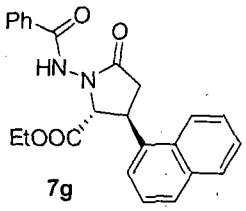
7e

EXAMPLE 49: (2R,3S)-ethyl 1-benzamido-5-oxo-3-(p-tolyl)pyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 2.41, CH_2Cl_2) = - 46.8°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (t, J = 7.2 Hz, 3H), 2.36 (s, 3H), 2.65 (dd, J = 17.6 Hz, 9.6 Hz, 1H), 3.02 (dd, J = 17.6 Hz, 9.6 Hz, 1H), 3.53–3.59 (m, 1H), 4.15–4.28 (m, 2H), 4.70 (d, J = 6.0 Hz, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.35–7.44 (m, 4H), 7.53 (t, J = 7.2 Hz, 1H), 7.85 (d, J = 7.2 Hz, 2H), 8.67 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.9, 171.0, 166.0, 138.3, 137.4, 132.5, 131.3, 129.8, 128.7, 127.6, 127.1, 67.4, 61.9, 40.3, 36.8, 21.1, 14.1;HRMS(ESI) calcd for $C_{21}H_{23}N_2O_4$ $(M+H)^+$: 367.1658, Found: 367.1657; 97:3 *e.r.* as determined by HPLC [Chiralcel IA, 75 : 20 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r (major) = 108.1 min, t_r (minor) = 86.0 min.



7f

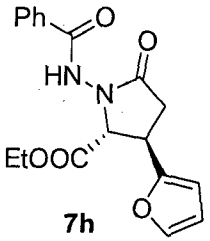
EXAMPLE 50: (2R,3S)-ethyl1-benzamido-3-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 2.2, CH_2Cl_2) = - 69.9°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.23 (t, J = 7.2 Hz, 3H), 2.65 (dd, J = 18.0 Hz, 6.8 Hz, 1H), 2.99 (dd, J = 17.6 Hz, 9.6 Hz, 1H), 3.51–3.57 (m, 1H), 3.82 (s, 3H), 4.16–4.29 (m, 2H), 4.68 (d, J = 5.6 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 7.39–7.47 (m, 4H), 7.55 (t, J = 7.2 Hz, 1H), 7.85 (d, J = 7.2 Hz, 2H), 8.42 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 171.0, 166.0, 159.1, 133.5, 132.6, 131.4, 128.8, 128.2, 127.5, 114.5, 67.5, 61.9, 55.3, 39.9, 36.8, 21.8, 14.2; HRMS(ESI) calcd for $C_{21}H_{23}N_2O_5$ $(M+H)^+$: 383.1607, Found: 383.1608; 97:3 *e.r.* as determined by HPLC [Chiralcel IA, 70 : 20 : 10 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r (major) = 82.2 min, t_r (minor) = 73.0 min.



7g

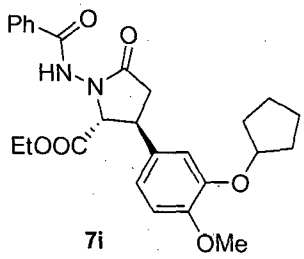
EXAMPLE 51: (2R,3S)-ethyl1-benzamido-3-(naphthalen-1-yl)-5-oxopyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 2.08, CH_2Cl_2) = - 11.1°; ^{1}H NMR (400 MHz,

$CDCl_3$) δ = 1.15 (t, J = 7.2 Hz, 3H), 2.79 (dd, J = 17.2 Hz, 5.6 Hz, 1H), 3.21 (dd, J = 17.6 Hz, 5.6 Hz, 1H), 4.16–4.26 (m, 2H), 4.43–4.48 (m, 1H), 5.02 (d, J = 4.8 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.52–7.61 (m, 4H), 7.83–7.94 (m, 5H), 8.11 (d, J = 8.4 Hz, 1H), 8.70 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 171.3, 166.2, 136.8, 134.1, 132.6, 131.4, 130.9, 129.3, 128.7, 128.3, 127.6, 126.6, 126.0, 125.8, 122.6, 66.4, 62.1, 36.3, 14.0; HRMS(ESI) calcd for $C_{24}H_{23}N_2O_4(M+H)^+$: 403.1658, Found: 403.1659; 97:3 *e.r.* as determined by HPLC [Chiralcel IA, 90 : 10 hexanes/*i*-PrOH, 0.7 mL/min)], t_r(major) = 93.4 min, t_r(minor) = 78.9 min.



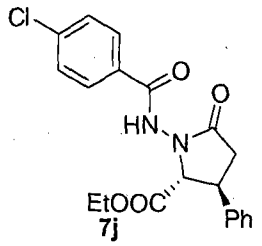
7h

EXAMPLE 52: (2R,3R)-ethyl 1-benzamido-3-(furan-2-yl)-5-oxopyrrolidine-2-carboxylate: colorless oil; $[\alpha]_D^{23}$ (c 1.55, CH_2Cl_2) = - 40.8°; ^1H NMR (400 MHz, $CDCl_3$) δ = 1.26 (t, J = 7.2 Hz, 3H), 2.80–2.95 (m, 2H), 3.74 (dd, J = 15.2 Hz, 7.2 Hz, 1H), 4.19–4.31 (m, 2H), 4.80 (d, J = 6.4 Hz, 1H), 6.36–6.39 (m, 2H), 7.43 (t, J = 7.6 Hz, 3H), 7.53 (t, J = 7.6 Hz, 1H), 7.83 (d, J = 7.6 Hz, 2H), 8.48 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 170.4, 165.8, 152.5, 142.4, 132.6, 131.3, 128.7, 127.5, 110.6, 106.8, 64.7, 62.1, 34.4, 33.6, 14.1; HRMS(ESI) calcd for $C_{18}H_{19}N_2O_5(M+H)^+$: 343.1294, Found: 343.1295; 95:5 *e.r.* as determined by HPLC [Chiralcel IA, 70 : 20 : 10 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r(major) = 63.7 min, t_r(minor) = 56.4 min.



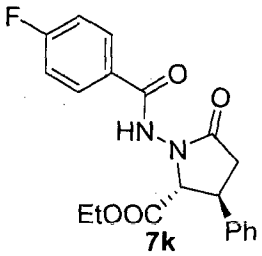
7i

EXAMPLE 53: (2R,3S)-ethyl1-benzamido-3-(3-(cyclopentyloxy)-4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 0.63, CH_2Cl_2) = -66.3°; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.24 (t, J = 7.2 Hz, 3H), 1.61–1.63 (m, 2H), 1.86–2.02 (m, 6H), 2.63 (dd, J = 17.2 Hz, 6.0 Hz, 1H), 2.99 (dd, J = 17.2, 6.0 Hz, 1H), 3.48–3.53 (m, 1H), 3.85 (s, 3H), 4.18–4.29 (m, 2H), 4.69 (d, J = 4.8 Hz, 1H), 4.90–4.92 (m, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 7.06 (s, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.84 (d, J = 7.2 Hz, 2H), 8.28 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.1, 171.0, 166.1, 150.7, 147.3, 134.2, 132.5, 128.6, 127.6, 119.3, 115.1, 110.7, 80.6, 67.5, 51.9, 56.4, 40.2, 36.9, 32.9, 24.1, 14.2,; HRMS(ESI) calcd for $C_{26}H_{31}N_2O_6$ $(M+H)^+$: 467.2182, Found: 467.2813; 96:4 *e.r.* as determined by HPLC (Chiralcel IA, 93:7 hexanes/i-PrOH, 0.7 mL/min), t_r (major) = 94.6 min, t_r (minor) = 73.1 min.



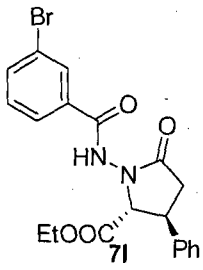
7j

EXAMPLE 54: (2R,3S)-ethyl1-(4-chlorobenzamido)-5-oxo-3-phenylpyrrolidine-2-carboxylate: white solid, *trans: cis* = 7: 1, 70% yield of both isomers; $[\alpha]_D^{23}$ (c 1.25, CH_2Cl_2) = - 26.8°. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.22 (t, J = 7.2 Hz, 3H), 2.72 (dd, J = 17.6 Hz, 6.8 Hz, 1H), 3.09 (dd, J = 17.6 Hz, 9.6 Hz, 1H), 3.59–3.64 (m, 1H), 4.15–4.28 (m, 2H), 4.70 (d, J = 5.6 Hz, 1H), 7.32–7.48 (m, 7H), 7.77 (d, J = 8.8 Hz, 2H), 9.19 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4, 170.8, 164.9, 141.2, 129.2, 129.0, 128.9, 127.8, 127.2, 67.3, 61.9, 40.6, 36.8, 14.1; HRMS(ESI) calcd for $C_{20}H_{20}N_2O_4Cl(M+H)^+$: 387.1112, Found: 387.1111; 96:4 *e.r.* as determined by HPLC [Chiralcel IA, 73 : 20 : 7 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r(major) = 125.9 min, t_r(minor) = 100.0 min.



7k

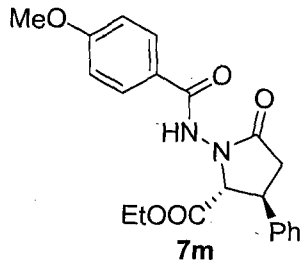
EXAMPLE 55: (2R,3S)-ethyl 1-(4-fluorobenzamido)-5-oxo-3-phenylpyrrolidine-2-carboxylate: White solid, *trans: cis* = 5: 1, 61% yield of both isomers; $[\alpha]_D^{23}$(c 1.0, $CHCl_3$) = -59.6 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.89–7.86 (m, 2H), 7.50–7.40 (m, 4H), 7.35–7.27 (m, 1H), 7.09–7.01 (m, 2H), 4.72 (d, J = 5.6 Hz, 1H), 4.36–4.10 (m, 2H), 3.65–3.60 (m, 1H), 3.10 (dd, J = 17.6, 10.0 Hz, 1H), 2.93 (dd, J = 17.2, 6.4 Hz, 1H), 1.22 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 171.0, 166.8, 165.0, 164.3, 141.5, 130.3 (d, J = 9.0 Hz), 129.3, 128.0, 127.5 (d, J = 13.0 Hz), 116.0 (d, J = 22.0 Hz), 69.6, 62.1, 40.8, 37.0. 14.3; HRMS for $C_{20}H_{20}N_2O_4$ $[M+1]^+$ Calculated: 371.1407, Found: 371.1398; 96:4 *e.r.* as determined by HPLC [Chiralcel IA, 75 : 20 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r(major) = 146.8 min, t_r(minor) = 111.6 min.



7l

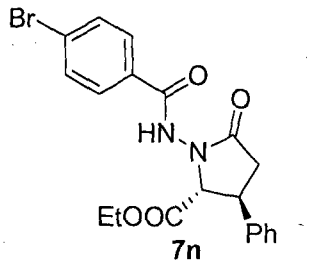
EXAMPLE 56: (2R,3S)-ethyl 1-(3-bromobenzamido)-5-oxo-3-phenylpyrrolidine-2-carboxylate: White solid, *trans: cis* = 5: 1, 59% yield of both isomers; $[\alpha]_D$

^{23} (c 1.1, $CHCl_3$) = - 45.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.97 (s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.34–7.26 (m, 2H), 4.71 (d, J = 5.6 Hz, 1H), 4.31–4.09 (m, 2H), 3.63–3.58 (m, 1H), 3.06 (dd, J = 17.2, 9.6 Hz, 1H), 2.70 (dd, J = 17.6, 6.8 Hz, 1H), 1.22 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 171.0, 164.7, 141.5, 135.6, 133.2, 131.1, 130.4, 129.3, 127.9, 127.4, 126.2, 123.1, 67.4, 62.2, 40.8, 36.9, 14.3; HRMS for $C_{20}H_{20}N_2O_4Br$ $[M+1]^+$ Calculated: 431.0606, Found: 431.0609; HPLC analysis: 96:4 *e.r.* as determined by HPLC [Chiralcel IA, 75 : 20 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r(major) = 47.4 min, t_r(minor) = 52.9 min.



7m

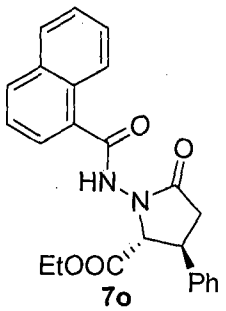
EXAMPLE 57: (2R,3S)-ethyl 1-(4-methoxybenzamido)-5-oxo-3-phenylpyrrolidine-2-carboxylate: White solid, *trans: cis* = 5: 1, 70% yield of both isomers; $[\alpha]_D^{23}$ (c 0.3, $CHCl_3$) = - 58.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.81–7.79 (m, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.32–7.25 (m, 1H), 6.93–6.88 (m, 2H), 4.71 (d, J = 5.6 Hz, 1H), 4.29–4.10 (m, 2H), 3.84 (s, 3H), 3.59–3.54 (m, 1H), 3.02 (dd, J = 17.6, 10.0 Hz, 1H), 2.67 (dd, J = 17.6, 6.8 Hz, 1H), 1.20 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 171.2, 165.8, 163.3, 141.7, 129.7, 129.3, 127.9, 127.4, 123.8, 114.2, 67.5, 62.1, 55.7, 40.8, 37.0, 14.4; HRMS for $C_{21}H_{23}N_2O_5$ $[M+1]^+$ Calculated: 383.1607, Found: 383.1637; HPLC analysis: 97:3 *e.r.* as determined by HPLC [Chiralcel IA, 65 : 30 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r(major) = 96.6 min, t_r(minor) = 103.0 min.



7n

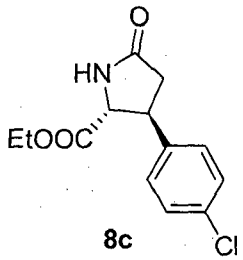
EXAMPLE 58: (2R,3S)-ethyl 1-(4-bromobenzamido)-5-oxo-3-phenylpyrrolidine-2-carboxylate: White solid, *trans: cis* = 5: 1, 65% yield of both isomers; $[\alpha]_D^{23}$ (c 0.2, $CHCl_3$) = - 10; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.39–7.25 (m, 3H), 4.69 (d, J = 5.6 Hz, 1H), 4.29–4.10 (m, 2H), 3.62–3.56 (m, 1H), 3.05 (dd, J = 17.6, 9.6 Hz, 1H), 2.69 (dd, J = 17.6, 6.4 Hz, 1H), 1.21 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 171.0, 165.3, 141.5, 132.2, 130.2, 129.4, 129.3, 128.0, 127.7, 127.4, 67.5, 62.2, 40.8, 36.9, 14.3; HRMS for $C_{20}H_{20}N_2O_4Br$ $[M+1]^+$ Calculated: 431.0606, Found: 431.0626; 95:5 *e.r.* as determined by HPLC [Chiralcel IA, 65 : 30

: 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r (major) = 66.1 min, t_r (minor) = 60.0 min.



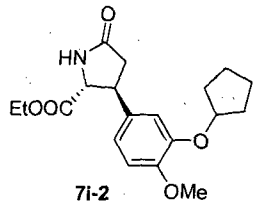
7o

EXAMPLE 59: (2R,3S)-ethyl 1-(1-naphthamido)-5-oxo-3-phenylpyrrolidine-2-carboxylate: White solid, *trans: cis* = 6: 1, 71% yield of both isomers; $[\alpha]_D^{23}$ (c 0.9, $CHCl_3$) = - 15; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 6.8 Hz 1H), 7.62–7.41 (m, 7H), 7.36- 7.34 (m, 1H), 4.85 (d, J = 5.6 Hz, 1H), 4.29–4.18 (m, 2H), 3.65–3.59 (m, 2H), 3.03 (dd, J = 17.6, 8.0 Hz, 1H), 2.74 (dd, J = 17.6, 6.8 Hz, 1H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (mixture of both isomers, 100 MHz, $CDCl_3$) δ 172.6, 171.1, 168.3, 141.5, 133.9, 132.1, 130.7, 130.5, 129.4, 128.7, 128.6, 128.0, 127.8, 127.4, 127.0, 126.4, 125.5, 125.2, 124.8, 124.7, 67.5, 62.2, 62.0, 40.9, 36.9. 14.4; HRMS for $C_{24}H_{23}N_2O_4$ $[M+1]^+$ Calculated: 403.1658, Found: 403.1643; 95:5 *e.r.* as determined by HPLC [Chiralcel IA, 75 : 20 : 5 hexanes/(hexanes:*i*-PrOH:CH_3OH = 90:5:5)/*i*-PrOH, 0.7 mL/min)], t_r(major) = 107.2 min, t_r(minor) = 120.6 min.



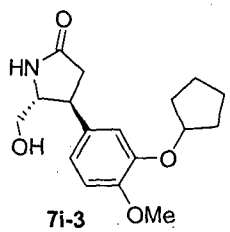
8c

EXAMPLE 60: (2R,3S)-ethyl 3-(4-chlorophenyl)-5-oxopyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 0.67, CH_2Cl_2) = - 66.6°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.27 (t, J = 7.2 Hz, 3H), 2.49 (dd, J = 17.6 Hz, 6.8 Hz, 1H), 2.86 (dd, J = 17.2, 9.6 Hz, 1H), 3.68–3.74 (m, 1H), 4.17–4.27 (m, 3H), 6.14 (bs, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.6, 171.1, 140.3, 133.3, 129.2, 128.4, 62.9, 61.9, 43.3, 38.0, 14.1; HRMS(ESI) calcd for $C_{13}H_{15}NO_3Cl$ $(M+H)^+$: 268.0740, Found: 268.0743; 96:4 *e.r.* as determined by HPLC [Chiralcel IB, 95 : 5 hexanes/*i*-PrOH, 0.7 mL/min)], t_r(major) = 60.4 min, t_r (minor) = 53.8 min.



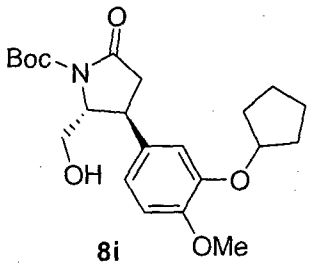
7i-2

EXAMPLE 61: (2R,3S)-ethyl3-(3-(cyclopentyloxy)-4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate: yellow oil; $[\alpha]_D^{23}$ (c 1.42, CH_2Cl_2) = -38.2°; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.27 (d, J = 7.2 Hz, 3H), 1.60–1.66 (m, 2H), 1.81–1.92 (m, 6H), 2.51 (dd, J = 17.2 Hz, 6.4 Hz, 1H), 2.84 (dd, J = 17.2, 6.4 Hz, 1H), 3.62–3.68 (m, 1H), 3.84 (s, 3H), 4.18–4.27 (m, 3H), 4.75–4.78 (m, 1H), 6.17 (bs, 1H), 6.80–6.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.4, 171.3, 149.5, 148.0, 134.3, 119.0, 113.8, 112.3, 80.6, 63.1, 61.8, 56.1, 43.5, 37.9, 32.8, 24.0, 14.2; HRMS(ESI) calcd for $C_{19}H_{26}NO_5$ $(M+H)^+$: 348.1811, Found: 348.1813; 96:4 *e.r.* as determined by HPLC [Chiralcel IA, 90 : 10 hexanes /*i*-PrOH, 0.7 mL/min)], t_r(major) = 28.2 min, t_r(minor) = 24.6 min.



7i-3

EXAMPLE 62: (4S,5R)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)-5-(hydroxymethyl)pyrrolidin-2-one: colorless oil; $[\alpha]_D^{23}$ (c 0.52, CH_2Cl_2) = -14.6°; ^{1}H NMR (400 MHz, $CDCl_3$) δ =1.59 (dd, J = 7.0, 5.1 Hz, 2H), 2.02–1.69 (m, 6H), 2.53 (dd, J = 17.2, 8.8 Hz, 1H), 2.77 (dd, J = 17.2, 9.3 Hz, 1H), 3.36–3.12 (m, 1H), 3.50–3.55 (m, 1H), 3.76 (d, J = 7.3 Hz, 2H), 3.81 (s, 3H), 4.14 (brs, 1H), 4.76 (dd, J = 5.9, 2.7 Hz, 1H), 6.86 – 6.60 (m, 3H), 7.46 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 24.0, 32.79, 32.82, 39.4, 42.0, 56.2, 64.0, 64.4, 80.6, 112.3, 114.3, 119.3, 133.9, 147.9, 149.3, 178.0; HRMS(ESI) calcd for $C_{17}H_{24}NO_4$ $(M+H)^+$: 306.1705, Found: 306.1705.



8i

EXAMPLE 63: (2R,3S)-tert-butyl3-(3-(cyclopentyloxy)-4 methoxyphenyl)-2-(hydroxymethyl)-5-oxopyrrolidine-1-carboxylate: colorless oil; $[\alpha]_D^{23}$ (c 0.4, CH_2Cl_2) = -8.5°; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.48 (s, 9H), 1.60–1.63 (m, 2H), 1.82–1.94 (m, 6H), 2.53 (dd, J = 17.3, 9.0 Hz, 1H), 2.79 (dd, J = 17.3, 9.3 Hz, 1H), 3.22 (dd, J = 16.5, 9.0 Hz, 1H), 3.83 (s, 3H), 3.85–3.87 (m, 1H), 3.94 (dd, J = 11.0, 6.0 Hz, 1H), 4.25 (dd, J = 11.5, 3.0 Hz, 1H), 4.76–4.78 (m, 1H), 6.77 (dd, J = 12.0, 2.0 Hz, 2H), 6.82 (d, J = 8.5 Hz, 1H); ^{13}CNMR

(125Hz, $CDCl_3$): δ = 24.0, 27.7, 32.8, 38.7, 42.6, 56.1, 60.8, 68.0, 80.6, 82.9, 112.3, 113.9, 119.3, 133.1, 148.1, 149.5, 153.3, 176.2; HRMS(ESI) calcd for $C_{22}H_{32}NO_6$ $(M+H)^+$: 406.2230, Found: 406.2236. 96:4 *e.r.* as determined by HPLC [Chiralcel IA, 90 : 10 hexanes /*i*-PrOH, 0.7 mL/min)], t_r(major) = 15.7 min, t_r(minor) = 11.3 min.

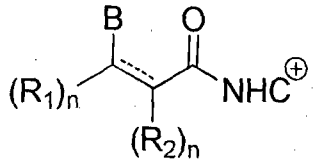
[077] While particular preferred and alternative embodiments of the present invention have been disclosed, it will be apparent to one of ordinary skill in the art that many various modifications and extensions of the above described technology may be implemented using the teaching of this invention described herein. All such modifications and extensions are intended to be included within the true spirit and scope of the invention as discussed in the appended claims.

[078] References:

1. Reed, P. E. & Katzenellenbogen, J. A. Beta-Substituted Beta-Phenylpropionyl Chymotrypsins - Structural and Stereochemical Features in Stable Acyl Enzymes. *J. Med. Chem.* **1991**, *34*, 1162-1176.
2. Kerr, M. S., de Alaniz, J. R. & Rovis, T. An efficient synthesis of achiral and chiral 1,2,4-triazolium salts: Bench stable precursors for N-heterocyclic carbenes. *J. Org. Chem.* **2005**, *70*, 5725-5728.
3. Matsuoka, Y., Ishida, Y., Sasaki, D. & Saigo, K. Cyclophane-Type Imidazolium Salts with Planar Chirality as a New Class of N-Heterocyclic Carbene Precursors. *Chem.-Eur. J.* **2008**, *14*, 9215-9222.
4. Raup, D. E. A., Cardinal-David, B., Holte, D., Scheidt, K. A. Cooperative Catalysis by Carbenes and Lewis Acids in a Highly Stereoselective Route to γ-Lactams. *Nat. Chem.* **2010**, *2*, 766-771.
5. Oba, M., Saegusa, T., Nishiyama, N. & Nishiyama, K. Synthesis of non-proteinogenic amino acids using Michael addition to unsaturated orthopyroglutamate derivative. *Tetrahedron* **2009**, *65*, 128-133.
6. Diaz, A. et al., A stereoselective synthesis of (R)-(-)-rolipram from L-glutamic acid. *Synthesis*, **1997**, 559-562.
7. Chiang, P., Kaeobamrung, J. & Bode, J. W. Enantioselective, cyclopentene-forming annulations *via* NHC-catalyzed benzoin-oxy-Cope reactions. *J. Am. Chem. Soc.* **2007**, *129*, 3520-3521.

CLAIMS

1. Method for synthesizing a compound of Formula (I)



(I)

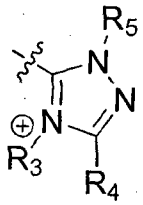
wherein

------ is a single or a double bond, wherein if it is a double bond n is 1 and if it is a single bond n is 2;

each R_1 and R_2 is independently selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety;

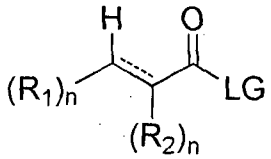
B is an electrophilic group; and

NHC^+ is



comprising:

(i) activating a compound of Formula (II)

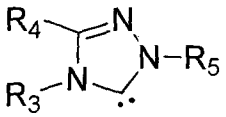


(II)

wherein

LG is a leaving group;

by reacting said compound of Formula (II) with a compound of Formula (III) in the presence of a base

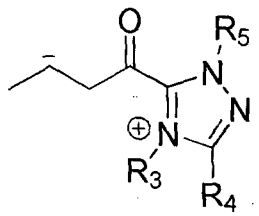


(III)

wherein

R_3, R_4, and R_5 are independently from each other selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety;

to obtain a compound of Formula (IV)



(IV)

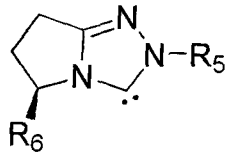
and

(ii) reacting the compound of Formula (IV) with an electrophile to obtain the compound of Formula (I).

2. Method according to claim 1, wherein the organic moiety is independently selected from the group consisting of linear or branched, substituted or unsubstituted C_1-C_x alkyl; linear or branched, substituted or unsubstituted alkenyl with 2 to x carbon atoms; linear or branched, substituted or unsubstituted alkinyl with 2 to x carbon atoms; linear or branched, substituted or unsubstituted alkoxy with 1 to x carbon atoms; substituted or unsubstituted cycloalkyl with 3 to x carbon atoms; substituted or unsubstituted cycloalkenyl with 3 to x carbon atoms; substituted or unsubstituted aryl with 6 to x carbon atoms; and substituted or unsubstituted heteroaryl with 3 to x carbon atoms; with x being any integer of 2 or more, preferably up to 50, more preferably up to 30.

3. Method according to claim 1 or 2, wherein R_3 and R_4 combine to form together with the carbon atoms to which they are attached a substituted or unsubstituted 5- to 40-membered cycloalkyl, cycloalkenyl, heteroalicyclic, aryl, or heteroaryl ring.

4. Method according to claim 3, wherein compound of Formula (III) is a compound of Formula (V)



(V)

wherein

R_6 is hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety.

5. Method according to claim 4, wherein R_6 is selected from the group consisting of substituted or unsubstituted, linear or branched alkyl with 1 to 20 carbon atoms; substituted or unsubstituted, linear or branched alkenyl with 1 to 20 carbon atoms; substituted or unsubstituted cycloalkyl with 5 to 20 carbon atoms; substituted or unsubstituted cycloalkenyl with 5 to 20 carbon atoms; substituted or unsubstituted aryl with 5 to 14 carbon atoms; and substituted or unsubstituted heteroaryl with 5 to 14 carbon atoms.

6. Method according to claim 5, wherein R_6 is selected from the group consisting of -*iso*-Pr, -*tert*-Bu, $-CH_2Ph$, $-CH_2$-*iso*-Pr, and $-CH_2$-*tert*-Bu.

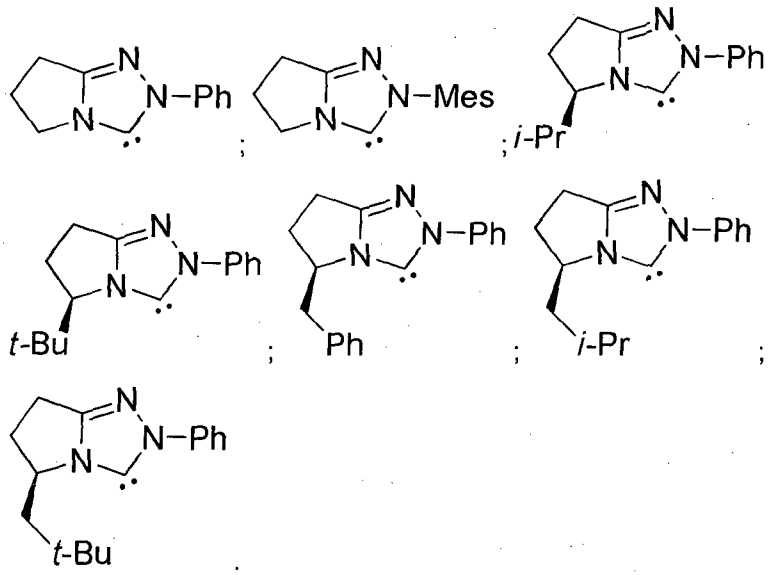
7. Method according to claim 6, wherein R_6 is selected from the group consisting of $-CH_2$-*tert*-Bu and $-CH_2$-*iso*-Pr.

8. Method according any one of claims 4 to 7, wherein R_5 is a substituted or unsubstituted aryl.

9. Method according to claim 8, wherein R_5 is selected from the group consisting of phenyl and mesitylene.

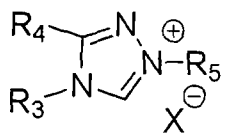
10. Method according to claim 9, wherein R_5 is phenyl.

11. Method according to any one of claims 4 to 10, wherein the compound of Formula (V) is selected from the group consisting of



; and

12. Method according to any one of claims 1 to 11, wherein the compound of Formula (III) or (V) is synthesized from a compound of Formula (VI)



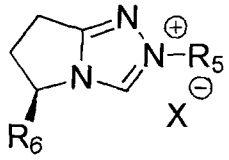
(VI)

wherein

X is any anion.

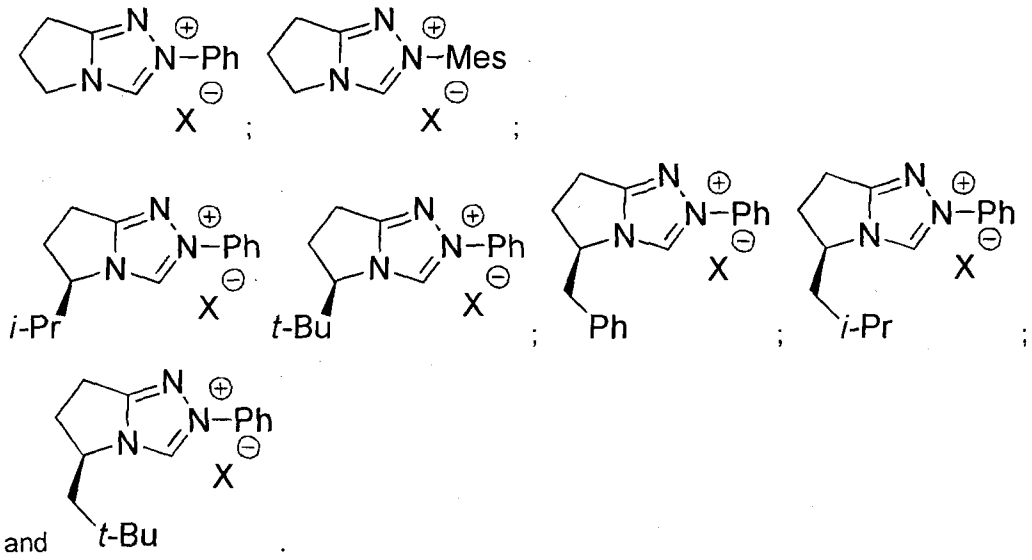
13. Method according to claim 12, wherein X is selected from the group consisting of F^-, Cl^-, Br^-, I^-, BF_4^-, OTf^-, and acetate.

14. Method according to claim 12 or 13, wherein the compound of Formula (VI) is a compound of Formula (VII)



(VII)

15. Method according to any one of claims 12 to 14, wherein the compound of Formula (VII) is selected from the group consisting of



16. Method according to any one of claims 1 to 15, wherein the compound of Formula (III) or Formula (V) according to any one of claims 1 to 11 is generated *in situ* from a compound according to claims 12 to 15.

17. Method according to any one of claims 1 to 16, wherein the leaving group is selected from the group consisting of hydrogen, halogen, $-N_2^+$, $-OR_2^+$, $-OSO_2C_4F_9$, $-OSO_2CF_3$, $-OSO_2F$, -OTs, -OMs, $-OH_2^+$, $-OHR^+$, $-ONO_2$, $-OPO(OH)_2$, $-SR_2$, $-NR_3$, -OCOR, $-NH_3^+$, and $-O-C_6H_4$-*para*-NO_2, and R can be any organic residue.

18. Method according to claim 17, wherein the leaving group is $-O-C_6H_4$-*para*-NO_2.

19. Method according to claims 1 to 18, wherein the method is carried out in a solvent selected from the group consisting of *tert*-Butanol, toluene, THF, CH_3CN, CH_2Cl_2, dioxane, ethyl acetate, and mixtures thereof.

20. Method according to any one of claims 1 to 19, wherein the base is present in an amount of 100 to 300 mol-% based on the total amount of the compound of Formula (I).

21. Method according to claim 20, wherein the base is present in an amount of 115 to 250 mol-% based on the total amount of the compound of Formula (I).

22. Method according to claim 20 or 21, wherein the base is present in an amount of 130 to 200 mol-% based on the total amount of the compound of Formula (I).

23. Method according to any one of claims 20 to 22, wherein the base is present in an amount of about 150 mol-% based on the total amount of the compound of Formula (I).

24. Method according to any one of claims 1 to 23, wherein the electrophile is selected from the group consisting of F_2, Cl_2, Br_2, I_2, alkyl-LG, alkenyl-LG, alkoxy-LG, acyl-LG, aryl-LG, heteroaryl-LG, hydrazone, and a carbonyl compound, wherein LG is a leaving group.

25. Method according to claim 24, wherein the electrophile is selected from the group of optionally α,β-unsaturated, linear or branched, substituted or unsubstituted ketone; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted aldehyde; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted esters; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted trifluoroketone; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted carboxamide; optionally α,β-unsaturated, linear or branched, substituted

or unsubstituted amide; optionally α,β-unsaturated, linear or branched, substituted or unsubstituted nitrile; and optionally α,β-unsaturated, linear or branched, substituted or unsubstituted hydrazone.

26. Method according to claim 24 or 25, wherein the electrophile is selected from the group consisting of α,β-unsaturated, linear or branched, substituted or unsubstituted ketone, trifluoroketone, and hydrazone.

27. Method according to any one of claims 1 to 26, wherein the base contains one or more nitrogen atom(s).

28. Method according to claim 27, wherein the base is selected from the group consisting of pyrrolidine; $N(CH_3)_3$; $N(CH_2CH_3)_3$; (*iso*-Propyl)$_2$NH; 2,2,6,6-Tetramethyl-1-piperidin; LDA (Lithium di*iso*propylamid); LHMDS (Lithium bis(trimethylsilyl)amide); LTMP (Lithium tetramethylpiperidide); and 4-aminopyridine.

29. Method according to claim 27, wherein the base is an amidine.

30. Method according to claim 29, wherein the amidine is selected from the group consisting of DBU (1,8-Diazabicyclo[5.4.0]undec-7-en), DBN (1,5-Diazobicyclo[3.4.0]non-5-ene); and DABCO (1,4-Diazobicyclo[2.2.2]octan).

31. Method according to claim 27, wherein the base is a phosphazine.

32. Method according to claim 31, wherein the phosphazine is selected from the group consisting of P_1-*tert*-Bu-tris(tetramethylene); 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine; and 1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene).

33. Method according to any one of claims 1 to 32, wherein the reaction temperature of steps (i) and (ii) is from 0 °C to 85 °C.

34. Method according to claim 33, wherein the reaction temperature of steps (i) and (ii) is from 15 °C to 55 °C.

35. Method according to claim 33 or 34, wherein the reaction temperature of steps (i) and (ii) is about 25 °C.

36. Method according to any one of claims 1 to 35, wherein the reaction time is from 0.1 hours to 72 hours.

37. Method according to claim 36, wherein the reaction time is from 1 hour to 48 hours.

38. Method according to claim 36 or 37, wherein the reaction time is from 5 hours to 36 hours.

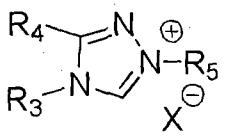
39. Method according to any one of claims 36 to 38, wherein the reaction time is about 24 hours.

40. Method according to any one of claims 1 to 39, wherein a molecular sieve is present during the reaction.

41. Method according to claim 40, wherein the molecular sieve has apertures of a size of approximately 4 Å.

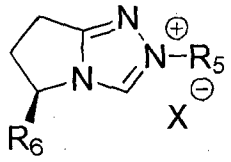
42. Method according to any one of claims 1 to 41, wherein the method comprises further reaction steps selected from catalyst regeneration, michael reaction, aldol reaction, lactonization, and/or decarboxylation.

43. Compound of Formula (VI)



(VI)

or Formula (VII)

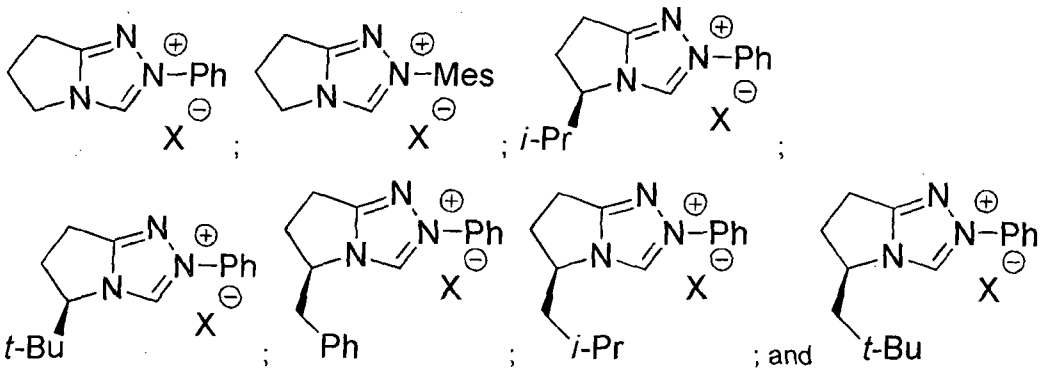


(VII)

wherein R_3, R_4, R_5, and R_6 are independently from each other selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety; and

X is any anion.

44. Compound according to claim 43, wherein the compound is selected from the group consisting of

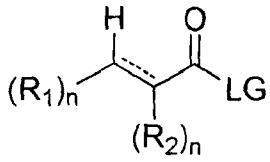


wherein

X is any anion.

45. Compound of claim 43 or 44, wherein X is selected from the group consisting of F^-, Cl^-, Br^-, I^-, BF_4^-, OTf^-, and acetate.

46. Use of a compound of Formula (VI) and (VII) according to any one of claims 43 to 45 for activating a compound of Formula (II)



(II)

wherein

------ is a single or a double bond, wherein if it is a double bond n is 1 and if it is a single bond n is 2;

each R_1 and R_2 is independently selected from the group consisting of hydrogen, halogen, -OH, -OOH, $-NH_2$, $-NO_2$, $-ONO_2$, -CHO, -CN, -CNOH, -COOH, -SH, -OSH, -CSSH, -SCN, $-SO_2OH$, $-CONH_2$, $-NH-NH_2$, -NC, -CSH, or any organic moiety; and

LG is a leaving group.