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PAPER

Amphiphilic allylation of arylidene-1,3-oxazol-5(4*H*)-one using bis-π-allylpalladium complexes: an approach to synthesis of cyclohexyl and cyclohexenyl α-amino acids†

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An efficient method for synthesis of cyclohexyl and cyclohexenyl α-amino acids *via* palladium-catalyzed three-component assemblies followed by ring-closing metathesis (RCM) is described. The present catalytic reaction is successfully extended to substituted benzylidene azlactones **2a–j** RCH=(1,3-oxazole): R = alkyl or aryl. The amphiphilic bis-allylation of these substrates has been achieved by replacing toxic allylstannanes with allyltrifluoroborate and the reaction proceeded smoothly to afford the corresponding 1,7-diene derivatives **3a–j** in acceptable to good yields. RCM of the resulting octadienes using the first generation Grubbs catalyst gave easy access to stereodefined substituted cyclohexene derivatives **7–11** in high yields. Acid hydrolysis of the oxazolone ring of **7–10** gave protected amino acids **12–16**. Debenzoylation of **13** and **15** afforded 1-amino-6-aryl-cyclohex-3-enecarboxylic acids **17** and **18** in excellent yields, respectively. Moreover, catalytic reduction of **13** gave the corresponding cyclohexane derivative **19** which could be debenzoylated to give 1-amino-2-phenylcyclohexene-1-carboxylic acid (**20**). The structures of compounds **9, 12** and **13** were confirmed by X-ray structural analysis. It is an excellent method for creating a wide range of cyclic α,α-disubstituted α-amino acids.

Introduction

Transition metal-catalyzed multicomponent assembling reactions provide an efficient route for the construction of complex organic molecules.[1] Catalytic transformations involving nucleophilic attack on (η^3-allyl)palladium intermediates have been widely applied in a number of important chemical processes,[2–7] including allylic substitution and the oxidation of alkenes and conjugated dienes. Palladium-catalyzed allylation with various nucleophiles (Tsuji–Trost-type reaction) is now a very important modern organic transformation for the construction of carbon–carbon or carbon–heteroatom bonds.[8] Furthermore, it has been demonstrated that, under catalytic conditions, bis-π-allylpalladium complexes can undergo an initial electrophilic attack on one of the allyl moieties followed by a nucleophilic attack on the other.[9–14] This bis-π-allylpalladium complex can act as an amphiphilic reagent reacting with activated olefins and arynes to form the corresponding bis-allylation products. Subsequently, several modifications of this reaction with variation of allyl sources, activated alkenes and catalysts have been reported by different groups.[15,16] This catalytic amphiphilic bis-allylation could also be applied to the synthesis of medium-sized carbocycles.[17] Moreover, regioselective unsymmetrical tetra-allylation of C_{60} was reported recently using the catalytic amphiphilic bis-allylation reaction.[18]

In the past decade, organotrifluoroborates have become important reagents in organoboronate chemistry, in particular for transition-metal-catalyzed coupling reactions.[16,19,20] These reagents are air- and thermostable species, which are usually easy to handle and purify. Moreover, allyltrifluoroborates have been shown to be effective allylating reagents for aldehydes.[22] Recently, Batey and co-workers[21,22] described the synthesis of a new class of allylboron compounds containing a trifluoroborate functionality. Due to the toxicity as well as the byproducts of organostannanes, we preferred the use of allyltrifluoroborate in catalytic bis-π-allylpalladium reactions. On the other hand, azlactones are important synthons for the synthesis of several biologically active compounds.[23] They are also particularly useful precursors for the synthesis of amino acids,[24] peptides,[25] heterocycles,[26] biosensors,[27] and antitumor[28] or anticancer[29] compounds.

The construction of suitably functionalized cyclohexene frameworks plays a central role in many natural product syntheses.[30] Although the Diels–Alder reaction is among the most powerful tools for generating such carbocycles,[31] it is often difficult to form

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **3a–j** and **7–20**, and X-ray crystallographic files for compounds **9, 12** and **13**. CCDC reference numbers 82954–82956. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05952a

systems that are highly congested or possess substituent arrays that are incompatible with the reaction.[32] A number of alternative methods for synthesizing cyclohexenes have arisen from catalytic approaches, such as the phosphine-catalyzed Rauhut–Currier reaction,[33] transition-metal-catalyzed ring-closing metathesis (RCM),[34] and cycloisomerization reactions.[35] In contradistinction to the widespread use of these intramolecular processes, intermolecular counterparts for catalytic cyclohexene synthesis are less well developed.[36,37] With the development of air-stable, functionally compatible, and highly active ruthenium catalysts, such as the first-generation Grubbs catalyst[38] and second-generation Grubbs catalyst,[39] the ring-closing metathesis (RCM) reaction has become one of the most powerful methods to synthesize many kinds of cyclized products from acyclic diene or enyne precursors.[40] In this study, the first-generation Grubbs catalyst was used in the metathesis reaction of the resulting bis-allylated azlactones giving the corresponding cyclohexenes in excellent yields.

α,α-Disubstituted α-amino acids are nonproteinogenic modified amino acids, in which the hydrogen atom at the α-position of natural α-amino acids is replaced with an alkyl substituent.[41] The α-alkyl substituents in α,α-disubstituted amino acids severely restrict the conformational freedom of peptides containing such residues, and these amino acids are used as a probe to investigate the biologically active conformation,[42] to study the secondary structure of peptides,[43] and to search for the origin of chirality.[44] Furthermore, α,α-disubstituted α-amino acids are also found in many biologically active compounds, including antibiotics such as altemicidin.[45] Certain cyclic α,α-disubstituted amino acids, notably those with 3-, 5-, and 6-membered rings, tend to induce α-helical conformations when incorporated into peptides.[46] One of the challenges is to have procedures that provide flexible and simple methods for obtaining optically active α,α-disubstituted α-amino acids and that, furthermore, give diversity in structural and electronic properties.

Here we demonstrate a new protocol in amino acids synthesis; bis-allylated azlactones can act as excellent precursors for the synthesis of cyclic amino acids by bis-allylation of unsaturated azlactones. To the best of our knowledge, this is the first bis-allylation of azlactones. Catalytic cyclization of the resulting 1,7-diene afforded cyclohexene–azlactone adducts.

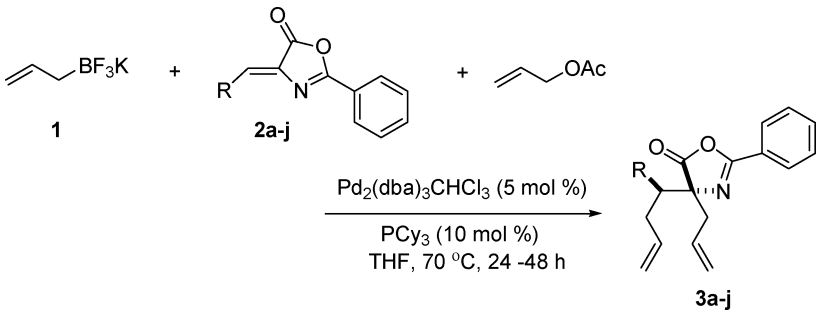
Results and discussion

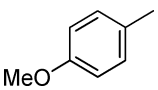
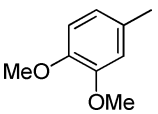
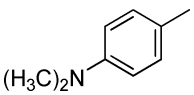
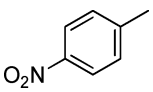
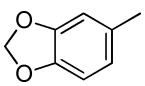
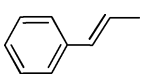
Catalytic amphiphilic bis-allylation

The three-component assembling reactions such as bis-allylation gave the corresponding α,β-functionalized products in high yields. Although these reactions are limited to highly activated olefins,[16] we succeeded in utilizing substituted azlactones **2a–j** as substrates. In the current study, we used an alternative catalytic system of bis-π-allylpalladium complexes generated from allyltrifluoroborate (**1**). Arylidene azlactones **2a–g** and **2i** were prepared according to the classic Erlenmeyer synthesis,[47] whereas **2h** and alkylidene azlactone **2j** were prepared under mild conditions using alumina as a catalyst.[48] In a preliminary study,[49] we reported suitable conditions for the amphiphilic bis-allylation of arylidene malononitrile with allyl acetate and allyltrifluoroborate to give substituted 1,7-diene derivatives. The results prompted us to extend this methodology into other olefins such as arylidene azlactones in bis-allylation reactions as a masked amino acid fragment. Moreover, we examined the optimization of palladium catalysts and ligands for amphiphilic bis-allylation of activated alkenes by replacing allylstannanes with allyltrifluoroborate.[49] According to these results we found that the amphiphilic bis-allylation reaction with allyltrifluoroborate and allyl acetate proceeded smoothly using $Pd_2(dba)_3CHCl_3$/tricyclohexylphosphine (PCy_3) in THF. These reaction conditions could be applied to azlactones **2**. The reaction of benzylidene azlactone **2a** (1 equiv.), allyltrifluoroborate **1** (1.5 equiv.), and allyl acetate (1.5 equiv.) in THF proceeded in the presence of $Pd_2(dba)_3CHCl_3$ (5 mol%) and PCy_3 (10 mol%) in an argon atmosphere at 70 °C for 24 h to furnish 1,7-diene derivative **3a** in 45% yield. The low yield of **3a** could be explained by the formation of mono-allylated byproduct which was identified by ESI mass spectrometry. Increasing the reaction time had no effect on the bis-allylated yield. Moreover, allyl acetate gave the highest yield of three-component assembling product. Other substrates such as allyl chloride, which was considered the most appropriate for the amphiphilic bis-allylation with allyltributylstannane, were less effective for the reaction, affording **3a** in lower yield (26%). So, in another attempt to enhance the yield of the bis-allylated product, we performed the bis-allylation reaction using 3 equiv. of allyl acetate. It was found that the yield of **3a** increased to 49% (Table 1, entry 1). To study the scope of the reaction, attempting to enhance the activity of the double bond in azlactone, we used different aryl derivatives of azlactones. Several diversely substituted benzylidene azlactones underwent bis-allylations by this procedure to produce the corresponding 1,7-octadiene derivatives. The results are summarized in Table 1. This procedure is compatible with a wide range of substituents including electron donating and electron withdrawing groups substituted on the phenyl ring. Various substituted arylethylidene azlactones **2b–i** underwent bis-allylation with **1** and allyl acetate to give the corresponding three-component assembling products **3b–3i** in good yields (entries 2–9).

Arylethylidene azlactones with electron donating groups (entries 2–4) are more effective substrates for the assembling reaction than that bearing an electron withdrawing group on the phenyl ring (entry 5). The lower yield of **3d** compared to the yields of **3b** and **3c** was attributed to the insolubility of **2d** in THF and using DMF as the solvent (entry 4). The present protocol is successfully extended to azlactones with a heterocyclic substituent, such as furyl and pyridyl groups. Thus, treatment of furylidene azlactone (**2f**) and pyridylidene azlactone (**2h**) with **1** as well as allyl acetate in the presence of $Pd_2(dba)_3CHCl_3/PCy_3$ afforded the corresponding 1,7-diene derivatives **3f** and **3h** in 73% and 62% yields, respectively (entries 6 and 8). Under similar conditions, the reaction of piperonylidene azlactone (**2g**) with **1** and allyl acetate produced the corresponding assembling product **3g** in 75% yield (entry 7). The bis-allylation reaction also proceeded with *E*/*Z*-cinnamylidene azlactone **2i** to give (*E*/*Z*)-4-allyl-2-phenyl-4-(1-phenylhexa-1,5-dien-3-yl)oxazol-5(4*H*)-one (**3i**) in 32% yield (entry 9). It should be noted that the allylation reaction is completely regioselective, adding to the β and α carbons of **2i**. No other regioisomer was detected as evidenced by the ^{1}H NMR spectrum of the crude reaction mixture, indicating that the catalytic allylation is highly regioselective. The three-component assembling reaction of alkylidene azlactone **2j** gave **3j** in 68% yield (entry 10). The purification of the bis-allylation product was

Table 1 Palladium-catalyzed double allylation of olefins **2a–j** with allyltrifluoroborate **1** and allyl acetate



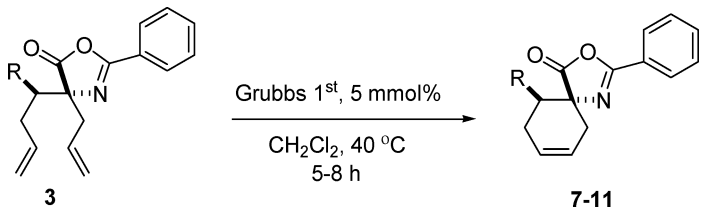
Entry	R	Product	Time (h)	Yield (%)[a]	d.r.[b]
1		**3a**	24	45	5 : 1
2		**3b**	24	58	4 : 1
3		**3c**	48	67	3 : 1
4		**3d**[c]	24	47	3 : 1
5		**3e**	48	49	4 : 1
6		**3f**[c]	24	73	5 : 1
7		**3g**	24	75	4 : 1
8		**3h**	24	62	3 : 1
9		**3i**	48	32	—
10		**3j**	24	68	4 : 1

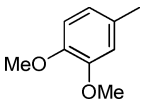
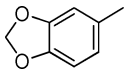
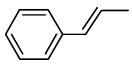
[a] Combined isolated yields of two diastereomers based on **2**. [b] Diastereomer ratio determined by ^{1}H NMR. [c] DMF was used as the solvent.

performed by preparative thin layer chromatography (TLC) using hexane/ethyl acetate as the mobile phase. Diastereoselectivity (3–5 : 1) of the bis-allylation reactions was observed in all substituted azlactones **2a–j** except **2i** (Table 1). The major diastereomers were isolated by preparative TLC and identified.

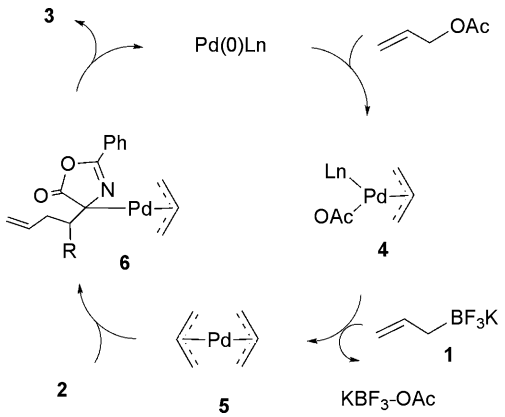
The proposed mechanism for the reaction course of this transformation is summarized in Scheme 1. On the basis of the known palladium chemistry and the mechanisms for the catalytic reactions involving bis-π-allylpalladium complexes as key intermediates,[9,17,50–52] a mechanism is proposed to account for the present catalytic amphiphilic bis-allylation reaction. The first step likely involves the oxidative addition of allyl acetate to Pd(0) to give π-allylpalladium acetate **4**. Transmetalation of allyltrifluoroborate **1** to π-allylpalladium acetate **4** gives bis-π-allylpalladium intermediate **5** and KBF_3OAc. Reaction of olefin **2** with **5** gives the complex **6**, which undergoes reductive elimination

Table 2 Metathesis reaction of **3**



Entry	3	Product	R	Yield (%)[a]
1	**a3**	**7**		85
2	**c3**	**8**		87
3	**f3**	**9**		92
4	**g3**	**10**		76
5	**i3**	**11**		70

[a] Isolated yields based on **3**.



Scheme 1 Palladium-catalysis mechanism.

to afford the corresponding bis-allylated product **3** and regenerate the Pd(0) catalyst.

Metathesis of bis-allylated compounds

Catalytic olefin metathesis transformed some of these bis-allylated products (**3a, 3c, 3f, 3g** and **3i**) to the corresponding cyclohexenes (**7–11**) in 70–92% yields (Table 2).

In our experiments the metathesis of bis-allylated products to cyclohexenes worked with excellent results when the reaction was carried out in dichloromethane at reflux for 5–8 h in the presence of 1st generation Grubbs' catalyst, allowing the formation of the corresponding cyclohexenes. The metathesis of **3i** is highly chemoselective giving the cinnamyl-substituted product **11**, exclusively (entry 5). The ^{1}H NMR spectrum of compound **11** showed δ- and γ-CH protons resonate at 5.9 and 6.5 ppm, respectively. It was possible to obtain X-ray quality crystals from **9** by slow evaporation of a CH_2Cl_2/hexane solution at room temperature. The solid state structure of the cyclohexene **9**, determined by X-ray diffraction, is depicted in Fig. 1. The cyclohexene **9** consists of a cyclohexene ring having azlactone and furan moieties as substituents at positions 1 and 6. The C–C bond lengths of the cyclohexene ring span over a narrow range of 1.495(2)–1.555(2) Å compared with the C═C bond distance 1.322(2) Å.

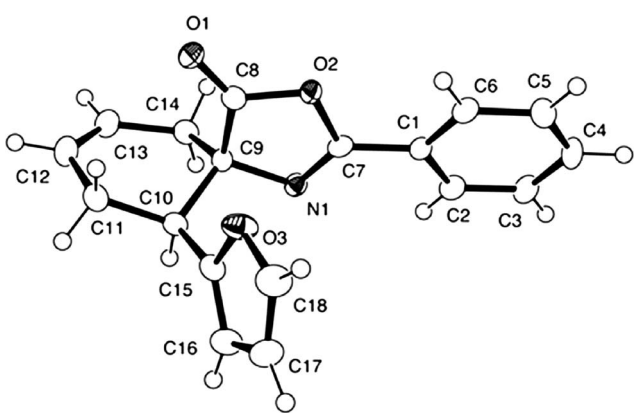
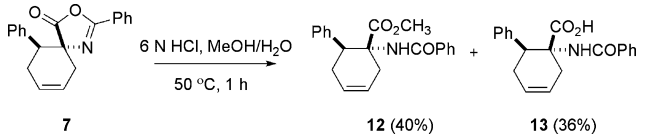


Fig. 1 ORTEP representation of **9**, showing 50% probability thermal ellipsoids.

Hydrolysis of oxazolone ring

One of the goals of our synthetic work was the successful preparation and characterization of a structurally diverse series of α,α-disubstituted α-amino acids derived from compounds **7**–**11**. Incubation of azlactone **7** in a mixture of MeOH/H_2O (1 : 1) and HCl (6 N) at room temperature for 1 h resulted in cleavage of the oxazolone ring to give a mixture of **12** and **13** which could be isolated by preparative TLC to give 40% and 36% yields, respectively (Scheme 2).



7 **12** (40%) **13** (36%)

Scheme 2 Cleavage of azlactone **7**.

In the ^{1}H NMR spectra of **12** and **13**, the new signals at 6.8 and 6.7 ppm indicated the presence of an NH group. ^{13}C NMR spectra showed a low field shift of C═N of the former oxazolone ring in compounds **7**–**11**, from *ca.* 160.2 ppm to *ca.* 166.8 ppm, whereas a high field shift of *ca.* 7 ppm for the carbonyl carbon of compounds **12** and **13** (172.8 ppm) compared with compound **7** (180.3 ppm) was observed. The expected deviations in these positions were attributed to oxazolone ring opening. Alternative conditions using a mixture of THF/aq. HCl (6 N) for direct conversion of **7** to the corresponding free carboxylic compound (**13**) were also possible. The compounds **12** and **13** crystallize in the monoclinic space groups $P2_1/c$ and $C2/c$, respectively (Fig. 2, Table 3).

Similarly, compounds **8**–**10** were hydrolysed producing benzoylated amino acids **14**–**16** (Scheme 3). The structures of these compounds were also confirmed by both ^{1}H and ^{13}C NMR spectroscopy, which showed the disappearance of the benzoyl CH and NH signals and appearance of high field NH_2 broad singlet at *ca.* 4.6 ppm. Amino acids **17** and **18** could be obtained from **13** and **15** in good yields by treatment with ammonia solution (Scheme 3).

Reduction of cyclohexene

Cyclohexene **13** was quantitatively hydrogenated in MeOH at room temperature, using 10% palladium/carbon as a catalyst to give cyclohexane **19**, which is the direct precursor of the cyclohexane amino acid **20** (Scheme 4). The chemical shift of the CH═CH group of the former cyclohexene (compound **13**) disappeared with appearance of new high field signals at 1.6 and 1.8 ppm of two methylene groups (compound **20**) upon reduction. The ^{13}C NMR spectrum showed new signals at approximately 25 ppm for the new methylene carbons of compound **20**.

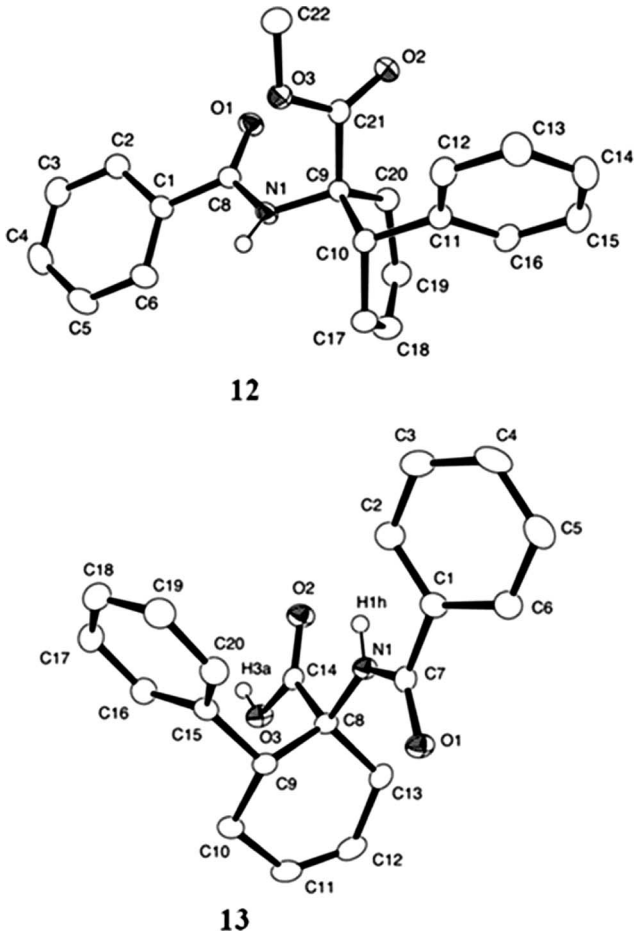
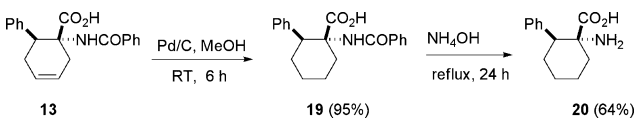


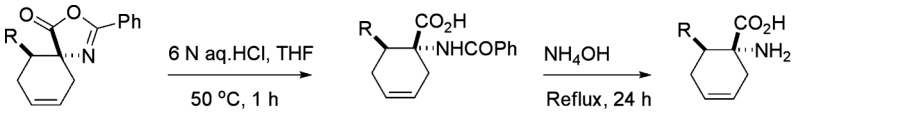
Fig. 2 X-Ray crystal structures of **12** and **13**. Thermal probability ellipsoids are drawn at the 50% probability level (hydrogen atoms are omitted for clarity).



13 **19** (95%) **20** (64%)

Scheme 4 Reduction of cyclohexene **13**.

Azlactones and amino acids have characteristic stretching modes that are suitable for study by IR spectroscopy. The IR spectra of **3a**–**j** contained weak and strong absorption bands located at *ca.* 1654, 1778, and 1816 cm^{-1}, which could be attributed to the vibrational modes of the C═C, C═N and C═O groups, respectively. These bands were not sensitive to the metathesis reactions in compounds **7**–**11**. However, hydrolysis of azlactone followed by debenzoylation led to the complete disappearance of



7: R = Ph
8: R = 3,4-$(OMe)_2C_6H_3$
9: R = furan-2-yl
10: R = piperonyl

13: R = Ph, 79%
14: R = 3,4-$(OMe)_2C_6H_3$, 80%
15: R = furan-2-yl, 69%
16: R = piperonyl, 71%

17: R = Ph, 76%
18: R = furan-2-yl, 65%

Scheme 3 Conversion of azalactones to cyclic amino acids.

Table 3 Details of crystallographic data collection for **9, 12** and **13**

	9	**12**	**13**
Formula	$C_{18}H_{15}NO_3$	$C_{22}H_{21}NO_3$	$C_{20}H_{19}NO_3$
Fw	293.31	347.40	321.36
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	Fdd2	$P2_1/c$	$C2/c$
a/Å	18.004(3)	10.6098(13)	29.149(6)
b/Å	39.249(6)	18.036(2)	7.5081(15)
c/Å	8.1408(11)	9.5122(12)	15.387(3)
α (°)	90	90	90
β (°)	90	98.7510(10)	107.300(2)
γ (°)	90	90	90
V/nm^3	5.7526(14)	1.7991(4)	3.2152(11)
Z	16	4	8
D_c/g cm^{-3}	1.355	1.283	1.328
F(000)	2464	736	1360
μ/mm^{-1}	0.093	0.085	0.089
λ/Å	0.71073	0.71073	0.71073
Range (2θ) for data collection/°	2.08–27.57	2.25–27.46	2.77–27.52
GOF	1.675	1.027	1.03
T/K	123	123	123
$R_1{}^a$ ($I > 2\sigma(I)$)	0.0391	0.0403	0.0448
$_wR_2{}^b$ ($I > 2\sigma(I)$)	0.0546	0.0985	0.0954
$R_1{}^a$ (all data)	0.0476	0.0495	0.0693
$_wR_2{}^b$ (all data)	0.0557	0.1039	0.1059

$^a R_1 = \Sigma \| F_o | - | F_c \| / \Sigma | F_o |$. $^b wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2)]^{1/2}$.

the vibrational mode of C═N in the IR spectra of compounds **7–11**, which was replaced with a new strong absorption band (compounds **17**, **18** and **20**) at *ca.* 3500 cm^{-1}, which is characteristic of the NH_2 group, whereas ν(C═O) is shifted from *ca.* 1816 to 1725 cm^{-1}.

Conclusion

We have developed a procedure for the bis-allylation of activated azlactones *via* the three-component assembling reaction between arylidene azlactones, trifluoroborate and allyl acetate in the presence of palladium catalysts. In combination with our previously reported methodologies on the activated olefins, this methodology provides a novel process for the 1,2-bisfunctionalization of activated C═C bonds. This method allows an efficient synthesis of various 1,7-diene derivatives in good to excellent yields. The present catalytic reaction proceeds with various substituted azlactones. Metathesis cyclization of the resulting bis-allylated azlacones yielded the corresponding 3-oxa-1-aza-spiro[4.5]deca-1,7-dienes which could be either hydrolysed to the corresponding cyclohexenyl α-amino acids or reduced to the corresponding cyclohexyl α-amino acids.

Experimental section

Materials and methods

Most chemicals and solvents were of analytical grade and used without further purification. Aldehydes and Grubbs' catalyst were commercially available. Starting materials **1, 2a–h** and **2i–j** were prepared as described in the literature.[22,47,48] NMR spectra (^{1}H and ^{13}C) were measured on 400 MHz spectrometer. Chemical shifts of ^{1}H NMR and ^{13}C NMR were expressed in parts per million (ppm, δ units), and coupling constant (J) values were expressed in units of hertz (Hz). IR (cm^{-1}) spectra were determined as KBr disc on an FTIR-8600PC spectrometer. Electron spray ionization (ESI) mass spectra were recorded on an LCMS-2010 eV spectrometer. Elemental analyses were performed by 2400 automatic elemental analyzer. All compounds gave elemental analysis within ±0.4% of the theoretical values. Analytical thin layer chromatography (TLC) was performed on glass plates of silica gel 60 GF_{254}. Visualization was accompanied by UV light (254 nm), I_2 or $KMnO_4$. Melting points (mp) were determined on ATM-01 melting point apparatus. Preparative TLC was carried out using 0.75 mm layers of silica gel 60 GF_{254} made from water slurries on glass plates of dimensions 20 × 20 cm^2, followed by drying in air at 100 °C.

General procedure of amphiphilic bis-allylation of azlactone 2

To a solution of azlactone **2** (0.65 mmol), allyltrifluoroborate (145 mg, 0.98 mmol), and $Pd(dba)_3{\cdot}CHCl_3$ (35 mg, 0.033 mmol) in THF (10 ml) was added allyl acetate (2.1 ml, 1.96 mmol) and tricyclohexylphosphine (18 mg, 0.066 mmol) under nitrogen. The reaction mixture was heated with stirring at 70 °C for 24–48 h (TLC). The reaction was quenched with water, and the reaction mixture was extracted with ether, dried over anhydrous magnesium sulphate, and concentrated. Purification by preparative TLC with n-hexane/ethylacetate (9 : 1) as eluent gave the major diastereomer of bis-allylated product as a yellow oil.

Allyl-2-phenyl-4-(1-phenyl-but-3-enyl)-4*H*-oxazol-5-one (3a). Yield (97 mg, 45%); yellow oil; R_f 0.37 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 2H, J = 7.2 Hz), 7. 57-7.28 (m, 8H), 5.45 (m, 2H), 5.02 (dd, 2H, J = 8 Hz, J = 3.5 Hz), 4.83 (dd, 2H, J = 8.0 Hz, J = 3.5 Hz), 3.18 (dd, 1H, J = 4.0 Hz, J = 4.0 Hz), 2.43 (m, 2H), 2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 160.2, 138.7, 135.2, 132.7, 130.5, 129.7, 128.8, 128.3, 128.0, 127.4, 125.8, 120.7, 117.1, 76.7, 52.1, 40.7, 36.2; IR (KBr disc) 3062, 2931, 1816, 1778, 1654, 972, 883, 702 cm^{-1}; MS, m/z

(ESI) 332.41 [100, M + 1]$^+$; Anal. Calc. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23%. Found: C, 79.73; H, 6.32; N, 4.18%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ 7.98 (d, 2H, J = 7.00 Hz), 7.55-7.13 (m, 8H), 5.61 (m, 2H), 5.14 (dd, 2H, J = 8 Hz, J = 3.5 Hz), 4.95 (t, 2H, J = 7.5 Hz), 3.17 (dd, 1H, J = 4.0 Hz, J = 4.0 Hz), 2.67 (m, 2H), 2.51 (m, 2H).

4-Allyl-4-[1-(4-methoxy-phenyl)-but-3-enyl]-2-phenyl-4*H*-oxazol-5-one (3b). Yield (136 mg, 58%); yellow oil; R_f 0.53 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (d, 2H, J = 8.2 Hz), 7.55-7.43 (m, 3H), 7.38 (m, 2H), 7.23 (m, 2H), 5.49 (m, 2H), 5.16 (t, 2H, J = 10.5 Hz), 4.78 (t, 2H, J = 10.3 Hz), 3.75 (s, 3H), 3.23 (m, 1H), 2.43 (m, 2H), 2.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.0, 162.3, 149.2, 147.7, 137.8, 136.6, 133.6, 129.4, 128.3, 128.3, 127.4, 125.6, 121.7, 115.0, 76.9, 55.8, 53.7, 39.4, 37.2; IR (KBr disc) 3065, 2935, 1808, 1774, 1655, 976, 885, 705 cm^{-1}; MS, m/z (ESI) 362.43 [100, M + 1]$^+$; Anal. Calc. for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88%. found: C, 76.32; H, 6.37; N, 3.79%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 7.90 (d, 2H, J = 8.0 Hz), 7.41-7.35 (m, 3H), 7.36 (m, 2H), 7.22 (m, 2H), 5.54 (m, 2H), 5.23 (t, 2H, J = 10.5 Hz), 4.71 (t, 2H, J = 10.3 Hz), 3.75 (s, 3H), 3.29 (m, 1H), 2.73 (m, 2H), 2.52 (m, 2H).

4-Allyl-4-[1-(3,4-dimethoxy-phenyl)-but-3-enyl]-2-phenyl-4*H*-oxazol-5-one (3c). Yield (170 mg, 67%); yellow oil; R_f 0.43 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (dd, 2H, J = 1.5 Hz, J = 1.5 Hz), 7.93 (d, 1H, J = 6.5 Hz), 7.57-7.49 (m, 3H), 6.84 (d, 1H, J = 8.0 Hz), 6.70 (m, 1H), 5.51 (m, 2H), 5.02 (t, 2H, J = 10.0 Hz), 4.86 (t, 2H, J = 10.0 Hz), 3.92 (s, 3H), 3.86 (s, 3H), 3.15 (m, 1H), 2.41 (m, 2H), 2.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.3, 166.2, 149.2, 147.7, 137.6, 136.8, 133.1, 129.7, 128.8, 128.3, 127.4, 125.8, 121.6, 115.2, 77.0, 55.4, 55.2, 53.7, 39.5, 37.9; IR (KBr disc) 3058, 2936, 1812, 1772, 1655, 970, 882, 742 cm^{-1}; MS, m/z (ESI) 392.46 [100, M + 1]$^+$; Anal. Calc. for $C_{24}H_{23}NO_4$: C, 73.64; H, 6.44; N, 3.58%. found: C, 73.59; H, 6.39; N, 3.47%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 7.93 (d, 2H, J = 4 Hz), 7.90 (d, 1H, J = 6.5 Hz), 7.54-7.45 (m, 3H), 6.83 (d, 1H, J = 8.0 Hz), 6.68 (m, 1H), 5.71 (m, 2H), 5.14 (t, 2H, J = 10.0 Hz), 4.79 (t, 2H, J = 10.0 Hz), 3.92 (s, 3H), 3.85 (s, 3H), 3.28 (m, 1H), 2.77 (m, 2H), 2.46 (m, 2H).

4-Allyl-4-[1-(4-dimethylamino-phenyl)-but-3-enyl]-2-phenyl-4*H*-oxazol-5-one (3d). Yield (114 mg, 47%); yellow oil; R_f 0.6 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (d, 2H, J = 3.5 Hz), 7.91 (d, 1H, J = 4.0 Hz), 7.73-7.40 (m, 5H), 5.47 (m, 2H), 4.99 (t, 2H, J = 7.5 Hz), 4.83 (t, 2H, J = 7.5 Hz), 3.17 (m, 1H), 2.99 (s, 3H), 2.83 (s, 3H), 2.42 (m, 2H), 2.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.2, 168.3, 146.8, 137.6, 135.8, 131.5, 130.0, 129.6, 128.4, 127.4, 114.8, 115.7, 78.6, 40.5, 40.1, 35.8; IR (KBr disc) 3060, 2934, 1815, 1775, 1656, 987, 880, 725 cm^{-1}; MS, m/z (ESI) 375.48 [100, M + 1]$^+$; Anal. Calc. for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00; N, 7.48%. found: C, 76.92; H, 6.97; N, 7.43%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 7.93 (d, 2H, J = 3.5 Hz), 7.90 (d, 1H, J = 4.0 Hz), 7.70-7.42 (m, 5H), 5.82 (m, 2H), 4.93 (t, 2H, J = 7.5 Hz), 4.80 (t, 2H, J = 7.5 Hz), 3.25 (m, 1H), 3.00 (s, 3H), 2.82 (s, 3H), 2.53 (m, 2H), 2.31 (m, 2H).

4-Allyl-4-[1-(4-nitro-phenyl)-but-3-enyl]-2-phenyl-4*H*-oxazol-5-one (3e). Yield (120 mg, 49%); yellow oil; R_f 0.42 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, 2H, J = 8.0 Hz), 8.04 (d, 2H, J = 8.0 Hz), 7.66-7.51 (m, 5H), 5.47 (m, 2H), 5.06 (dd, 2H, J = 9.0 Hz, J = 8.5 Hz), 4.86 (dd, 2H, J = 10.4 Hz, J = 9.6 Hz), 3.32 (dd, 1H, J = 6.0 Hz, J = 4.8 Hz), 2.45 (m, 2H), 2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.4, 160.7, 147.3, 146.5, 134.0, 133.0, 130.6, 129.7, 128.8, 128.0, 125.4, 123.5, 121.2, 118.0, 76.7, 51.5, 40.6, 36.0; IR (KBr disc) 3061, 2939, 1820, 1771, 1652, 976, 885, 741 cm^{-1}. MS, m/z (ESI) 454 [100, M + 2K]$^+$; Anal. Calc. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44%. found: C, 70.17; H, 5.33; N, 7.40%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 8.13 (d, 2H, J = 8.0 Hz), 8.07 (d, 2H, J = 8.0 Hz), 7.66-7.51 (m, 5H), 5.61 (m, 2H), 5.14 (dd, 2H, J = 9.0 Hz, J = 8.5 Hz), 4.84 (dd, 2H, J = 10.4 Hz, J = 9.6 Hz), 3.74 (dd, 1H, J = 6.0 Hz, J = 4.8 Hz), 2.84 (m, 2H), 2.61 (m, 2H).

4-Allyl-4-(1-(furan-2-yl)but-3-enyl)-2-phenyloxazol-5(4*H*)-one (3f). Yield (152 mg, 73%); yellow oil; R_f 0.77 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, 2H, J_{CH} = 10.0 Hz), 7.58-7.47 (m, 3H.), 7.35 (d, 1 H, J = 8.0 Hz), 6.28 (d, 2H, J = 8.8 Hz) 5.57 (m, 2H), 5.12 (m, 2H), 4.85 (t, 2H, J = 10.0 Hz), 3.29 (m, 1H), 2.50 (m, 3H), 2.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.4, 169.1, 157.7, 141.9, 137.6, 135.5, 131.4, 128.4, 115.7, 111.1, 105.7, 78.3, 43.5, 37.8, 29.6; IR (KBr) 3067, 2933, 1814, 1774, 1655, 973, 885, 719 cm^{-1}; MS, m/z (ESI) 321 [75, M]$^+$; Anal. Calc. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36%. found: C, 74.62; H, 5.87; N, 4.27%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 7.96 (d, 2H, J_{CH} = 10.0 Hz), 7.56-7.48 (m, 3H.), 7.31 (d, 1 H, J = 8.0 Hz), 6.17 (d, 2H, J = 8.8 Hz) 5.73 (m, 2H), 5.07 (m, 2H), 4.81 (t, 2H, J = 10.0 Hz), 3.31 (m, 1H), 262 (m, 3H), 2.41 (m, 1H).

4-Allyl-4-(1-benzo[1,3]dioxol-5-yl-but-3-enyl)-2-phenyl-4*H*-oxazol-5-one (3g). Yield (182 mg, 75%); yellow oil; R_f 0.35 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (d, 2H, J = 8.0 Hz), 7.57-7.44 (m, 3H), 6.81-6.61 (m, 3H), 5.94 (s, 2H), 5.49 (m, 2H), 5.02 (m, 2H), 4.85 (m, 2H), 3.09 (m, 1H), 2.39 (m, 2H), 2.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.7, 169.0, 148.5, 146.1, 136.8, 136.0, 132.7, 129.5, 128.7, 128.2, 121.6, 115.7, 113.6, 102.4, 78.6, 42.6, 42.3, 32.0; IR (KBr) 3066, 2932, 1815, 1775, 1656, 976, 885, 723 cm^{-1}; MS, m/z (ESI) 375.42 [100, M + 1]$^+$. Anal. Calc. for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73%. found: C, 73.53; H, 5.59; N, 3.71%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 7.91 (d, 2H, J = 8.0 Hz), 7.56-7.45 (m, 3H), 6.73-6.60 (m, 3H), 5.82 (s, 2H), 5.67 (m, 2H), 5.00 (m, 2H), 4.81 (m, 2H), 3.15 (m, 1H), 2.84 (m, 2H), 2.65 (m, 2H).

4-Allyl-2-phenyl-4-(1-(pyridin-4-yl)but-3-enyl)oxazol-5(4*H*)-one (3h). Yield (133 mg, 62%); yellow oil; R_f 0.45 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75 (d, 2H, J = 8.5 Hz), 8.25 (d, 2H, J = 8.5 Hz), 8.0 (d, 2H, J = 8.5 Hz), 7.72 (m, 1H), 7.51 (m, 2H), 5.65 (m, 2H), 4.95 (m, 2H), 4.81 (m, 2H), 3.19 (m, 1H), 2.49, 2.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.2, 160.1, 154.0, 149.1, 139.0, 135.0, 129.6, 128.4, 126.3, 120.9, 117.1, 76.8, 52.1, 40.7, 36.2; IR (KBr disc) 3065, 2932, 1817, 1771, 1653, 975, 886, 722 cm^{-1}; MS, m/z (ESI) 333.40 [100, M + 1]$^+$; Anal. Calc. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43%. found: C, 75.84; H, 6.03; N, 8.40%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 8.73 (d, 2H, J = 8.5 Hz), 8.25 (d, 2H, J = 8.5 Hz), 8.1 (d, 2H, J = 8.5 Hz), 7.68 (m, 1H), 7.53 (m, 2H), 5.74

(m, 2H), 5.06 (m, 2H), 4.92 (m, 2H), 3.27 (m, 1H), 2.64, 2.45 (m, 4H).

(*E*/*Z*)-4-allyl-2-phenyl-4-(1-phenylhexa-1,5-dien-3-yl)oxazol-5(4*H*)-one (3i). Yield (74 mg, 32%); yellow oil; R_f 0.5 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, 2H, J = 7.0 Hz), 7.61-7.21 (m, 8H), 6.55 (m, 1H), 6.21 (m, 1H), 5.63 (m, 2H), 5.12 (m, 4H), 3.31 (m, 1H), 2.75 (m, 2H), 2.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 179.8, 160.4, 136.7, 135.2, 134.4, 132.7, 130.5, 128.8, 128.5, 128.5, 128.0, 127.6, 127.3, 126.5, 126.4, 125.8, 120.7, 117.0, 76.5, 50.0, 40.7, 35.0; IR (KBr disc) 3065, 2937, 1815, 1778, 1659, 972, 886, 735 cm^{-1}; MS, m/z (ESI) 356 [100, M - 1]$^-$; Anal. Calc. for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92%. found: C, 80.59; H, 6.47; N, 3.87%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 8.00 (d, 2H, J = 7.0 Hz), 7.60-7.23 (m, 8H), 6.73 (m, 1H), 6.30 (m, 1H), 5.71 (m, 2H), 5.19 (m, 4H), 3.43 (m, 1H), 2.83 (m, 2H), 2.64 (m, 2H).

4-Allyl-4-(1-cyclohexylbut-3-enyl)-2-phenyloxazol-5(4H)-one (3j). Yield (138 mg, 63%); yellow oil; R_f 0.6 (n-hexane/AcOEt = 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.04 (m, 2H), 7.64-7.41 (m, 3H), 5.53 (m, 2H), 5.02 (m, 2H), 4.86 (m, 2H), 3.26 (m, 1H), 2.97 (t, 1H, J = 10.0 Hz), 2.62, 2.38 (m, 4H), 2.23, 1.95 (m, 3H), 1.71-1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.5, 167.2, 137.9, 136.1, 131.3, 128.4, 115.8, 76.5, 41.5, 33.2, 31.7, 29.4, 28.4, 28.3, 26.8; IR (KBr disc) 3062, 2939, 1822, 1779, 1656, 975, 887, 741 cm^{-1}; MS, m/z (ESI) 337 [100, M]$^+$; Anal. Calc. for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15%. found: C, 78.27; H, 8.03; N, 4.11%. ^{1}H NMR (400 MHz, $CDCl_3$) of the minor diastereomer: δ = 7.87 (m, 2H), 7.63-7.40 (m, 3H), 5.76 (m, 2H), 5.14 (m, 2H), 4.88 (m, 2H), 3.37 (m, 1H), 3.11 (t, 1H, J = 10.0 Hz), 2.83, 2.46 (m, 4H), 2.35, 2.06 (m, 3H), 1.82-1.68 (m, 4H).

General procedure for ring closing diene metathesis: synthesis of cyclohexene derivatives (7–11)

The typical procedure for the ring closing diene metathesis is as follows: precursor diene **3c, 3f, 3g**, or **3j** (1 mmol) was dissolved in freshly distilled and degassed dichloromethane (17 mL) under a nitrogen atmosphere. After stirring for 10 min at room temperature, ruthenium catalyst 1st generation (41.2 mg, 0.05 mmol) dissolved in dichloromethane (3 mL) was added by syringe. After 5–8 h of reflux at 40 °C, the reaction was complete as indicated by TLC. The solution was concentrated *via* rotavapor. TLC of the crude oil gave the corresponding cyclohexene derivatives as white solids.

2,10-Diphenyl-3-oxa-1-aza-spiro[4.5]deca-1,7-dien-4-one (7). Yield (257 mg, 85%); white solid; R_f 0.2 (n-hexane/AcOEt = 9 : 1); mp = 140–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75 (d, 2H, J = 6.0 Hz), 7.46-7.10 (m, 8H), 6.04 (bs, 1H), 5.79 (bs, 1H), 3.45 (t, 1H, J = 6.6 Hz), 3.08 (t, 1H, J = 15.0 Hz), 2.90 (d, 1H, J = 18.0 Hz), 2.45 (t, 2H, J = 18.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0, 161.0, 138.4, 136.4, 131.6, 128.6, 126.7, 68.5, 39.0, 34.2, 27.6; IR (KBr disc) 3065, 2935, 1825, 1775, 1658, 1045, 887, 742 cm^{-1}; MS, m/z (ESI) 304 [100, M + 1]$^+$. Anal. Calc. for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62%. found: C, 79.11; H, 5.58; N, 4.57%.

10-(3,4-Dimethoxy-phenyl)-2-phenyl-3-oxa-1-aza-spiro[4.5]-deca-1,7-dien-4-one (8). Yield (315 mg, 87%); white solid; R_f 0.15 (n-hexane/AcOEt = 9 : 1); mp = 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (t, 2H, J = 6.5 Hz), 7.47-7.34 (m, 4H), 6.79-6.69 (m, 2H), 6.05 (m, 1H), 5.68 (m, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.40 (dd, 1H, J = 6.0, 6.5 Hz), 3.05 (t, 1H, J = 12.0 Hz), 2.85 (m, 1H), 2.43 (t, 2H, J = 12.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.0, 163.2, 147.6, 146.0, 136.4, 132.0, 128.6, 126.3, 115.8, 68.2, 54.5, 40.0, 33.8, 27.4; IR (KBr disc) 3059, 2928, 1810, 1775, 1652, 1025, 887, 738 cm^{-1}; MS, m/z (ESI) 364 [100, M + 1]$^+$; Anal. Calc. for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85%. found: C, 72.63; H, 5.77; N, 3.81%.

10-Furan-2-yl-2-phenyl-3-oxa-1-aza-spiro[4.5]deca-1,7-dien-4-one (9). Yield (269 mg, 92%); white solid; R_f 0.25 (n-hexane/AcOEt = 9 : 1); mp = 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (d, 2H, J = 8 Hz), 7.52-7.49 (m, 1H), 7.43-7.40 (m, 2H), 7.18 (s, 1H), 6.15 (dd, 2H, J = 8.0, 6.5 Hz), 5.96 (m, 1H), 5.73 (m, 1H), 3.55 (t, 1H, J = 10.0 Hz), 2.95 (t, 1H, J = 12.0 Hz), 2.78 (d, 1H, J = 12.5 Hz), 2.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.2, 161.5, 153.3, 141.7, 132.6, 128.6, 127.8, 127.0, 125.7, 121.2, 110.0, 106.0, 69.4, 40.0, 33.7, 27.3; IR (KBr disc) 3057, 2932, 1821, 1775, 1656, 975, 889, 729 cm^{-1}; MS, m/z (ESI) 295 [100, M + 2H]$^+$; Anal. Calc. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78%. found: C, 73.68; H, 5.11; N, 4.75%.

10-Benzo[1,3]dioxol-5-yl-2-phenyl-3-oxa-1-aza-spiro[4.5]deca-1,7-dien-4-one (10). Yield (263 mg, 76%); white solid; R_f 0.3 (n-hexane/AcOEt = 9 : 1); mp = 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (m, 2H), 7.46-7.34 (m, 4H), 6.72-6.53 (m, 3H), 6.02 (m, 1H), 5.87 (m, 2H), 5.72 (m, 1H), 3.37 (q, 1H, J = 8.0 Hz), 2.96 (t, 1H, J = 11.5 Hz), 2.79 (d, 1H, J = 11.5 Hz), 2.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.0, 162.8, 148.0, 146.7, 136.6, 135.7, 132.6, 129.6, 128.9, 121.3, 115.7, 113.4, 101.8, 68.5, 40.6, 36.0, 28.0; IR (KBr disc) 3065, 2935, 1813, 1772, 1654, 972, 885, 725 cm^{-1}; MS, m/z (ESI) 347 [100, M]$^+$; Anal. Calc. for $C_{20}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03%. found: C, 72.58; H, 4.88; N, 3.99%

2-Phenyl-10-styryl-3-oxa-1-aza-spiro[4.5]deca-1,7-dien-4-one (11). Yield (230 mg, 70%); white solid; R_f 0.28 (n-hexane/AcOEt = 9 : 1); mp = 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (m, 2H), 7.54-7.41 (m, 3H), 7.22-7.15 (m, 5H), 6.54 (m, 1H), 5.94 (m, 2H), 5.73 (m, 1H), 2.96 (m, 1H), 2.64 (m, 2H), 2.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.8, 160.3, 136.8, 134.1, 133.7, 129.0, 128.7, 128.4, 128.1, 126.5, 126.4, 126.3, 125.8, 122.0, 121.3, 69.7, 43.5, 42.9, 34.5, 32.8, 28.5, 27.7; IR (KBr disc) 3068, 2932, 1815, 1775, 1656, 977, 889, 741 cm^{-1}; MS, m/z (ESI) 352 [100, M + Na]$^+$; Anal. Calc. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25%. found: C, 80.19; H, 5.79; N, 4.21%.

General procedure of hydrolysis of azlactones

Method A. 6 N aq. HCl (10 mL) was added to a solution of azlactone **7** (303 mg, 1 mmol) in 10 mL methanol at room temperature in a 50 mL round flask. The reaction mixture was heated at 50 °C for 1 h and the formation of the products was monitored by TLC. The solvents were evaporated under vacuum to yield a white solid of the crude product which was purified by preparative TLC using CH_2Cl_2/methanol (90 : 5) as eluent to yield colorless crystalline solids.

Method B. A solution of aq. HCl (6 M, 10 mL) was added to a solution of azlactone **7, 8, 10** or **11** (1 mmol) in 5 mL THF at room temperature in a 25 mL round flask. The reaction mixture was heated at 70 °C for 1 h and the formation of the products was monitored by TLC. The solvents were evaporated under vacuum to yield a white solid of the crude product which was purified by preparative TLC using CH_2Cl_2/methanol (90 : 5) as eluent to yield colorless solids.

Methyl(1-benzoylamino-6-phenyl-cyclohex-3-enecarboxylate) (12). Yield (134 mg, 40%); white solid; R_f 0.57 (CH_2Cl_2/MeOH = 90 : 5); mp = 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, 2H, J = 6 Hz), 7.47-7.16 (m, 8H), 6.79 (s, 1H), 5.9 (m, 1H), 5.82 (m, 1H), 3.72 (m, 1H), 3.69 (s, 3H), 3.15 (d, 1H, J = 8.5 Hz), 2.74 (d, 1H, J = 8.5 Hz), 2.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.7, 166.8, 140.2, 134.7, 131.5, 128.5, 128.4, 128.1, 127.5, 126.9, 125.3, 125.0, 61.7, 43.8, 29.9, 29.3; IR (KBr disc) 3389, 3059, 2929, 1725, 1685, 1645, 979, 882, 742 cm^{-1}; MS, m/z (ESI) 358 [100, M + Na]$^+$; Anal. Calc. for $C_{21}H_{21}NO_3$: C, 75.2; H, 6.31; N, 4.18%. found: C, 74.93; H, 6.15; N, 4.07%.

1 - Benzoylamino - 6 - phenyl - cyclohex - 3 - enecarboxylic acid (13). Yield (253 mg, 79%); white solid; R_f 0.15 (CH_2Cl_2/MeOH = 90 : 5); mp = 219–221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69 (d, 2H, J = 6.3 Hz), 7.54 (m, 2H), 7.43 (m, 2H), 7.28 (m, 6H), 6.73 (s, 1H), 6.01 (m, 1H), 5.85 (m, 1H), 4.06 (m, 1H), 2.77 (t, 2H, J = 8.0 Hz), 2.60 (t, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.5, 165.8, 141.1, 135.6, 131.9, 128.5, 128.4, 128.2, 127.5, 126.9, 125.3, 124.9, 61.7, 43.9, 30.2, 30.1; IR (KBr disc) 3391, 3057, 2931, 1727, 1681, 1642, 974, 887, 740 cm^{-1}; MS, m/z (ESI) 344 [100, M + Na]$^+$; Anal. Calc. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36%. found: C, 74.71; H, 5.93; N, 4.34%.

1-Benzoylamino-6-(3,4-dimethoxy-phenyl)-cyclohex-3-enecarboxylic acid (14). Yield (305 mg, 80%); white solid; R_f 0.42 (CH_2Cl_2/MeOH = 90 : 5); mp = 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68-7.49 (m, 4H), 6.86-6.72 (m, 4H), 6.25 (s, 1H), 5.90 (m, 1H), 5.75 (m, 1H), 3.83 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.21 (d, 1H, J = 12.0 Hz), 2.75-2.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 167.5, 147.6, 146.3, 135.2, 131.5, 127.2, 125.0, 116.6, 62.2, 54.3, 42.0, 39.5, 28.4; IR (KBr disc) 3395, 3062, 2932, 1727, 1682, 1647, 975, 886, 741 cm^{-1}; MS, m/z (ESI) 382 [100, M + 1]$^+$; Anal. Calc. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67%. found: C, 69.24; H, 6.03; N, 3.65%.

1 - Benzoylamino - 6 - furan - 2 - yl - cyclohex - 3 - enecarboxylic acid (15). Yield (214 mg, 69%); white solid; R_f 0.23 (CH_2Cl_2/MeOH = 90 : 5); mp = 201–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, 2H, J = 6.8 Hz), 7.53-7.31 (m, 4H), 7.26 (s, 1H), 6.29 (d, 2H, J = 7.2 Hz), 6.20 (s, 1H), 5.85 (m, 2H), 4.14 (bs, 1H), 2.96 (bs, 1H), 2.74-2.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.5, 162.1, 139.5, 136.4, 130.3, 128.7, 126.0, 63.9, 38.8, 33.8, 25.2; IR (KBr disc) 3397, 3056, 2935, 1725, 1686, 1645, 975, 886, 745 cm^{-1}; MS, m/z (ESI) 334 [60, M + Na]$^+$; Anal. Calc. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50%. found: C, 69.40; H, 5.48; N, 4.47%.

6-Benzo[1,3]dioxol-5-yl-1-benzoylamino-cyclohex-3-enecarboxylic acid (16). Yield (259 mg, 71%); white solid; R_f 0.26 (CH_2Cl_2/MeOH = 90 : 5); mp = 187–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63-7.25 (m, 5H.), 6.78-6.59 (m, 4H), 5.79 (m, 4H), 3.91 (bs, 1H), 3.00 (bs, 1H), 2.58 (m, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.1, 163.5 (C═N), 151.5, 148.1, 140.2, 135.7, 131.7, 128.2, 127.0, 125.5, 122.3, 115.6, 107.8, 100.6, 64.4, 44.6, 34.2, 30.3, 21.1; IR (KBr disc) 3400, 3065, 2935, 1724, 1685, 1643, 977, 885, 742 cm^{-1}; MS, m/z (ESI) 366 [100, M + 1]$^+$; Anal. Calc. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83%. found: C, 69.00; H, 5.21; N, 3.79%.

General procedures for debenzoylation of compounds 13 and 16

Ammonium hydroxide solution (3 mL) was added to a solution of **13** or **16** (1 mmol) in methanol (15 mL) at room temperature. The mixture was refluxed for 24 h. When the reaction mixture had reached room temperature, the solvents were evaporated under vacuum and the crude substance was purified by TLC using CH_2Cl_2/methanol (80 : 20) as the mobile phase to give cream colored solids.

1-Amino-6-phenyl-cyclohex-3-enecarboxylic acid (17). Yield (165 mg, 76%); white solid; R_f 0.24 (CH_2Cl_2/Methanol = 9 : 1); mp = 219–221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73, 7.63, 7.40 (m, 5H), 6.08 (m, 1H), 5.81 (m, 1H), 4.51 (bs, 2H), 4.05 (m, 1H), 2.85 (m, 2H), 2.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 178.5, 138.2, 129.2, 129.0, 127.8, 126.8, 126.0, 71.1, 46.8, 31.1, 27.5; IR (KBr disc) 3512, 3052, 2937, 1705, 1645, 979, 882, 743 cm^{-1}; MS, m/z (ESI) 240 [100, M + Na]$^+$; Anal. Calc. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45%. found: C, 71.84; H, 6.93; N, 6.41%.

1-Amino-6-furan-2-yl-cyclohex-3-enecarboxylic acid (18). Yield (134 mg, 65%); white solid; R_f 0.21 (CH_2Cl_2/Methanol = 9 : 1); mp = 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, 1H, J = 8.0 Hz), 6.08 (d, 2H, J = 8.2 Hz), 5.95 (m, 1H), 5.73 (m, 1H), 4.68 (bs, 2H), 3.38 (d, 1H, J = 9.5 Hz), 2.98-2.77 (m, 2H), 2.41-2.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.6, 139.6, 136.5, 63.9, 38.8, 33.8, 25.2; IR (KBr disc) 3507, 3058, 2931, 1697, 1641, 976, 884, 742 cm^{-1}; MS, m/z (ESI) 230 [97, M + Na]$^+$; Anal. Calc. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76%. found: C, 63.61; H, 6.27; N, 6.71%.

Synthesis of 1-benzamido-2-phenylcyclohexanecarboxylic acid (19)

To a mixture of **13** (0.16 g, 0.5 mmol) and Pd/C (0.058 g) in dry MeOH (10 mL) solution was added one drop of AcOH under hydrogen atmosphere, and the reaction mixture was stirred at room temperature for 6 h. The palladium catalyst was removed by filtration through Celite, and the solvent was evaporated. The white solid was washed with CH_2Cl_2 to afford **19**. Yield (153 mg, 95%); mp = 208–210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.69-7.40 (m, 5H), 7.16 (m, 5H), 3.85 (d, 1H, J = 9.2 Hz), 2.75 (q, 1H, J = 8.0 Hz), 2.46 (q, 1H, J = 8.0 Hz), 2.10 (t, 2H, J = 14.0 Hz), 1.93 (d, 1H, J = 12.0 Hz), 1.78 (t, 2H, J = 12.0 Hz), 1.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.5, 166.1, 145.1, 134.0, 133.2, 127.0, 126.9, 126.4, 125.7, 62.0, 45.5, 29.3, 24.9, 20.5; IR (KBr disc) 3393, 3059, 2932, 1725, 1682, 975, 885, 741 cm^{-1}; MS, m/z (ESI) 346 [100, M + Na]$^+$; Anal. Calc. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33%. found: C, 74.24; H, 6.51; N, 4.30%.

1-Amino-2-phenyl-cyclohexanecarboxylic acid (20). This compound was prepared from **19** (323 mg, 1 mmol) and ammonium hydroxide solution (3 mL), using the debenzoylation procedure described for **13** to give **20** as a white solid.

Yield (140 mg, 64%); white solid; R_f 0.17 (CH_2Cl_2/Methanol = 9 : 1); mp = 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, 2H, J = 6.0 Hz), 7.62 (m, 3H), 4.21 (m, 1H), 3.85 (bs, 2H), 2.83 (t, 1H, J = 12.0 Hz), 2.43 (m, 1H), 2.20 (t, 2H, J = 12.0 Hz), 1.91-1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.0, 147.1, 128.0, 126.5, 126.4, 63.5, 43.0, 29.0, 25.1, 19.3; IR (KBr disc) 3503, 3062, 2933, 1706, 973, 885, 742 cm^{-1}; MS, m/z (ESI) 242 [93, M + Na]$^+$; Anal. Calc. for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39%. found: C, 71.20; H, 7.81; N, 6.37%.

Crystal structure determination of 9, 12 and 13

Colorless single crystals of **9** suitable for XRD analyses were obtained from slow evaporation of a CH_2Cl_2/hexanes solution at room temperature. However, colorless crystals of **12** and **13** were obtained by slow evaporation of methanol solutions at room temperature. Each crystal was mounted on a glass fiber, and the diffraction data of all the complexes were collected on an AXS APEX II CCD detector using graphite monochromated Mo-Kα radiation at 123 K. The crystal data and experimental details are listed in Table 3. All the structures were solved by the combination of direct methods and Fourier techniques, and all the non-hydrogen atoms were anisotropically refined by full-matrix least-squares calculations. The atomic scattering factors and anomalous dispersion terms were obtained from the International Tables for X-ray Crystallography IV.[53] Since the reflection data for the abovementioned crystals were insufficient for refining all the parameters of the hydrogen atoms, they were obtained from difference Fourier maps.

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References

1 (*a*) J. Tsuji,*Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, New York, 2002; (*b*) L. S. Hegedus, *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed. University Science Books, Sausalito, CA, 1999; (*c*) J. Montgomery and Acc, *Acc. Chem. Res.*, 2000, **33**, 467; (*d*) S. I. Ikeda, *Acc. Chem. Res.*, 2000, **33**, 511.
2 (*a*) Z. Wang, X. Lu, A. Lei and Z. Zhang, *J. Org. Chem.*, 1998, **63**, 3806; (*b*) N. Chatani, N. Amishiro and S. Murai, *J. Am. Chem. Soc.*, 1991, **113**, 7778; (*c*) S. A. Codleski, In *Comprehensive Organic Synthesis*, M. F. Semmelhack, Ed.; Pergamon Press, Oxford, 1991, **4**, 585.
3 J. P. Collman, L. S. Hegedus, J. R. Norton and R. G. Finke, In *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, 1987, 417.
4 S. A. Godleski, *Comprehensive Organic Synthesis*B. M. Trost and I. Fleming, Ed.; Pergamon Press, New York, 1991, **4**, Chapter 3.3.
5 P. J. Harrington, *Comprehensive Organometallic Chemistry II*, E. W. Abel, F. Gordon, A. Stone, G. Wilkinson and R. J. Puddephatt, ed.; Elsevier, New York, 1995, **12**, 797.
6 J.-E. Bäckvall, *Metal-catalyzed Cross Coupling Reactions*, VCH, Weinheim, 1998, 339.
7 B. M. Trost, *Acc. Chem. Res.*, 1980, **13**, 385.
8 J. Tsuji, Palladium *Reagents and Catalysis: Innovations in Organic Synthesis*, Wiley, Chichester, 1995; Chapters 3 and 4.
9 H. Nakamura, J.-G. Shim and Y. Yamamoto, *J. Am. Chem. Soc.*, 1997, **119**, 8113.
10 H. Nakamura, K. Nakamura and Y. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 4242.
11 K. Nakamura, H. Nakamura and Y. Yamamoto, *J. Org. Chem.*, 1999, **64**, 2614.
12 K. Ohno and J. Tsuji, *J. Chem. Soc. D*, 1971, 247.
13 J. Kiji, K. Yamamoto, H. Tomita and J. Furukawa, *J. Chem. Soc., Chem. Commun.*, 1974, 506.
14 K. Ohno, T. Mitsuyasu and J. Tsuji, *Tetrahedron*, 1972, **28**, 3705.
15 Y. Tamaru, *Eur. J. Org. Chem.*, 2005, **13**, 2647.
16 M. Jeganmohan, M. Shanmugasundaram and C-H. Cheng, *J. Org. Chem.*, 2004, **69**, 4053.
17 H. Nakamura, K. Aoyagi, J.-G. Shim and Y. Yamamoto, *J. Am. Chem. Soc.*, 2001, **123**, 372.
18 M. Nambo, A. Wakamiya, S. Yamaguchi, K. Itami and K. Szabó, *J. Am. Chem. Soc.*, 2009, **131**, 15112.
19 G. A. Molander and R. Figueroa, *Aldrichim. Acta*, 2005, **38**, 49.
20 S. Darses and J. P. Genet, *Chem. Rev.*, 2008, **108**, 288.
21 R. A. Batey, A. N. Thadani, D. V. Smil and A. J. Lough, *Synthesis*, 2000, 990.
22 R. A. Batey, A. N. Thadini and D. V. Smil, *Tetrahedron Lett.*, 1999, **40**, 4289.
23 K. Takenaka and T. Tsuji, *J. Heterocycl. Chem.*, 1996, **33**, 1367.
24 J. T. Konkel, J. Fan, B. Jayachandran and K. L. Kirk, *J. Fluorine Chem.*, 2002, **115**, 27.
25 F. Caveller and J. Verducci, *Tetrahedron Lett.*, 1995, **36**, 4425.
26 A. Avenoza, J. H. Pusto, C. Cativiela and J. M. Peregrina, *Tetrahedron Lett.*, 2002, **36**, 4167.
27 S. Kozima, H. Ohkawa, T. Hirano, S. Maki, H. Niwa, M. Oshashi, S. Inouye and F. I. Tsuji, *Tetrahedron Lett.*, 1998, **39**, 5239.
28 J. Penalva, R. Vuchades, A. Maquieira, S. Gee and B. D. Hammock, *Biosens. Bioelectron.*, 2000, **15**, 99.
29 K. Gottwald and D. Seeback, *Tetrahedron*, 1999, **55**, 723.
30 T. L. Ho, *Carbocycle Construction in Terpene Synthesis*, Wiley-VCH, Weinheim, 1988.
31 K. -I. Takao, R. Munakata and K. -I. Tadano, *Chem. Rev.*, 2005, **105**, 4779.
32 M. E. Jung and D. G. Ho, *Org. Lett.*, 2007, **9**, 375.
33 M. E. Krafft and T. F. N. Haxell, *J. Am. Chem. Soc.*, 2005, **127**, 10168.
34 R. H. Grubbs, S. J. Miller and G. C. Fu, *Acc. Chem. Res.*, 1995, **28**, 446.
35 H. Kim, S. D. Goble and C. Lee, *J. Am. Chem. Soc.*, 2007, **129**, 1030.
36 D. Enders, M. R. M. Huttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861.
37 Y. S. Tran and O. Kwon, *J. Am. Chem. Soc.*, 2007, **129**, 12632.
38 M. Scholl, T. M. Trnka, J. P. Morgan and R. H. Grubbs, *Tetrahedron Lett.*, 1999, **40**, 2247.
39 M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953.
40 Q. Yang, H. Alper and W.-J. Xiao, *Org. Lett.*, 2007, **9**, 769.
41 D. B. Berkowitz, J. M. McFadden and M. K. Sloss, *J. Org. Chem.*, 2000, **65**, 2907.
42 S. E. Gibson, N. Guillo and M. J. Tozer, *Tetrahedron*, 1999, **55**, 585.
43 K. N. Koch, A. Linden and H. Heimgartner, *Helv. Chim. Acta*, 2000, **83**, 233.
44 J. R. Cronin and S. Pizzarello, *Science*, 1997, **275**, 951.
45 T. Kan, Y. Kawamoto, T. Asakawa, T. Furuta and T. Fukuyama, *Org. Lett.*, 2008, **10**, 168.
46 (*a*) E. Benedetti, B. Di Blasio, V. Pavone, C. Pedone and A. Santini, *Biopolymers*, 1989, **28**, 175; (*b*) P. K. C. Paul, M. Sukumar, R. Bardi, A. M. Piazzesi, G. Valle, C. Toniolo and P. Balaram, *J. Am. Chem. Soc.*, 1986, **108**, 6363.
47 E. Erlenmeyer, *Annalen*, 1893, **275**, 1.
48 P. A. Conway, K. Devine and F. Paradisi, *Tetrahedron*, 2009, **65**, 2935.
49 H. Nakamura and K. J. Shimizu, *Tetrahedron Lett.*, 2011, **52**, 426.
50 E. Yoshikawa, K. V. Radhakrishnan and Y. Yamamoto, *Tetrahedron Lett.*, 2000, **41**, 729.
51 N. Solin, S. Narayan and K. J. Szabó, *J. Org. Chem.*, 2001, **66**, 1686.
52 M. Jeganmohan, M. Shanmugasundaram and C.-H. Cheng, *Org. Lett.*, 2003, **5**, 881.
53 J. A. Ibers, W. C. Hamilton, *International Tables for X-ray Crystallography*, Kynoch Press, Birmingham, 1974.