Transition metal-catalysed generation and application of dihydroaromatic compounds for the synthesis of dibenzo-azepine derivatives and polysubstituted benzenes

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To my family and in memory

of my brother Marco

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my girlfriend (and future wife) Francesca for all the support and help in difficult moments.

Every time you are tempted to react in the same old way,

ask if you want to be a prisoner of the past or a pioneer of the future.

Deepak Chopra

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A Introduction

Introduction

From practical, economical and environmental standpoints, transition-metal catalysed reactions are set to dominate the chemical industry in the 21st century. These reactions will have an impact on the production of fine chemicals, pharmaceuticals, agrochemicals, polymers, etc. It is not therefore surprising that the field of transition metal catalysis has been, and will remain, one of the top priorities of academic and industrial research. Transition metal catalysis continues to have a major impact in the area of carbon-carbon bond forming processes. Furthermore, carbon-carbon bond formation has the added potential of enabling the stereoselective assembly of the carbon skeleton of the target molecule rather than mere functionalisation.

1 Cycloaddition reactions

Cycloadditions, and the *Diels-Alder* reactions in particular, are only one example of the countless class of reactions which largely benefited from the spectacular advances that have been made in catalysis during the last decades. The synthetic utility of the *Diels-Alder* reaction for the synthesis of complex structures is well documented[1]. The vast majority of reports relate to thermal or *Lewis* acid[2] catalysed applications on substrates with normal and inverse electron demand. A variety of *Lewis* acids are effective catalysts, including SnCl$_4$, ZnCl$_2$, AlCl$_3$ and its derivatives such as Et$_2$AlCl. This type of reactions are governed by the principle of conservation of orbital symmetry. The orbital-symmetry rules (also called *Woodward-Hoffman* rules) apply only to concerted reactions, i.e., where two σ-bonds are formed (or broken) at about the same time. Thermal *Diels-Alder* reactions of non activated starting materials such as olefines and alkynes, are limited to few examples. Because of the harsh reaction conditions, yields are generally lower and accompanied by side products. Low-valent transition metal complexes can instead catalyse such reactions under mild conditions and in higher yields[3]. These catalysts are mostly based on iron[4], nickel[5], titanium[6], palladium[7], rhodium[8] and cobalt[9] complexes. When a transition metal catalyst is involved the reaction proceeds through a multistep mechanism within the ligand sphere of the metal and is not any more governed by the *Woodward-Hoffman* rules.

Nicolaou[10] recently reported the total synthesis of the terpenoid (–)-*Colombiasin A* (**6**). The core structure of the product (**3**) was generated by means of a selective asymmetric *Diels-Alder* reaction between the *Danishefsky*-type diene (**1**) and the quinone (**2**). After conversion of (**3**) to the precursor (**4**), thermal extrusion of SO$_2$ followed by an intramolecular *Diels-Alder* reaction completed the skeleton of the target molecule (**6**) (Scheme 1).
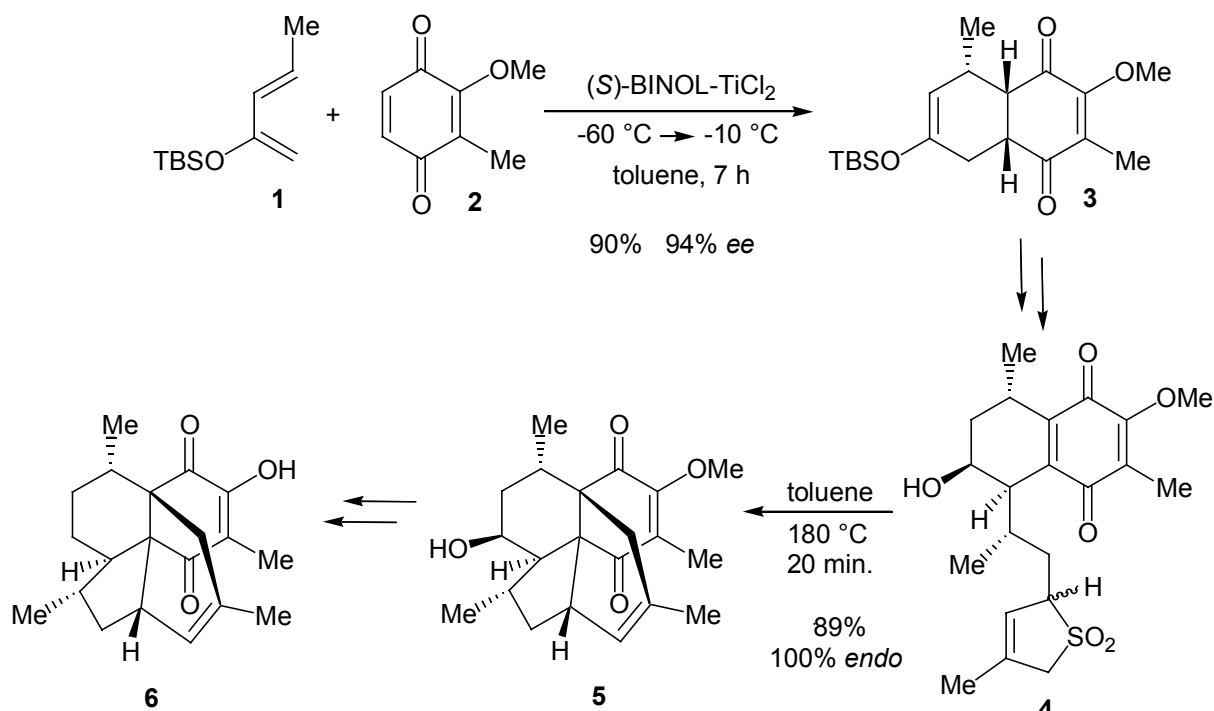
Scheme 1   Key steps in *Nicolaou* total synthesis of (−)-*Colombiasin A*

1.1   [4+2+2]-cycloadditions

A typical example of transition metal catalysed cycloaddition is the reaction between norbornadiene (**7**) and substituted butadienes[11] (**8**). This is an overall eight-electron [4+2+2] process which only occurs under metal catalysed conditions. No thermally promoted versions of this reaction are described. It results in the formation of polycyclic structures of type (**9**). *Carbonaro*[11a] first reported in 1970 the cycloaddition between norbornadiene (NBD) (**7**) and 1,3-butadiene (**8**, $R^1=R^2=H$) (Scheme 2 and Table 1) using an iron catalyst system consisting of Fe(acac)$_3$ and Et$_2$AlCl. The desired product was isolated in 25% yield (Table 1, Entry 1). Since the initial report of *Carbonaro* a growing number of transition metal catalysts for the [4+2+2]-cycloaddition of norbornadienes have been developed.
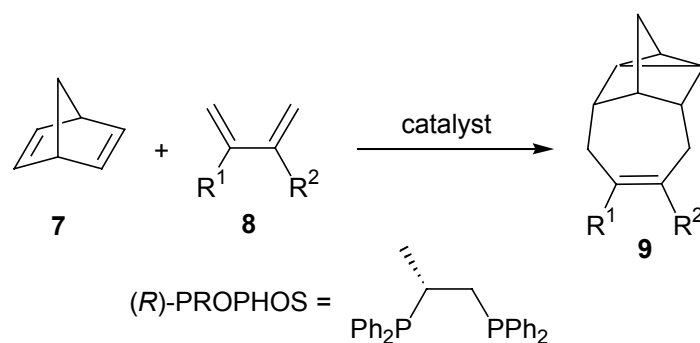
Scheme 2   Transition metal-catalysed [4+2+2]-cycloadditions

Table 1   Transition metal catalysed HDA reactions of NBD with unactivated alkenes

Entry	R^1	R^2	Catalyst	Yield
1	H	H	Fe(acac)$_3$/Et$_2$AlCl	25%[a]
2	H	H	CoCl$_2$/dppe/Et$_2$AlCl	68%[b]
3	H	H	Co(acac)$_3$/dppe/Et$_2$AlCl	89%[c]
4	H	Me	Co(acac)$_3$/dppe/Et$_2$AlCl	40%[d]
5	H	Me	Co(acac)$_2$/(R)-PROPHOS/Et$_2$AlCl	66%[e]

Conditions: [a] benzene, 80 °C; [b] toluene, 75 °C; [c] benzene, 35-50 °C; [d] benzene, 35-50 °C; [e] benzene, r.t. (72% *ee*)

Cobalt-based catalysts proved to be more effective[11b,12] and the corresponding cycloadducts were isolated in yields up to 89% (Table 1, Entry 2-5). An intramolecular cobalt-catalysed [4+2+2]-cycloaddition was also described by *Lautens*[13], but the product (**11**) was obtained only in modest yield (Scheme 3). A common feature of all catalyst systems is the reducing agent Et$_2$AlCl, which should reduce *in situ* the Co(II) or Co(III) pre-catalyst to the active species Co(0) or Co(I).
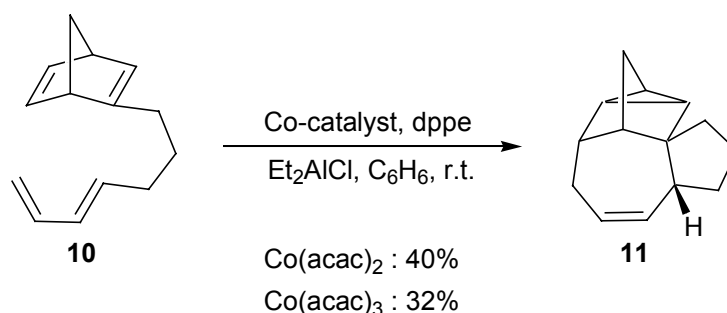
Scheme 3   *Lautens* intramolecular cobalt-catalysed cycloaddition

The additional ring which arises from the intramolecular cycloaddition may be useful for the synthesis of polycyclic compounds. *Snyder* recently reported the development of a new cobalt catalyst system for the [4+2+2] reaction of functionalised norbornadienes and butadiene[14]. The highly caged polycyclic compounds[15] of type (**12**) can be opened to yield bicyclo[4.2.1]nonanes[16] (**13**) or *perhydroazulenes*[17] (**14**), which are core structures of numerous natural products such as *Secolongifolenediol* (**15**) and *Portulal*[18] (**16**) (Scheme 4).
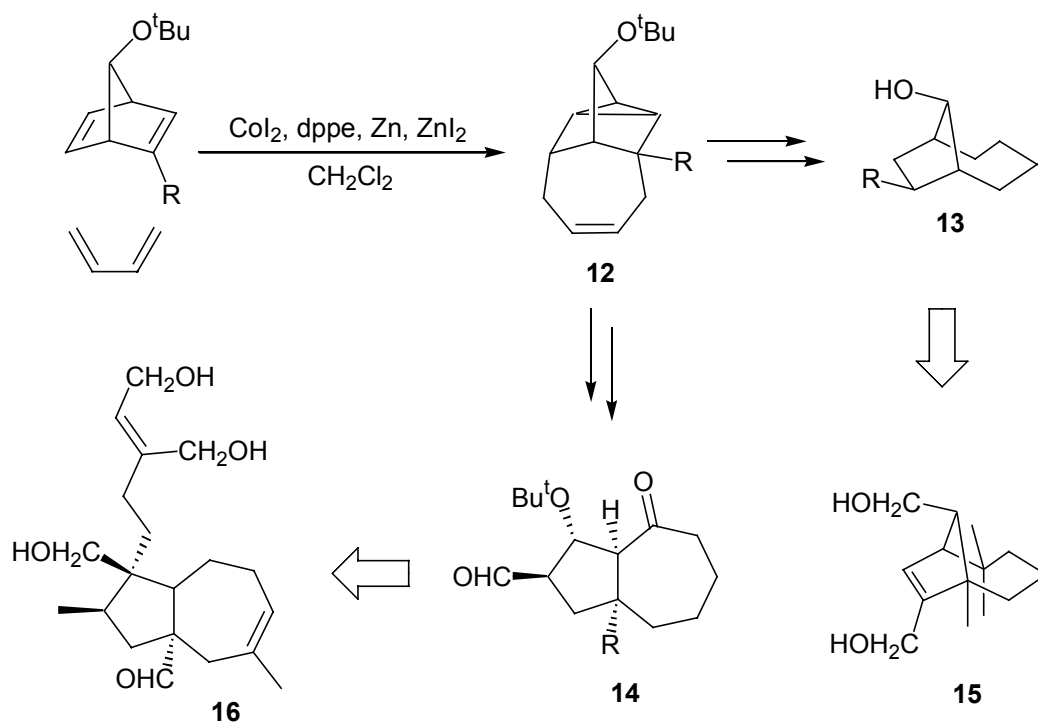
Scheme 4   Compounds of type (**13**) and (**14**) as precursors of natural products

1.2   [2+2+2]-cycloadditions

The *homo Diels-Alder* (*HDA*) of norbornadiene derivatives with alkenes and alkynes is an intriguing reaction from both mechanistic and structural point of view (Scheme 5).
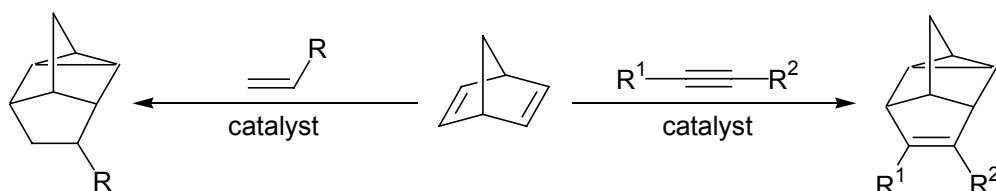
Scheme 5   *Homo Diels-Alder* reaction of NBD with alkenes and alkynes

The *homo Diels-Alder* reaction main difference to a normal *Diels-Alder* is that the diene component is not conjugated. The sp^3 carbon between the two double bonds, in addition to being responsible for the *homo* term in the reaction name, also results in cyclopropane rather than alkene formation. Because the diene component is *homo*-conjugated, the cycloaddition is formally referred to as a [2+2+2]-cycloaddition rather than a [4+2]-cycloaddition.

1.2.1 Homo Diels-Alder with alkenes

Norbornadiene reacts with activated alkenes such as methyl vinyl ketone (**18**) in the presence of a low valent nickel complexes[19]. The process is a six electron [2+2+2]-*HDA*. It affords strained polycyclic compounds of type (**19-20**) called *deltacyclanes* in excellent yields and selectivities (Scheme 6). The thermal reaction is also possible, although less efficient[20].

7 : R^1 = H
17 : R^1 = O^{t}Bu
18

19 : R^1 = H : 99%, *exo : endo* >20 :1
20 : R^1 = O^{t}Bu : 95%, 100% *exo*
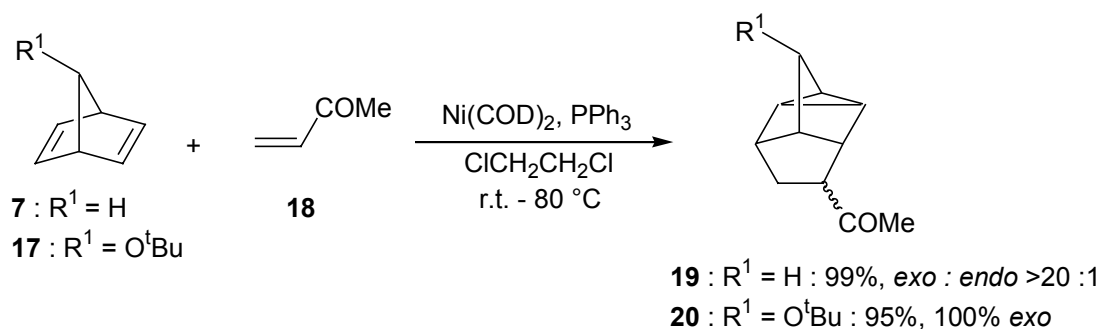
Scheme 6   Nickel-catalysed [2+2+2] cycloaddition

Deltacyclanes can be easily converted in synthetic useful intermediates such as *diquinanes* and *triquinanes*[21], which are core structures of numerous natural products (Scheme 7).

Angular *Triquinanes*

Pentalenene

Linear *Diquinanes*

Linear *Triquinanes*

Pentalenolactone E

Hirsutene
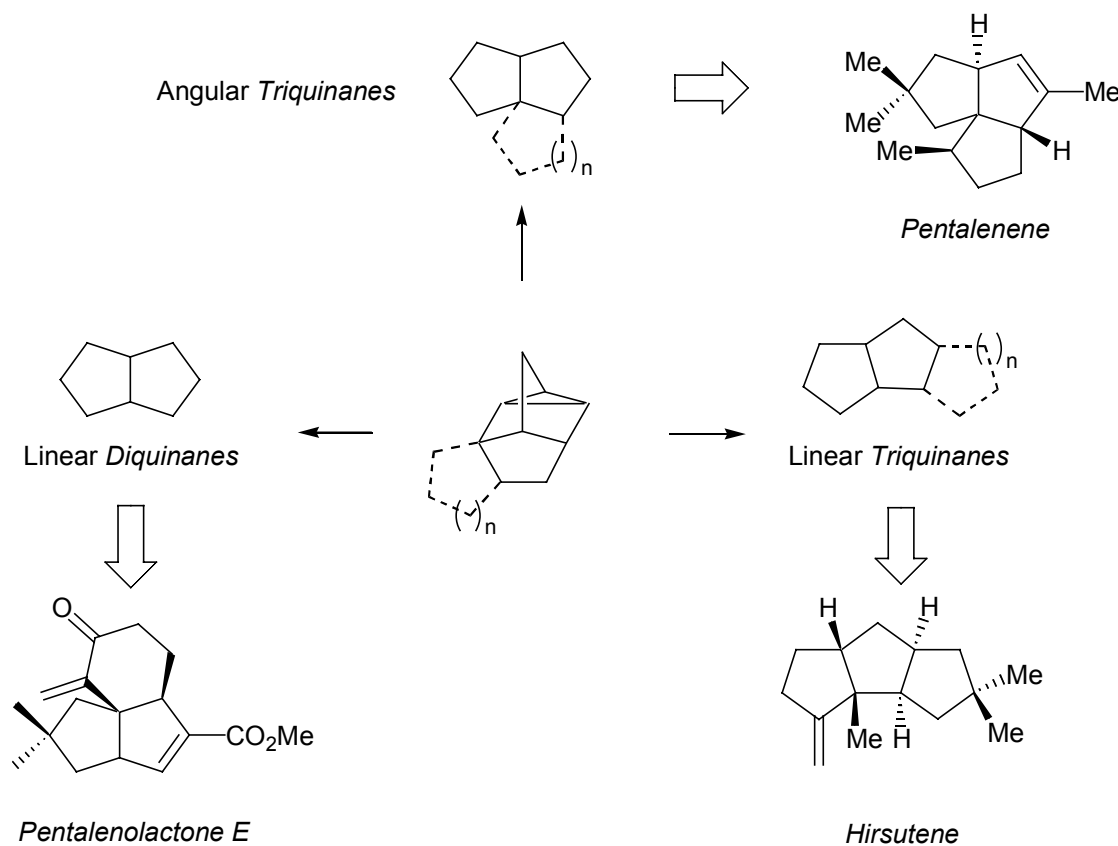
Scheme 7   Occurrence of *diquinane* and *triquinane* skeleton in natural products

As reported by *Lautens*[22], the *deltacyclane* (**20**) can be converted by means of a selective fragmentation-cyclisation sequence into the corresponding functionalised *diquinanes* (**21-22**) and *triquinanes* (**23**) (Scheme 8). These molecules are excellent starting materials for further manipulations.
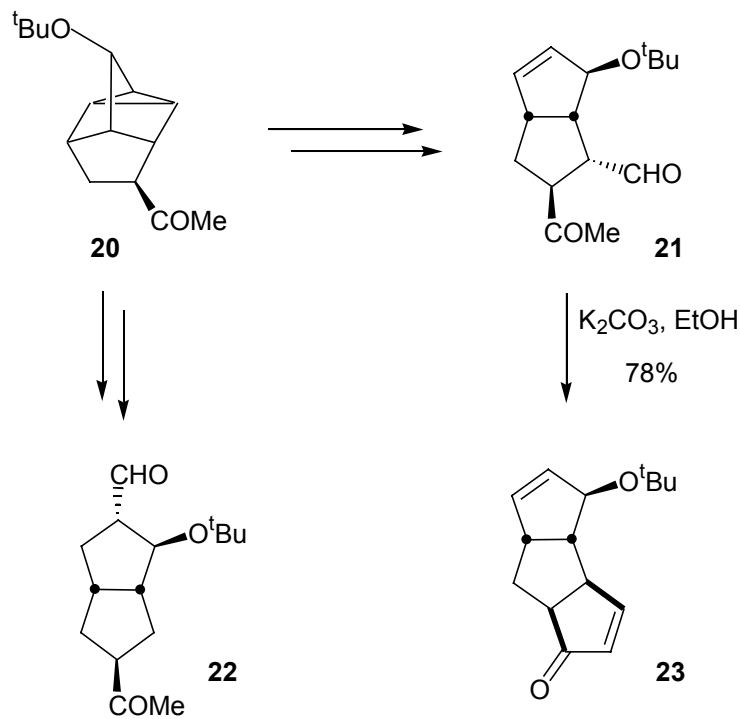
Scheme 8   A fragmentation-cyclisation approach to *diquinanes* and *triquinanes*

1.2.2   Homo Diels-Alder with alkynes

An alternative route to *deltacyclenes* is the [2+2+2]-*HDA* reaction between norbornadienes and alkynes. Unactivated alkynes are poor dienophiles in *Diels-Alder* cycloadditions[23] and thermal reactions, although possible, often results in low yields. In addition to nickel[19], low-valent cobalt[24] catalysts are active. A CoI$_2$/PPh$_3$/Zn catalyst system, developed by *Cheng*[25], afforded the expected *deltacyclene* products (**26-27**) in good to excellent yields (Scheme 9).
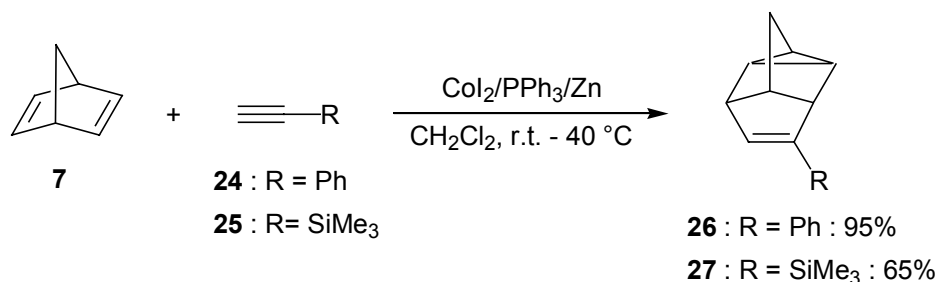
Scheme 9   *Cheng* cobalt-catalysed *HDA* reaction

The active cobalt(I) species is generated by *in situ* reduction with zinc. An intramolecular version has also been described by *Lautens*[24d] (Scheme 10).

28 : R = H
29 : R = Ph

30 : R = H : 78%
31 : R = Ph : 70%
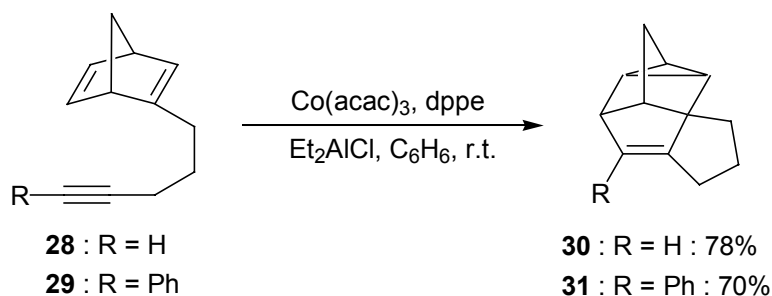
Scheme 10   Intramolecular [2+2+2] cobalt-catalysed cycloaddition

Recently *Tenaglia*[26] reported an unprecedented ruthenium(II)-catalysed *HDA* reaction of norbornadiene (**7**) and oxygen-functionalised alkynes (**32-33**) (Scheme 11).

7

32 : R^1 = R^2 = CH$_2$OH
33 : R^1 = R^2 = Et

34 : R^1 = R^2 = CH$_2$OH : 92%
35 : R^1 = R^2 = Et : 21%
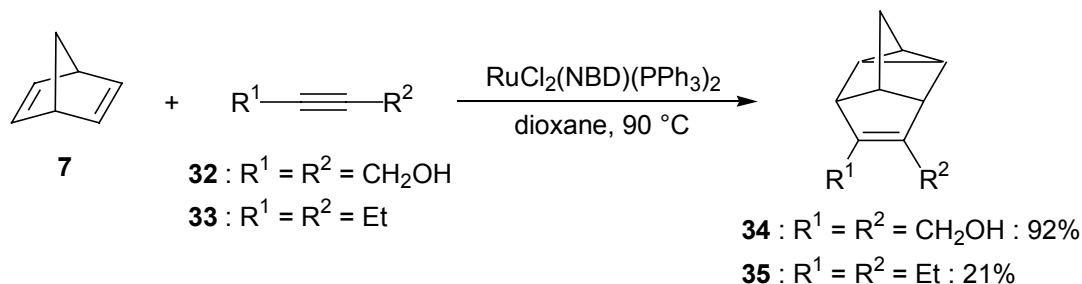
Scheme 11   *Tenaglia* cobalt-catalysed [2+2+2]-*HDA* of oxygen-functionalised alkynes

Up to date this is the first report of ruthenium-catalysed *HDA* reaction on alkynes bearing a free OH group. Interestingly, only low yields were obtained with alkynes bearing alkyl or aryl chains. Therefore, it nicely complements the activity of the already described cobalt-based catalysts and broadens the scope of the reaction considerably. It should also be noted that no co-catalysts (reducing agents or *Lewis* acids) are required.

1.3   [6+2]-cycloadditions

Thermal and photochemical higher order cycloadditions involving polyenes as enophiles often results in low yields and formation of complex mixtures[27]. Transition metal-mediated reactions are important synthetic tools for the construction of medium-sized ring compounds[28]. The same catalyst system (CoI$_2$/dppe/Zn/ZnI$_2$) developed by *Snyder* for the [4+2+2]-cycloaddition of norbornadienes was also reported by *Buono* to be active for [6+2]-cycloadditions of cycloheptatriene[29] (**36**) and cyclooctatetraene[30] (**39**) with terminal alkynes (Scheme 12 and 13).
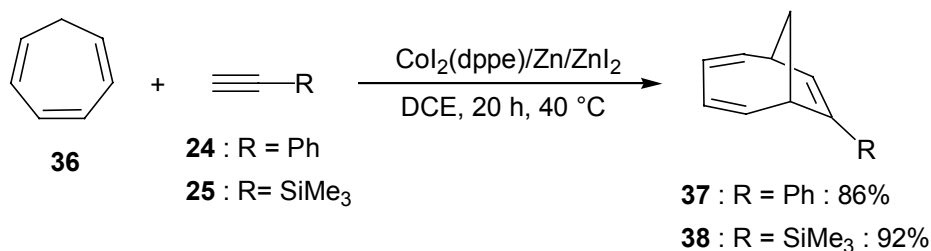
Scheme 12   Cobalt-catalysed [6+2]-cycloadditions of cycloheptatriene
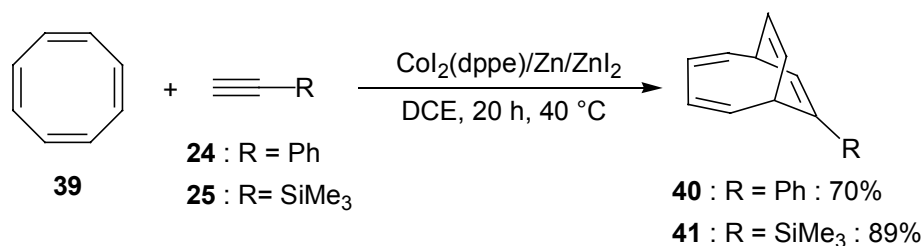
Scheme 13   Cobalt-catalysed [6+2]-cycloadditions of cyclooctatetraene

1.4   The *Hilt*-catalyst

The catalyst developed by *Hilt* is a versatile instrument for a wide range of transformations. The main advantages over similar catalyst systems are the mild reaction conditions and the relative tolerance to many functional groups. Herein a brief overview of the main reactions and the proposed mechanisms will be given.

1.4.1   Cycloaddition reactions

1.4.1.a   [2+2+2]-cycloadditions

The cobalt(I)-catalysed *HDA* reaction of terminal and internal alkynes with norbornadiene (**7**) has also been investigated by *Hilt*[31]. A catalyst system consisting of $CoBr_2(dppe)/ZnI_2/Zn$ (or Bu_4NBH_4 as alternative reducing agent) was highly effective for the synthesis of *deltacyclene* derivatives of type (**26-27**) under mild reaction conditions in excellent yields (Scheme **14**).
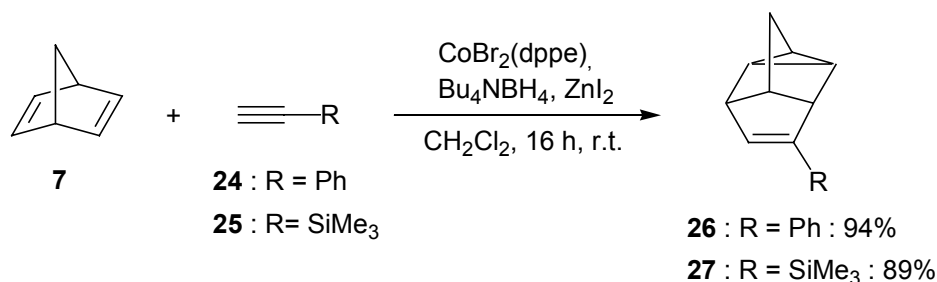
Scheme 14   Cobalt-catalysed [2+2+2]-*HDA* of terminal alkynes by *Hilt*

1.4.1.b   *[4+2]-cycloadditions*

When acyclic dienes such as 2,3-dimethyl-1,3-butadiene (**42**) and terminal or internal alkynes were used, the corresponding [4+2]-cycloaddition products[31a] were isolated in excellent yields (Scheme 15). Such a reactions were not described with the original *Cheng* or *Lautens* catalyst systems.

42

24 : R^1 = Ph, R^2 = H
25 : R^1 = SiMe$_3$, R^2 = H
33 : R^1 = R^2 = Et

43 : R^1 = Ph, R^2 = H : 84%
44 : R^1 = SiMe$_3$, R^2 = H : 82%
45 : R^1 = R^2 = Et : 98%
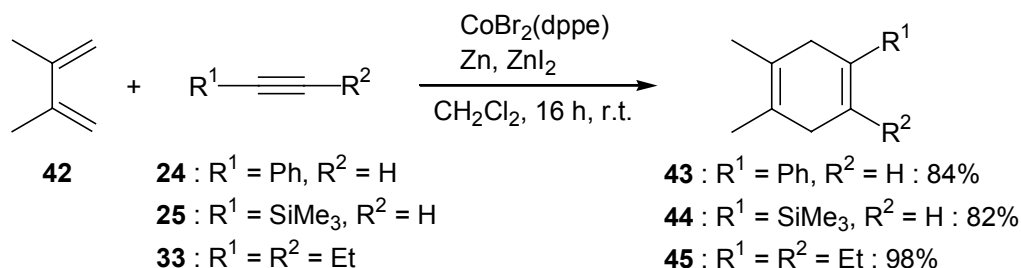
Scheme 15   Cobalt-catalysed [4+2]-cycloaddition of terminal and internal alkynes by *Hilt*

The *Hilt* catalyst also accepted boron[32] and sulfur[33] functionalised alkynes, as outlined in Scheme 16.

48

Ar = C$_6$H$_4$*p*-CO$_2$Me

85%

42

76%

49
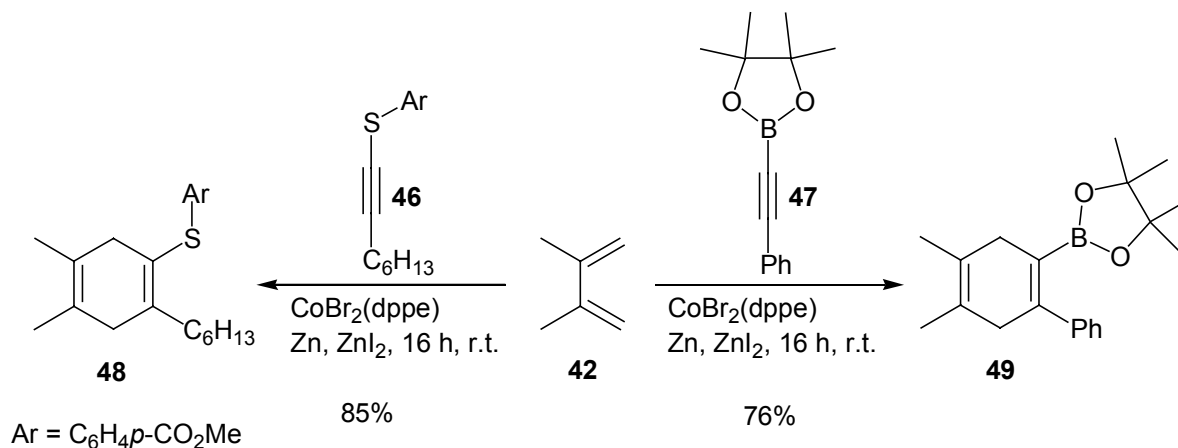
Scheme 16   Cobalt(I)-catalysed *Diels-Alder* reaction of boron and sulfur-functionalised alkynes with 2,3-dimethyl-1,3-butadiene

Oxygen-functionalysed alkynes[34] and acyclic 1,3-dienes[35] such as 2-trimethylsiloxy-1,3-butadiene (**51**) gave as well excellent yields (Scheme 17).

52

42

94%

50

51

91%

53
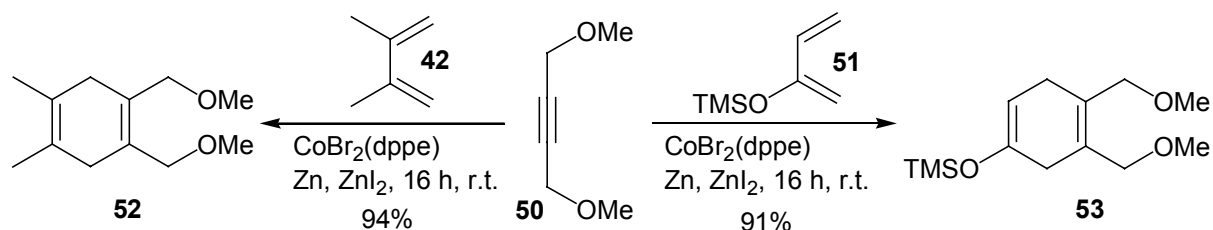
Scheme 17   Cobalt(I)-catalysed *Diels-Alder* reaction of oxygen-functionalised alkynes and 1,3-dienes

1.4.1.c   Proposed mechanism

For the cobalt-catalysed *Diels-Alder* reaction a cationic cobalt(I)-species (**56**) as the active catalyst was proposed. This low-valent cobalt-species is generated upon reduction of the catalyst precursor $CoBr_2(dppe)$ (**54**) with zinc or Bu_4NBH_4 and subsequent halide abstraction from the intermediate (**55**) by the *Lewis* acid ZnI_2 (Scheme 18).
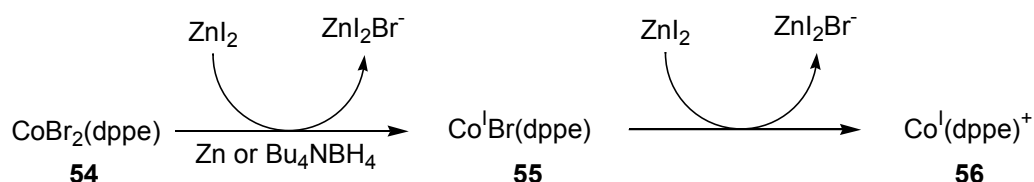
Scheme 18   Generation of the active catalyst species

The reagents then coordinate to the low-valent cobalt center (**56**). An insertion process leads to the five- and seven membered cobaltacycle (**58**) and (**59**), which are proposed to be in equilibrium *via* an allyl rearrangement. A reductive elimination from (**59**) leads to the desired dihydroaromatic compound (**60**) (Scheme 19).
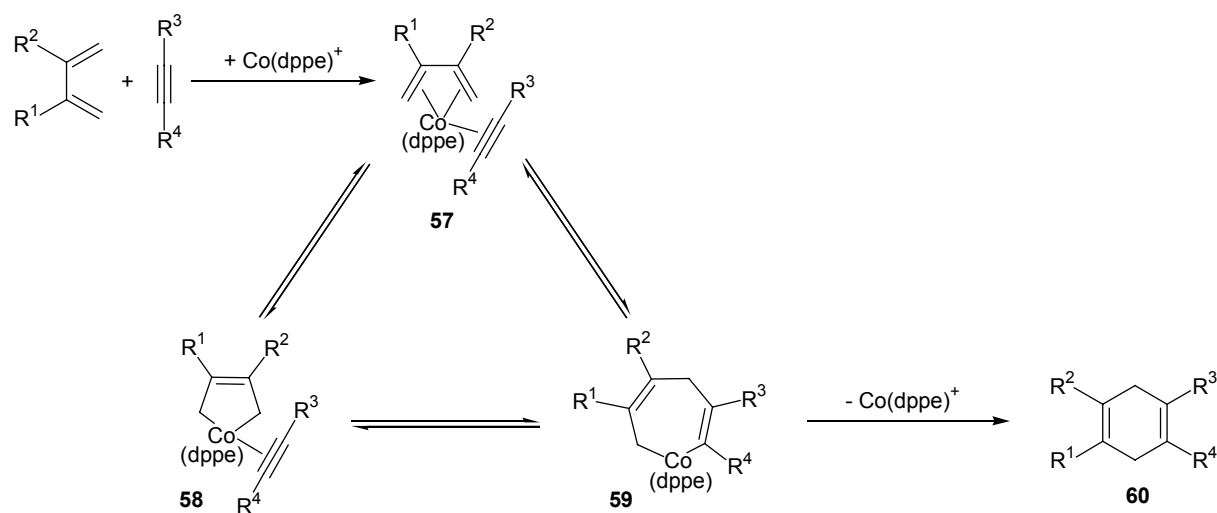
Scheme 19   Proposed mechanism for the cobalt(I)-catalysed *Diels-Alder* reaction

1.4.2 Hydrovinylation reactions

When substituted alkenes were used as dienophiles in the cobalt-catalysed reaction with acyclic 1,3-dienes, no *Diels-Alder* products could be isolated. Rather, selective 1,4-hydrovinylation occurred in excellent yields[36] (Scheme 20). The use of electron poor alkenes

led selectively to linear products of type (**62**) (Eq. 1). Branched products were instead obtained with neutral terminal alkenes such as 1-hexene (**63**) (Eq. 2).

$$\text{(1)}$$

$$\text{(2)}$$
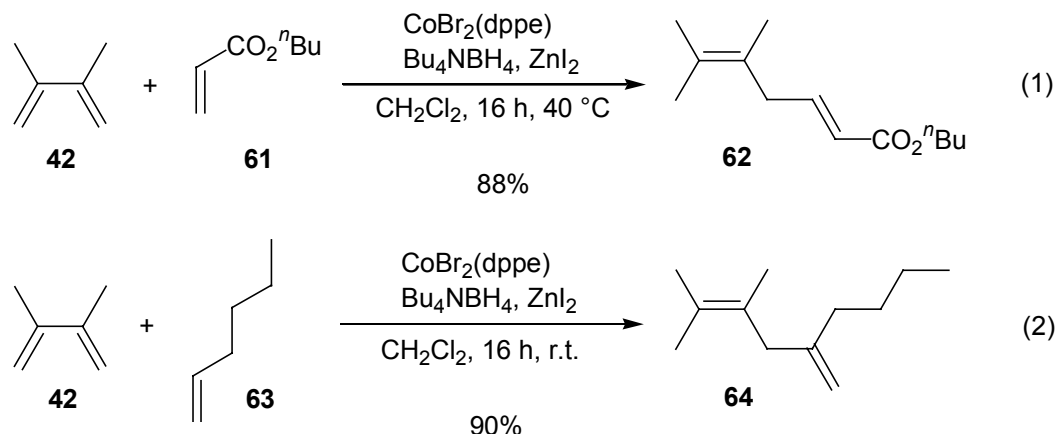
Scheme 20   Cobalt(I)-catalysed hydrovinylation reactions

1.4.2.a   *Proposed mechanism*

Following a mechanism similar to that proposed for the *Diels-Alder* reaction, from the seven member cobaltacycle (**67**) a *ß*-hydrid elimination leads to the intermediate (**68**). Subsequent reductive elimination yield the 1,4-hydrovinylation product (**69**) (Scheme 21).
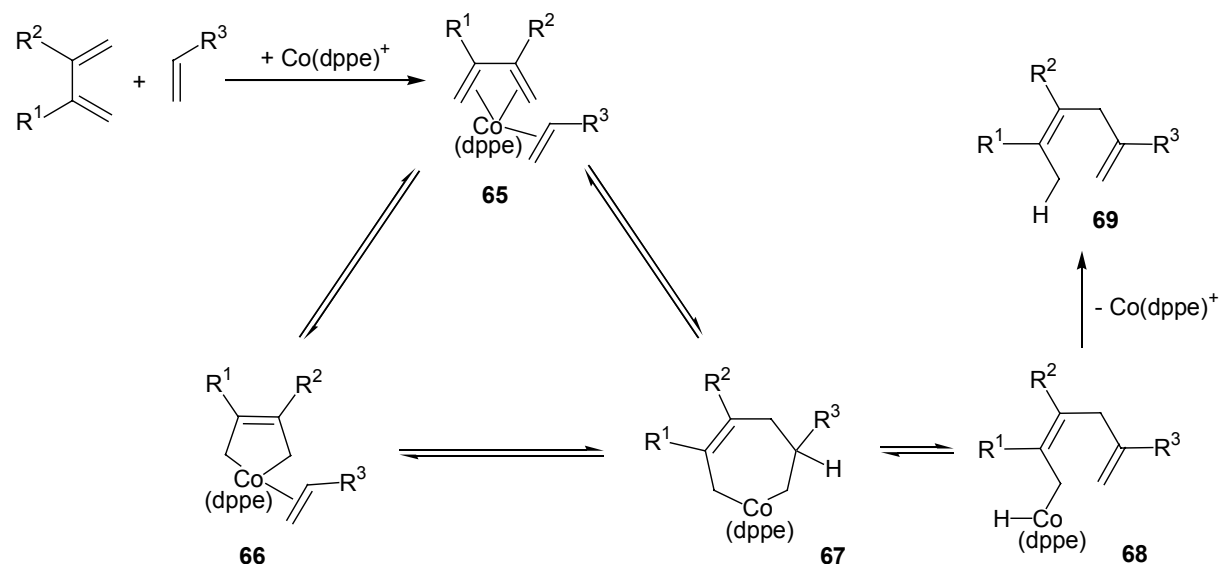
Scheme 21   Proposed mechanism for the cobalt(I)-catalysed 1,4-hydrovinylation reaction

1.4.3 *[2+2+2]-cyclotrimerisation*

Catalytic [2+2+2]-cyclotrimerisation of alkynes is valuable tool for the synthesis of polysubstituted aromatic compounds[37]. Complexes of many transition metals (i.e., Co, Rh, Ni) are effective catalysts for this process. During his earlier investigations over cobalt-

catalysed *homo Diels-Alder* reactions *Hilt* reported the formation of cyclotrimerisation side products[31a]. Further investigations led to the development of a simple $CoBr_2$(Cy-diimine) catalyst system for the regioselective cyclotrimerisation of alkynes[38] (Scheme 22).
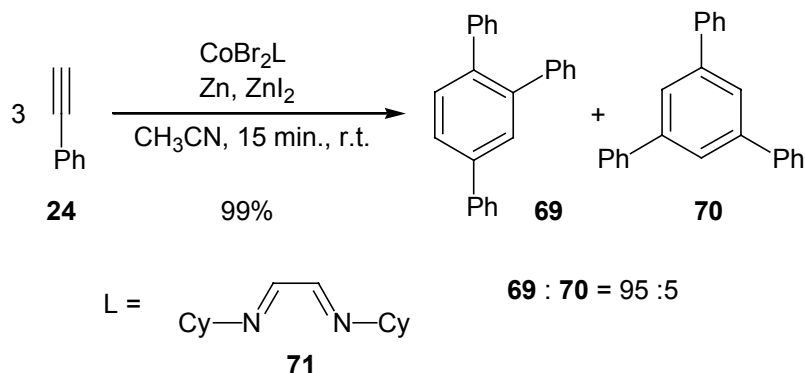
Scheme 22 Cobalt(I)-catalysed cyclotrimerisation of alkynes

Recently *Okamoto* reported a $CoCl_2 \cdot 6H_2O$ based catalyst for the intermolecular cyclotrimerisation of alkynes[39] (Scheme 23). Interestingly, simple internal alkynes such as 4-octyne were not accepted by the catalyst while the reaction proceeded smoothly with propargylic alcohols, propargylic ethers and α,β-acetylenic esters. The reaction showed also a relative tolerance to moisture and higher yields were obtained even in aqueous THF.
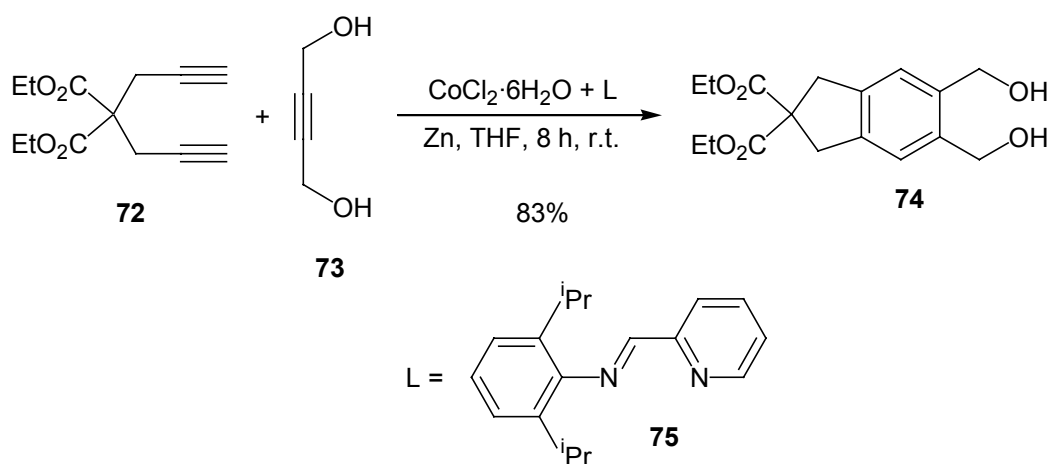
Scheme 23 *Okamoto* cobalt-catalysed cyclotrimerisation of alkynes

An intramolecular version has also been developed by *Okamoto*[40] (Scheme 24). Triynes of type (**76-77**) could be effectively converted to annulated benzenes (**79-82**) by treatment with a catalytic amount of the *N*-heterocyclic carbene (**78**), zinc powder and $CoCl_2$ or $FeCl_3$.

79: R^1 = R^2 = H : 91%   **76**: R^1 = R^2 = H   **81**: R^1 = R^2 = H : 98%
80: R^1 = H, R^2 = SiMe$_3$: 98%   **77**: R^1 = H, R^2 = SiMe$_3$ **82**: R^1 = H, R^2 = SiMe$_3$: 96%
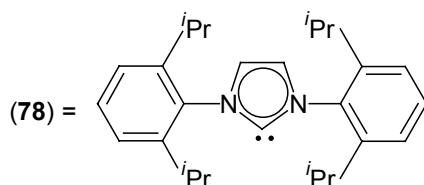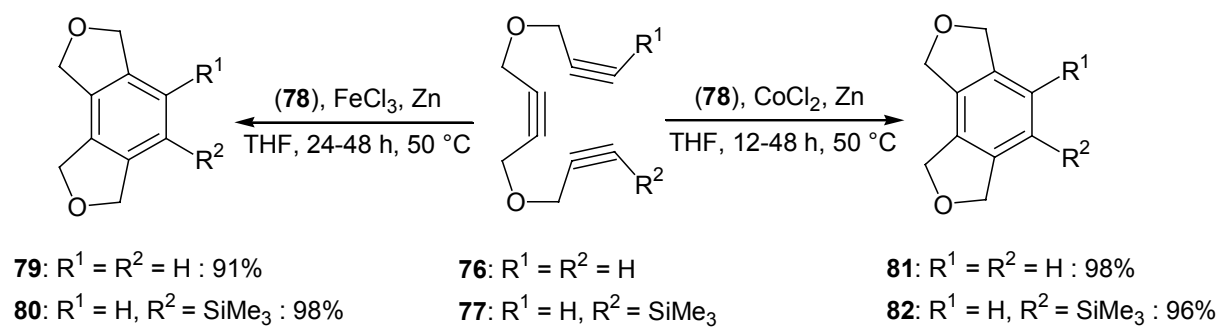
Scheme 24   Cobalt/iron catalysed intramolecular cyclotrimerisation

2 C-H activation reactions and cyclopropanations

α-Diazocarbonyl compounds have a long history of useful applications in organic chemistry. They are easily prepared from readily accessible precursors and can undergo a wide variety of chemical transformations under very mild conditions[41].

2.1 Synthesis of *α*-diazocarbonyl compounds

2.1.1 Acylation of diazoalkanes

The first recorded synthesis of an α-diazocarbonyl compound dates back to the *Curtius*[42] synthesis of ethyl diazoacetate by diazotisation of *glycine*. Althought *Wolff* discovered in 1912 the diazocarbonyl rearrangement, simple diazocarbonyl compounds became available in the late 1920s by the acylation of diazomethane with an acid chloride by *Arndt* and *Eistert*[43] and *Robinson*[44].

Acylation of diazomethane remains the most important route to acyclic terminal α-diazoketones and was used for the synthesis of the anticancer *L-glutamine* analog *Azotomycin*[45] (**83**) and the antibiotic *6-Diazo-5-oxo-L-norleucine*[46] (**84**) (Figure 1).
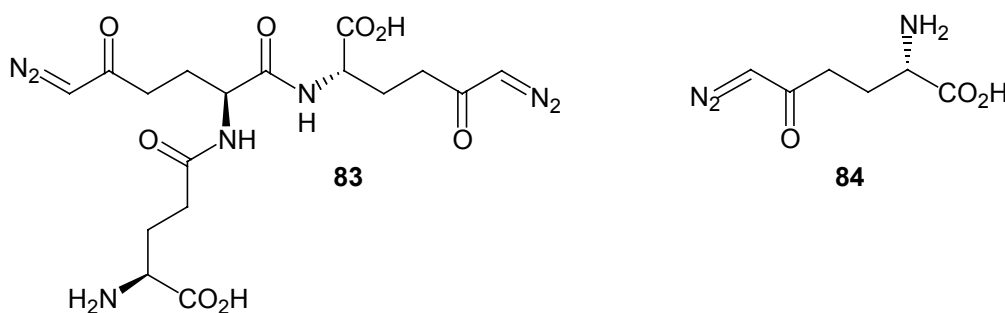
Figure 1   *Azotomycin* (**83**) and *6-Diazo-5-oxo-L-norleucine* (**84**)

2.1.2 Diazo-transfer reactions

A strong limitation of diazoalkane acylation is its unsuitability for cyclic α-diazoketones. Althought many routes to cyclic diazoketones have been developed, none can compete with the diazo transfer technique introduced by *Regitz*[47]. Diazotransfer is now the standard procedure to obtain not only cyclic α-diazoketones but also many acyclic systems not accessible by acyl-transfer processes. While the majority of diazotransfer reactions have been achieved with *p*-toluene-sulfonylazide[47] (tosylazide), several alternative reagents have been investigated[48], particularly regarding safety (pure tosylazide is officially classified as an explosive), easiness of product separation and substrate applicability. *p*-Acetamidobenzene

sulfonylazide (*p*-ABSA) (**85**) proved to be a practical and cheap reagent for use in diazotransfer reactions. The most important diazo derivatives are prepared from malonic esters, β-ketoesters and β-diketones by the standard procedures developed by *Regitz*[47] or *Davies*[48l] (Scheme 25).
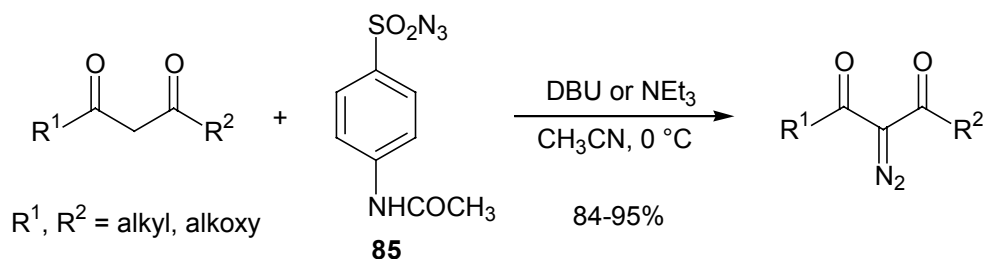
Scheme 25   *Davies* diazotransfer procedure

The diazotransfer reaction works efficiently for 1,3-dicarbonyl compounds, but it cannot be used when the methylene is activated by a single carbonyl group. Various alternative procedures have been developed and one in particular has found widespread application. This technique is known as "deformylating diazo-transfer"[47]. It involves *Claisen* condensation of the ketone with ethyl formate in order to introduce the strong activating formyl group which, during the diazotransfer, is released as sulfonamide (Scheme 26).
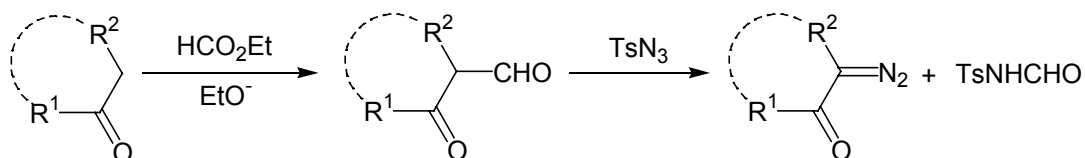
Scheme 26   Deformylating diazo-transfer

Variations of R^1 and R^2 allows the preparation of most types of acyclic and cyclic α-diazoketones[47,48b,49].

2.1.3   Other reactions

Since the introduction of the diazotransfer reaction other procedures[50] have lost importance. However in some particular cases they are still actual. Diazotisation remains the method of choice for the synthesis of the intermediates *6-diazopenicillinates* (**87**) from *6-aminopenicillanic esters*[51] (**86**) (Scheme 27).
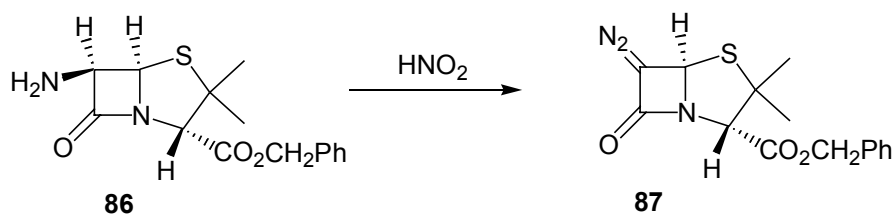
Scheme 27   Synthesis of *6-diazopenicillinates via* diazotisation

The antibiotic *L-Azaserine* (**89**), active against certain tumors, was prepared by diazotisation of the corresponding *O-glycylserine*[52] (**88**) (Scheme 28).
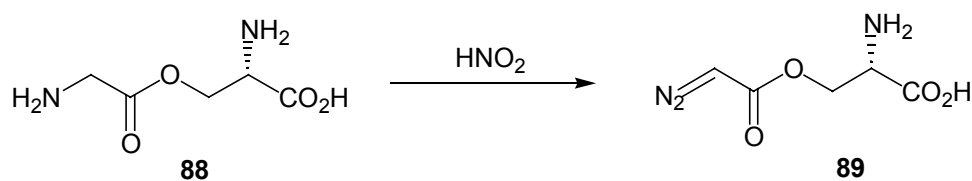
Scheme 28   Synthesis of *L-Azaserine*

Methyl 2-diazophenylacetate (**92**) was prepared *via Bamford-Stevens* reaction from the corresponding tosylhydrazone[53] (**91**) (Scheme 29).
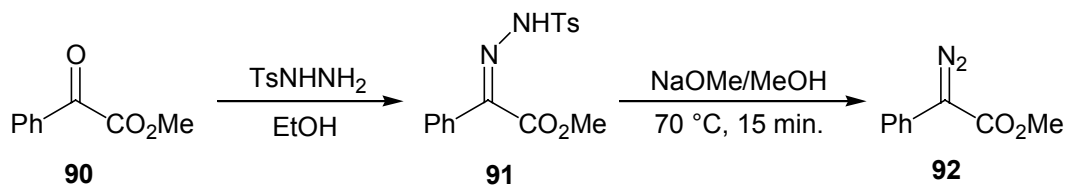
Scheme 29   Synthesis of methyl 2-diazophenylacetate

2.2   Diazocarbonyl reactions in synthesis

α-Diazocarbonyl compounds belong to a class of reagents of quite exceptional flexibility in synthesis. The most important reactions are those that proceed with loss of nitrogen which can be accomplished thermally, photochemically or catalytically. They include cyclopropanation, *Wolff* rearrangment, insertion in unactivated C-H bonds, aromatic cycloaddition, *α,α-*substitution, dipolar cycloaddition, acid catalysed cyclisation of unsaturated substrates, dimerisation, electrophilic aromatic substitution, oxidation and ylide formation followed by sigmatropic rearrangment[54]. Herein only some selected examples of C-H activation reactions leading to the synthesis of natural products and biologically active compounds will be discussed.

2.2.1 C-H and N-H activation reactions

A wide variety of metal complexes can be used to generate metal-carbenoids from diazo-compounds[55]. They all need a free coordination site for the diazo compound, whereupon nitrogen is lost and the carbenoid intermediate is formed. Subsequent insertion in unactivated C-H bonds and regeneration of the catalyst complete the catalytic process (Scheme 30). Up to date the most effective catalysts for carbenoid C-H activation are rhodium(II) complexes[56]. Copper-based catalysts[57] have sometimes been used, but they are more suitable for cyclopropanation reactions.
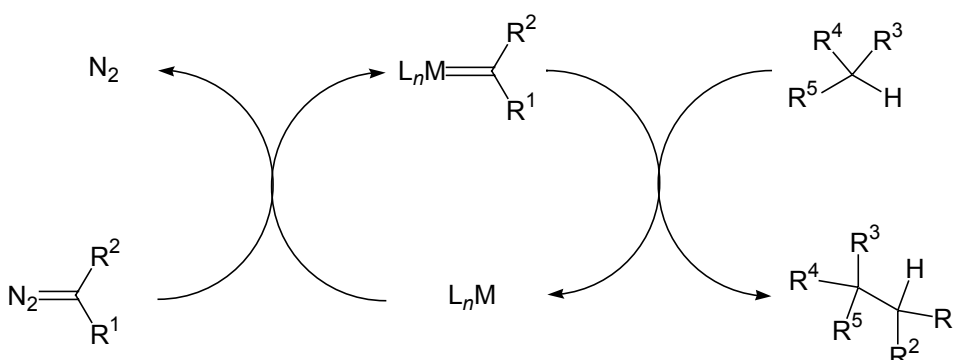
Scheme 30   Metal-carbenoid induced C-H insertion

Other carbenoid precursors such as phosphonium, iodonium, sulfonium, sulfoxonium and thiophenium ylides have been investigated. Their chemistry usually parallel that of carbenoids derived from diazo compounds[55b,58]. One of the most successful applications of carbene chemistry is the rhodium-catalysed intramolecular N-H insertion reaction, that is the key step in the *Merck* total synthesis of (+)-*Thienamycin*[59] (**93**) (Scheme 31).
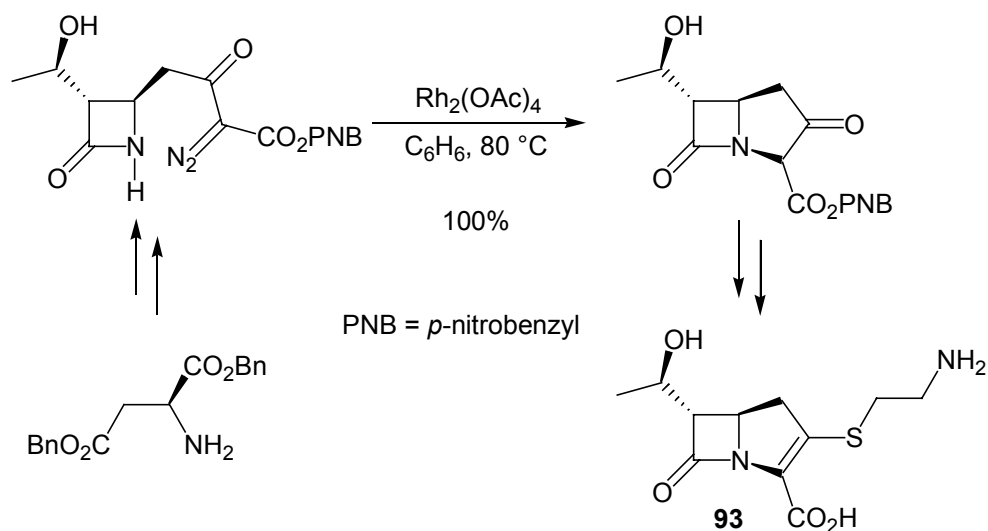
Scheme 31   *Merck* total synthesis of (+)-*Thienamycin*

Following *Davies*[56] classification carbenoids can be divided into three major groups according to their substituents: acceptor, acceptor/acceptor and donor/acceptor. The terms donor and acceptor refer to the electron donation or withdrawal capacity of the substituents through resonance effects. An electron withdrawing group makes the carbenoid more electrophilic and reactive, while an electron donating group makes it more stable.

2.2.1.a   *Acceptor substituted carbenoids*

The acceptor substituted carbenoids are derived from diazo compounds with a single electron withdrawing group, for example ethyl diazoacetate. The highly reactive metallocarbenoid intermediates are prone to dimerization and alkene formation by a 1,2-hydride shift. Acceptor substituted carbenoids have been mostly employed in intramolecular C-H activation reactions[41], such as the synthesis of various lignanes like (+)-*Isodeoxypodophyllotoxin*[60] (**94**) (Scheme 32). Lignan lactones are a broad class of natural products. Many of them have remarkable biological and medicinal properties[61].
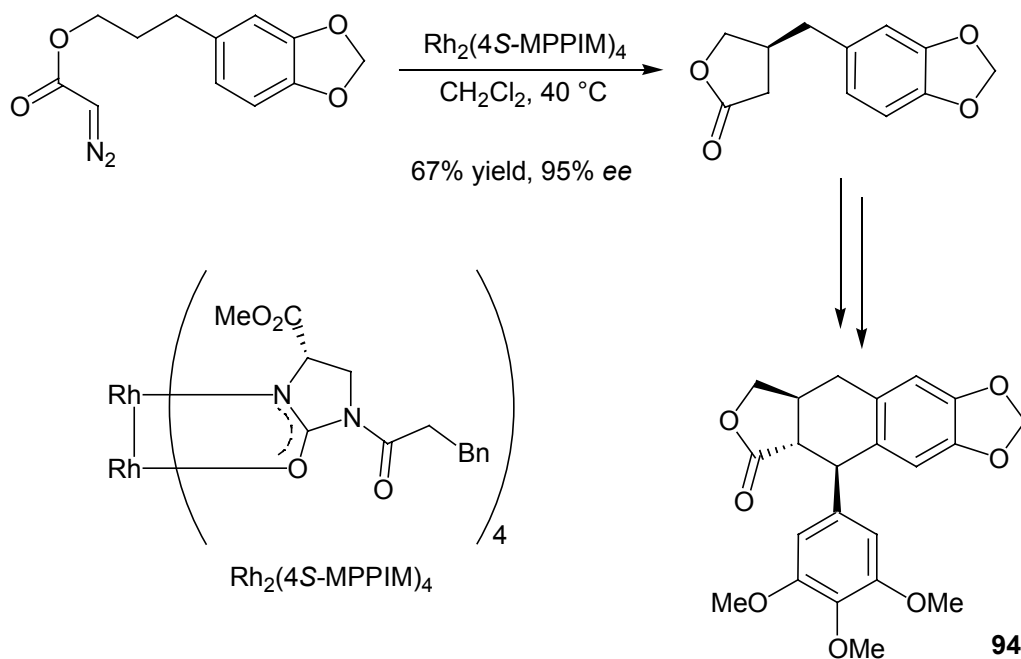
Scheme 32   Synthesis of (+)-*Isodeoxypodophyllotoxin*

2.2.1.b   *Acceptor/acceptor substituted carbenoids*

The acceptor/acceptor substituted carbenoids are derived from diazo compounds with two electron withdrawing groups, usually 1,3-dicarbonyls such as diazoacetoacetates, diazomalonates and diazodiketones. These diazocompounds are very stable and only active catalysts or higher temperatures are able to form the carbenoid[41]. Once it is formed, the

carbenoid is highly electrophilic and common side reactions are carbene dimerisation and hydride transfer to form zwitterionic intermediates. The most synthetically useful are intramolecular reactions[41]. Some pharmaceutically relevant molecules, such as the GABA$_B$ receptor agonist (R)-(–)-*Baclofen*[62] (**95**) (Scheme 33) and the cyclic AMP phosphodiesterase (PDE4) inhibitor (R)-(–)-*Rolipram*[63], were prepared with an intramolecular C-H activation as a key step. γ-Aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the mammalian central nervous system. The principle effect of GABA$_B$ agonists is muscle relaxation and control of the gastric acid secretion. The selective PDE4 inhibition is believed to exert a major role in the pharmacotherapy of depression.
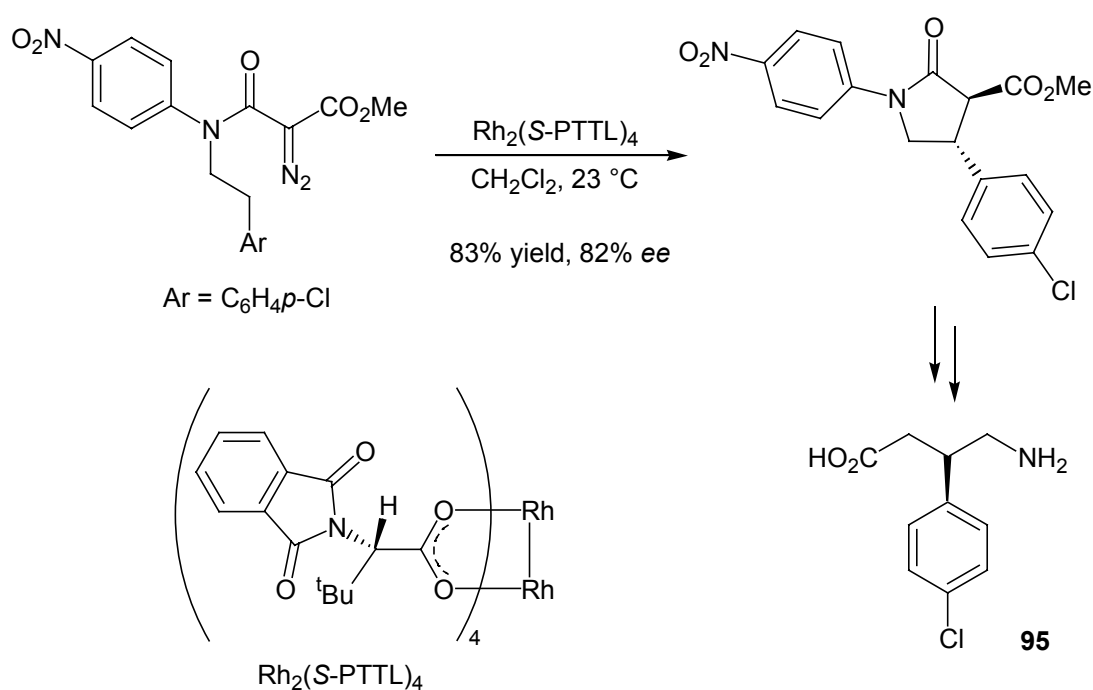
Scheme 33   Synthesis of *R*-(–)-*Baclofen*

2.2.1.c   Donor/acceptor substituted carbenoids

The donor/acceptor substituted carbenoids have been recently investigated[64]. In this molecules an electron donating substituent such as vinyl or aryl is stabilising the carbenoid through resonance. The diazo precursor is also stabilised so that very reactive catalysts are required to decompose the diazo compounds. This group of carbenoids is able to undergo chemoselective intermolecular C-H activations[65]. The monoamine re-uptake inhibitor (+)-*Indatraline*[66] (**96**) was synthesised by means of an intermolecular Rh$_2$(S-DOSP)$_4$ catalysed allylic C-H activation (Scheme 34). Inhibition of the re-uptake of monoamines such as dopamine, norepinephrine and serotonine is at the basis of pharmacological treatment of cocaine addiction.
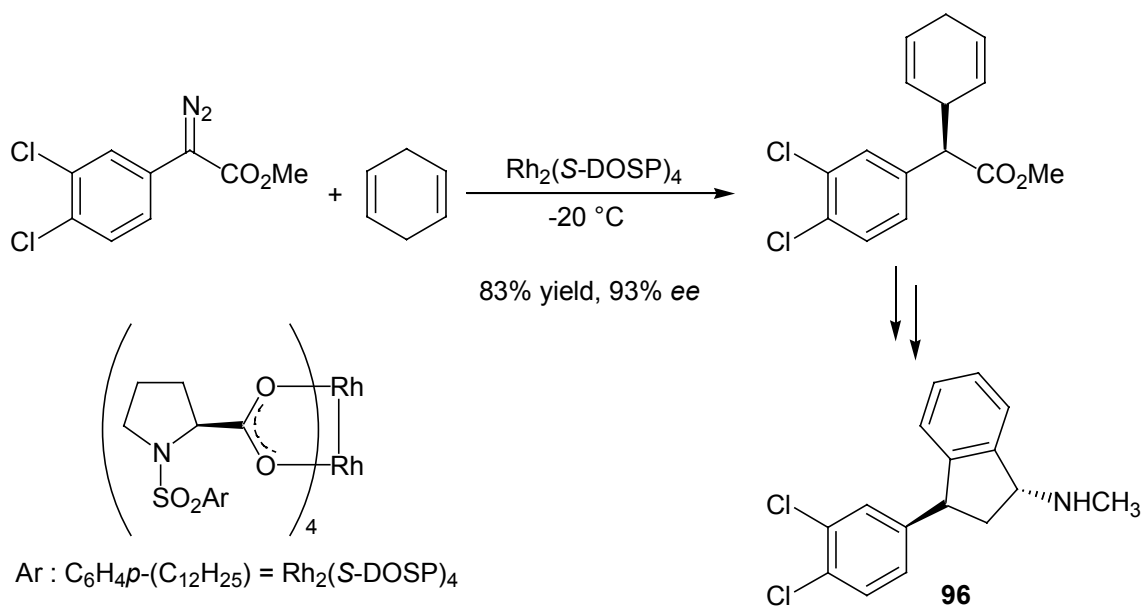
Scheme 34   Synthesis of (+)-*Indatraline*

Heterocyclic diazoacetates can also be used as starting materials for the synthesis of pharmaceutically relevant targets. An example is the enantioselective synthesis of the antiepileptic compound (+)-*Cetiedil*[67] (**97**) (Scheme 35).
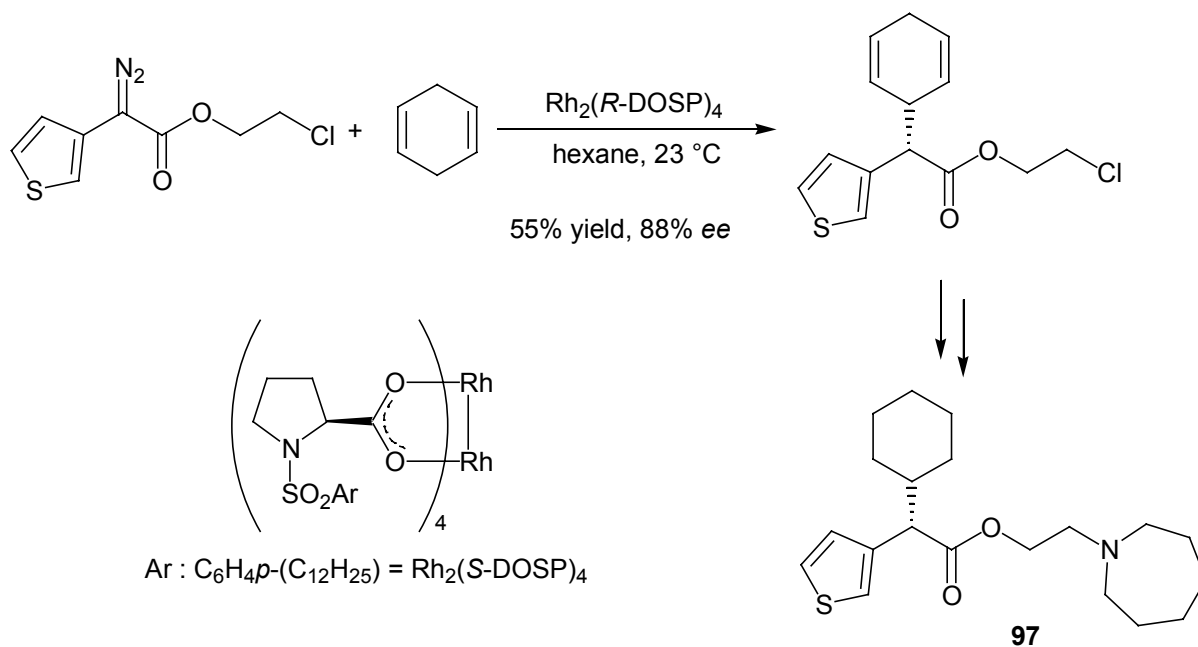
Scheme 35   Synthesis of (+)-*Cetiedil*

The ability of the catalyst to successfully effect the C-H activation in the presence of the electrophilic alkyl chloride and nucleophilic thiophene ring illustrates also the compatibility of rhodium-based catalysts with various functional groups.

2.2.2   Cyclopropanation reactions

Due to their widespread occurrence in natural products and in biologically active compounds, cyclopropanes have received considerable attention during the last decades[41]. Transition metal catalysed decomposition of diazocarbonyl compounds in the presence of alkenes provides a powerful tool for constructing cyclopropanes and both intra- and intermolecular reactions are known. With the appropriate choice of metal and supporting ligands, the carbene transfer to the double bond can proceed with high levels of stereoselectivity[41,68,69]. Although many transition metals may be used, copper[68] is attractive because of its low cost relative to other metals such as rhodium and ruthenium. However, the enhanced stability of ruthenium carbenes allows the isolation and characterisation of the metal-carbene complexes, demonstrating that they are intermediates in catalytic cyclopropanation reactions[70]. The mostly used ligands are C_2 symmetric bis-oxazolines developed by *Evans* and *Pfaltz*[71]. The complexes are usually generated *in situ* by reaction of the ligands with copper triflate or hexafluorophosphate. Some typical ligand structures are shown in Figure 2.

R = alkyl, aryl, benzyl
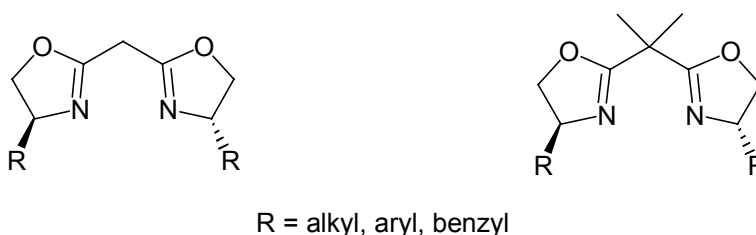
Figure 2   *Evans* and *Pfaltz* bis-oxazoline ligands

Herein some examples of cyclopropanation and subsequent ring opening reactions are reported.

2.2.2.a   Synthesis of cyclopropane-containing products

Many natural and synthetic products which contain the cyclopropyl ring have been prepared by the intramolecular reaction of a copper-carbenoid with a carbon-carbon double bond. For example (±)-*Cyclolaurene* (**100**), isolated from the sea hare *Aplysia dactylomela,* was synthesised from the diazocarbonyl (**98**) by an intramolecular cyclopropanation as the key step[72] (Scheme 36).
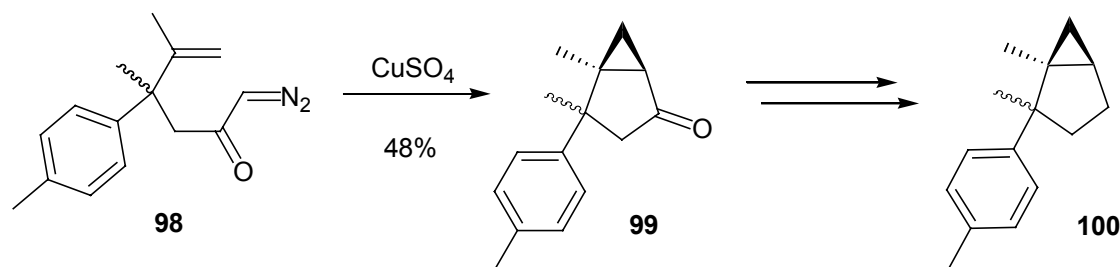
Scheme 36   Cyclopropanation step in the synthesis of (±)-*Cyclolaurene*

Since the discovery in 1970s of the antiinsectide activity of natural *pirethroids* the development of new synthetic derivatives has became of great interest. They combine both low toxicity and biodegradability with high activity against a large number of insect types, including the important *Lepidoptera* cotton pests. *Permethrinic acid* (**101**) and *Chrisantemic acid* (**102**) (Figure 3) are valuable intermediates for the preparation of synthetic *pirethroids*[73] and both are synthesised via a copper-catalysed intramolecular cyclopropanation.
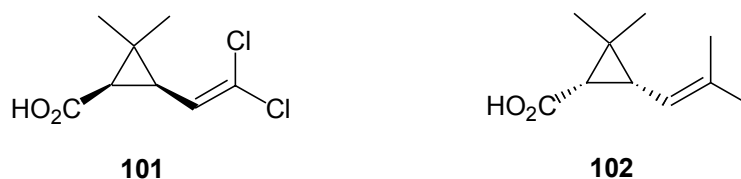
Figure 3   Synthetic *pirethroid* precursors *Permethrinic* and *Chrisantemic acid*

2.2.2.b   Cyclopropanation and subsequent reactions

Cyclopropanes are also valuable intermediates in organic synthesis. Carbenoid cyclopropanation followed by ring opening reactions is now a commonly used synthetic strategy[74]. Among all the procedures that have been developed, the intramolecular addition of a diazocarbonyl compound to a cyclic olefin followed by ring cleavage of the exterior cyclopropane bond to produce a spiro derivative is remarkable. (±)-*Spirolaurenone*[75] (**105**), an antifungal compound isolated from the red alga *Laurencia glandulifera*, was synthesised following this procedure from the diazoketone (**103**) (Scheme 37).
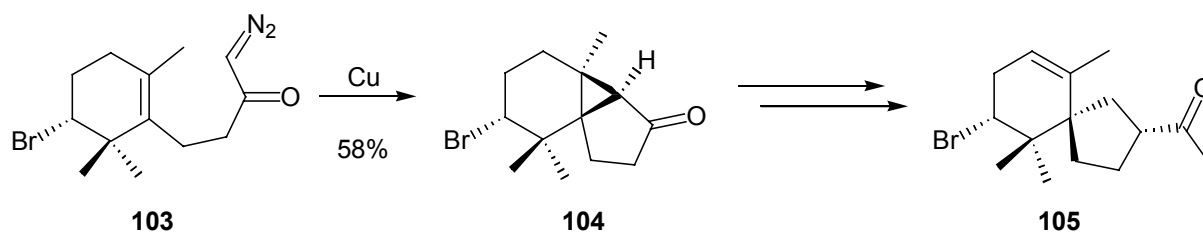
Scheme 37   Synthesis of spiro-derivatives *via* cyclopropanation-fragmentation

Copper-catalysed decomposition of dienoic diazocarbonyls (**106**) gives vinyl cyclopropanes (**107**). Subsequent pyrolysis results in cyclopentene annulation. When the diene function is part of a carbocyclic system this procedure affords products with a *triquinane* skeleton, such as (±)-*Hirsutene*[76] (**108**) (Scheme 38) .
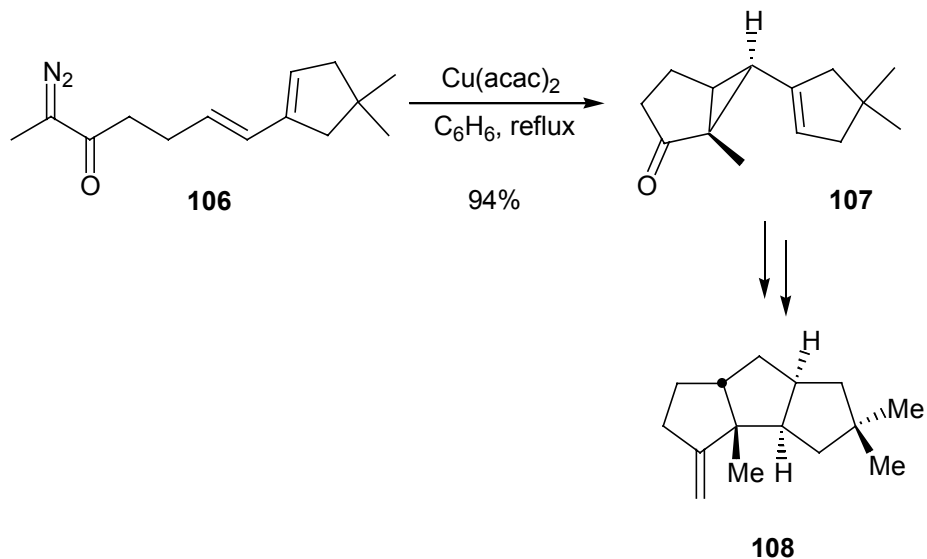
Scheme 38   Synthesis of (±)-*Hirsutene via* cyclopropanation-annulation

3   Research topic

The target of this thesis was the development of a cobalt(I)-catalysed *Diels-Alder* reaction with acyclic 1,3-dienes on nitrogen functionalised alkynes. As reported in the last years by *Hilt*, cobalt(I)-catalysed *Diels-Alder* reactions can be performed with several starting materials bearing various functional groups. While boron, silicon, oxygen and sulfur containing functionalities were accepted by the catalyst, nitrogen-functionalised starting materials could not be employed so far probably because of catalyst complexation and/or deactivation.

The inclusion of the nitrogen into a proper protecting group could reduce the basicity and the coordination capability to the cobalt catalyst (Scheme I).
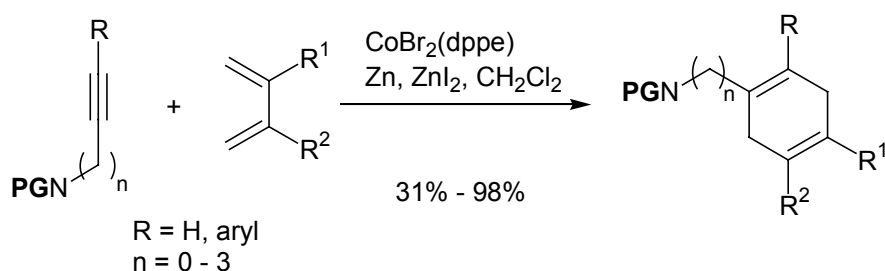
Scheme I

Therefore the following targets

a) identification of the proper protecting group,

b) modification of the chain lenghts

c) incorporation of internal alkynes (R ≠ H)

d) application of various 1,3-dienes

should be investigated.

After DDQ oxidation, the proposed cycloadducts are envisaged as potential starting materials for the synthesis of polycyclic polyfunctionalised heterocyclic compound. A straightforward reaction sequence consisting of chemoselective sodium borohydride reduction and an acid induced *Friedel-Crafts* type cyclisation could lead to the synthesis of dibenzo-azepine derivatives which are reported to have important biological activities (Scheme II).
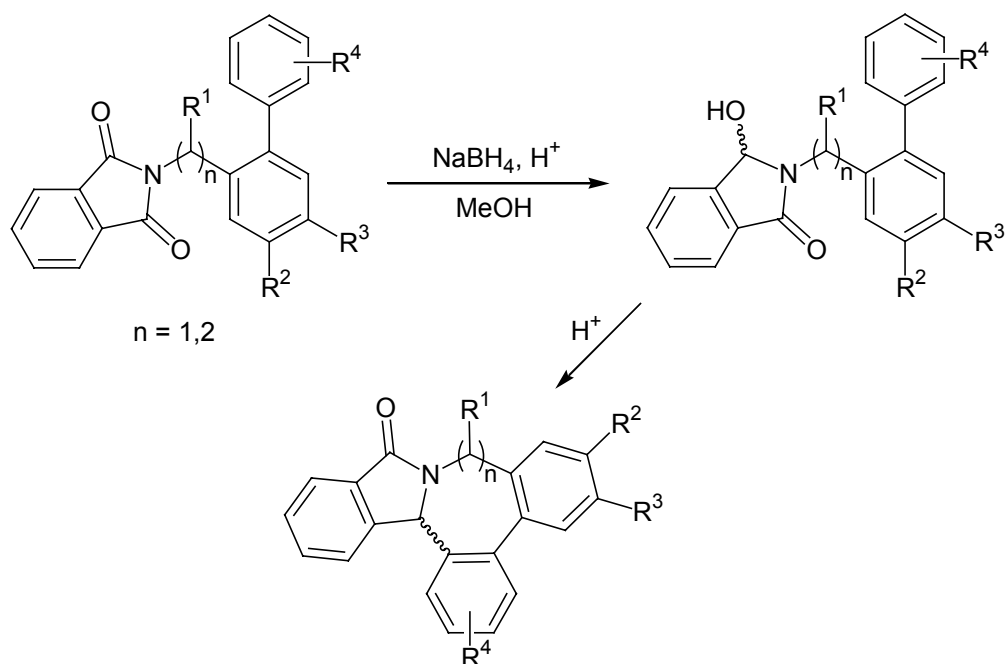
Scheme II

On the other side, the dihydroaromatic compounds could also be used as substrates for rhodium(II)-catalysed C-H activation reactions with diazo compounds as carbene precursors. Since the cobalt(I)-catalysed *Diels-Alder* reaction of alkynes and acyclic 1,3-dienes is a powerful tool for the generation of dihydroaromatic compounds in excellent yields, a possible approach to highly substituted benzene derivatives was envisioned (Scheme III).
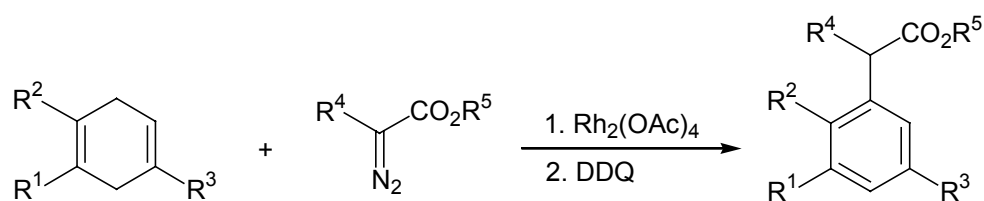
Scheme III

Due to the asymmetry of the dienes an additional target was the development of a regioselective reaction and the determination of functional group compatibility (R^1-R^5).

B   Results and discussion

1 Cobalt(I)-catalysed neutral *Diels-Alder* reactions of nitrogen-functionalised alkynes

In the last years *Hilt* reported that silicon[31], boron[32], sulfur[33] and oxygen[34,35] containing starting material were suitable for the cobalt(I)-catalysed *Diels-Alder* reaction. Nitrogen-functionalized reagents were not accepted by the catalyst. The nitrogen containing groups were neither tolerated in close proximity nor further away from the reaction center[77], probably because of coordination with the cobalt and subsequent loss of catalytic activity. When the nitrogen was included into a strong electron-withdrawing substituent, as the phthalimido group, the reaction with acyclic 1,3-dienes such as 2,3-dimethyl-1,3-butadiene (**42**) proceeded under mild conditions (5-10% catalyst, CH_2Cl_2, 16 hours, r.t.) to yield the corresponding aromatic compound (**110**) in an acceptable 36% yield after DDQ oxidation (Scheme 39).
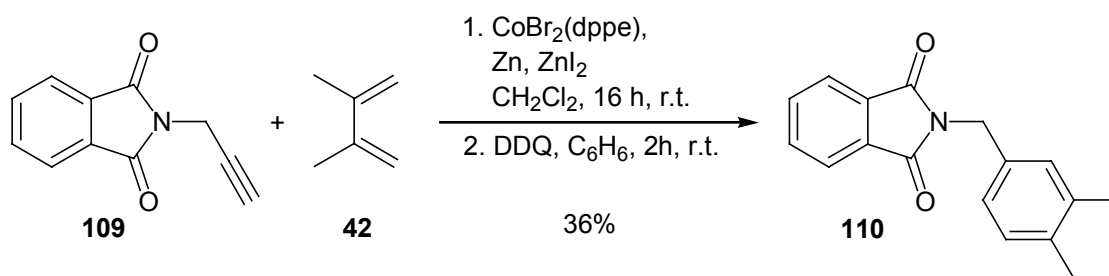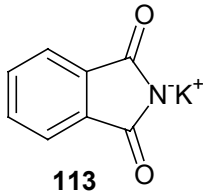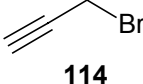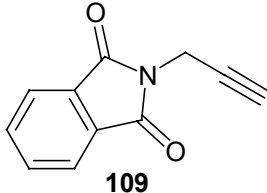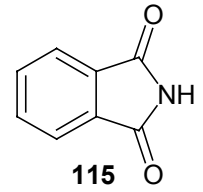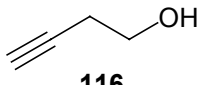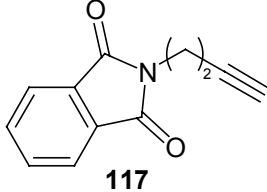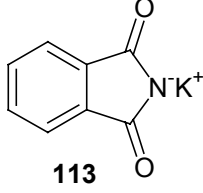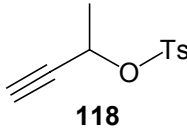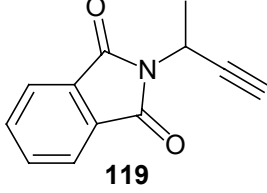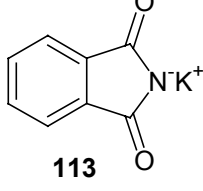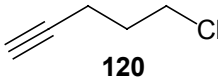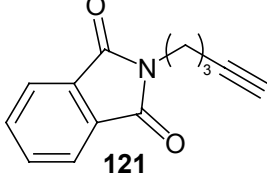
Scheme 39 First example of cobalt(I)-catalysed *Diels-Alder* reaction on nitrogen functionalised alkynes

After this result two new questions were raised: 1) how important is the distance of the nitrogen from the triple bond and 2) is the phthalimido group the only protecting group accepted by the catalyst. To answer the first question some imides with longer, shorter and branched chains were prepared. The results are summarised in Table 2. Since it was not possible to synthesise the corresponding ethynyl analogue of (**109**), the ynamide (**112**) was chosen as example of substrate with the triple bond next to the nitrogen. A copper-mediated *N*-alkynylation[78] of the carbamate (**111**) furnished the ynamide (**112**) in a 76% yield (Scheme 40).
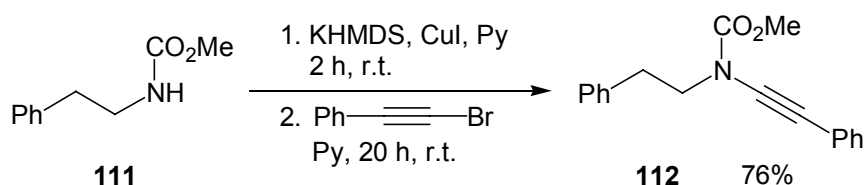
Scheme 40 Copper-mediated carbamate *N*-alkynylation

Table 2   Synthesis of imides with different chain lenghts

Entry	Protecting group	Alkyne	Protected amine	Yield (%)
1	**113**	**114**	**109**	86[a]
2	**115**	**116**	**117**	75[b]
3	**113**	**118**	**119**	56[c]
4	**113**	**120**	**121**	69[d]

Reagents and conditions: [a] DMF, 100 °C, 6 h; [b] PPh$_3$, DEAD, THF, r.t., 72 h; [c] DMF, 60 °C, 16 h; [d] KI, DMF, 100 °C, 6 h.

All the imides were prepared following or adapting known literature procedures. The tosylate (**118**) was preferred to 3-bromo-1-butyne[79] as reagent for the synthesis of (**119**) (Table 2, Entry 3). When tested in the cobalt(I)-catalysed *Diels-Alder* reaction with 2,3-dimethyl-1,3-butadiene (**42**) the corresponding aromatic products could be isolated in lower yield after DDQ oxidation (Table 3).

Table 3   Cobalt(I)-catalysed *Diels-Alder* reactions with different imide chain lenghts
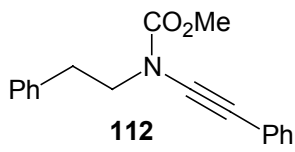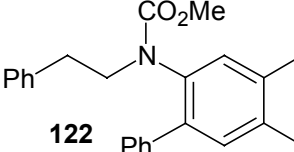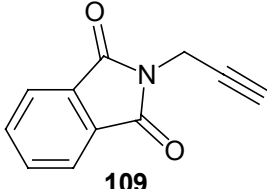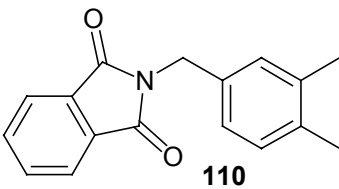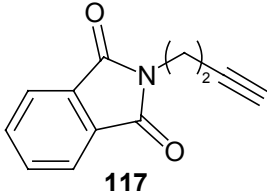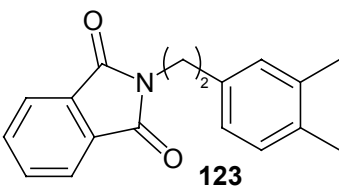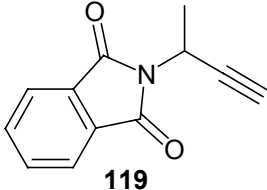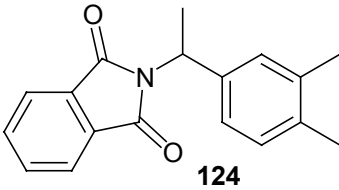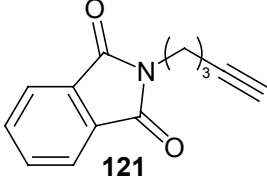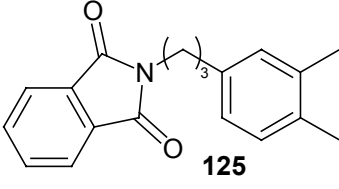
Entry	Protected amine	Product	Yield[a] (%)
1	**112**	**122**	0[b]

Table 3   Cobalt(I)-catalysed *Diels-Alder* reactions with different imide chain lenghts
(cont.)

Entry	Protected amine	Product	Yield[a] (%)
2	**109**	**110**	36
3	**117**	**123**	45
4	**119**	**124**	35
5	**121**	**125**	36

Reagents and conditions: alkyne (1.0 equiv.), CoBr$_2$(dppe) (10 mol%), Zn (50 mol%), ZnI$_2$ (50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (1.5 equiv.), CH$_2$Cl$_2$, 16 h, r.t.; [a] isolated yield after DDQ oxidation in benzene at r.t.; [b] no conversion.

With the ynamide (**112**) no reaction was observed, indicating that the triple bond and the nitrogen should be separated by at least one carbon atom (Table 3, Entry 1). The yields for the corresponding longer and branched chain imides did not improve significantly (Table 3, Entry 3-5). These results are in contrast to earlier reports indicating that other functionalised terminal alkynes can be used successfully as reactants in the cobalt(I)-catalysed *Diels-Alder* reaction[31a]. A possible explanation is that, as in the case of propargylic ethers, the imide functionality acts as a leaving group to generate a cobalt-stabilised propargylic cation which could undergo side reactions. The second question was investigated modifying the phthalimido protecting group and leaving unchanged the propargylic side chain. All the products in Table 4 were prepared following or adapting known literature procedures.

Table 4   Synthesis of propargyl derivatives
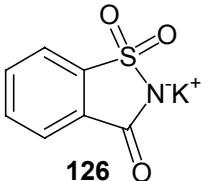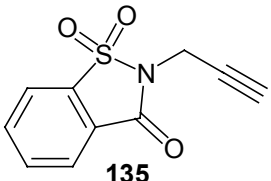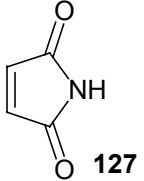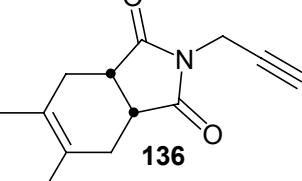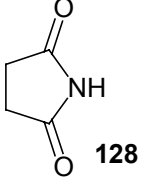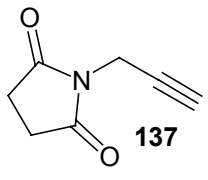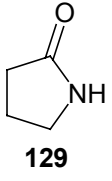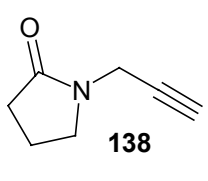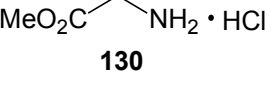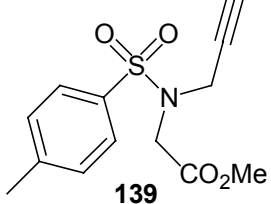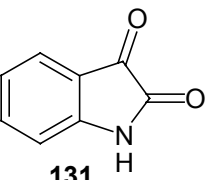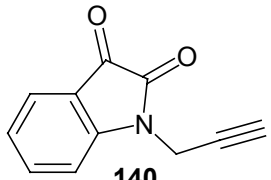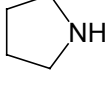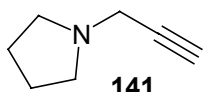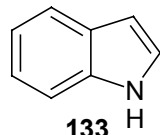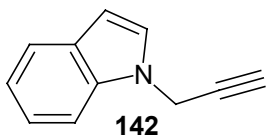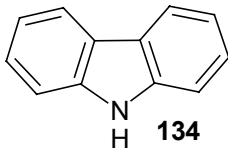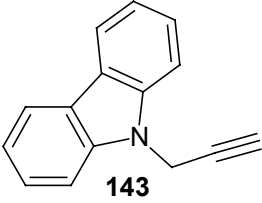
Entry	Protecting group	Product	Yield (%)
1	126	135	90[a]
2	127	136	83[b]
3	128	137	97[c]
4	129	138	85[d]
5	MeO$_2$C―NH$_2$ · HCl 130	139	82[e]
6	131	140	56[f]
7	132	141	95[g]
8	133	142	86[h]

Table 4   Synthesis of propargyl derivatives *(cont.)*

Entry	Protecting group	Product	Yield (%)
9	**134**	**143**	54[i]

Reagents and conditions: [a] propargyl bromide, DMF, 100 °C, 6 h; [b] i) 2,3-dimethyl-1,3-butadiene, toluene, 100 °C, 16 h; ii) NaH, propargyl bromide, THF, 0 °C, 3 h; [c] K$_2$CO$_3$, propargyl bromide, acetone, reflux, 6 h; [d] NaH, propargyl bromide, THF, 0 °C, 16 h; [e] i) Et$_3$N, DMAP, TsCl, CH$_2$Cl$_2$, 0 °C, 24 h; ii) HCl 2M; iii) NaH, propargyl bromide, DMF, 0 °C, 2 h; [f] ^{t}BuOK, propargyl bromide, DMF, 0 °C, 3 h; [g] propargyl bromide, Et$_2$O, reflux, 12 h; [h] 50% NaOH, propargyl bromide, Bu$_4$NBr, benzene, r.t., 1h; [i] 50% NaOH, propargyl bromide, Bu$_4$NBr, benzene, r.t., 4h.

The imides (**135-143**) were subsequently reacted with the catalyst system under standard conditions and the results are summarised in Table 5. By using saccharine or saturated imide derivatives the corresponding aromatic products could be isolated in 46% and 41% yield (Table 5, Entry 1 and 2), while with *N*-propargylsuccinimide the yield was only 31% (Table 5, Entry 3). An amide functionality was also well accepted by the cobalt catalyst, and the yields for cyclic or acyclic starting materials were quite similar (Table 5, Entry 4 and 5).

Table 5   Cobalt(I)-catalysed *Diels-Alder* reactions with different protecting groups
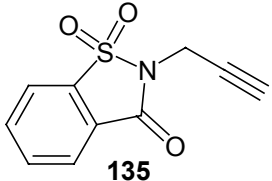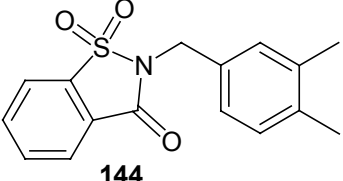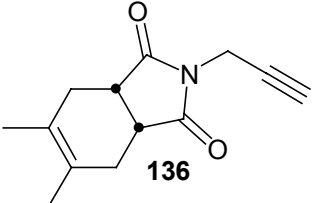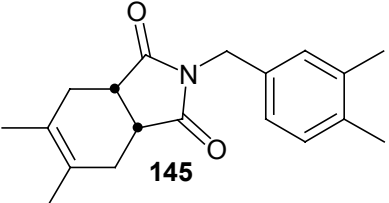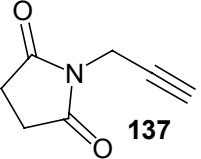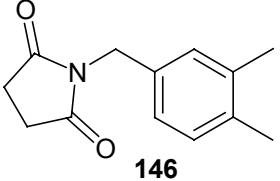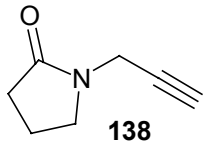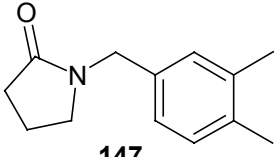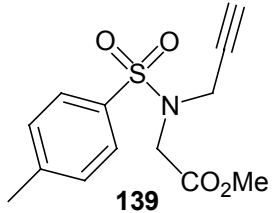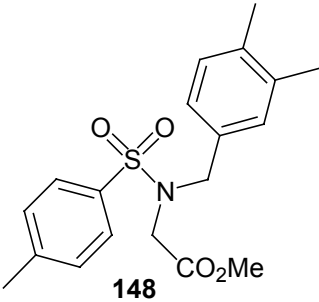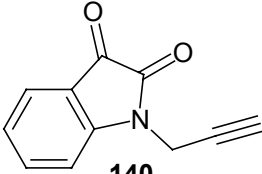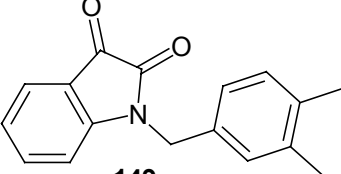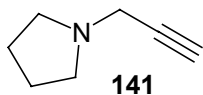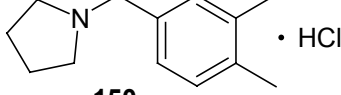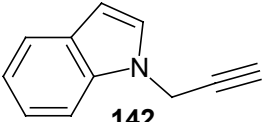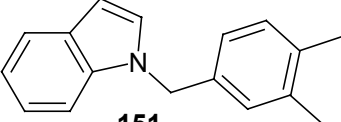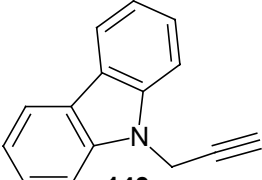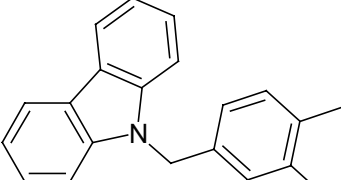
Entry	Protected amine	Product	Yield[a] (%)
1	**135**	**144**	41
2	**136**	**145**	46
3	**137**	**146**	31

Table 5   Cobalt(I)-catalysed *Diels-Alder* reactions with different protecting groups *(cont.)*

Entry	Protected amine	Product	Yield[a] (%)
4	**138**	**147**	48
5	**139**	**148**	46
6	**140**	**149**	0[b]
7	**141**	**150**	5[c]
8	**142**	**151**	16
9	**143**	**152**	47

Reagents and conditions: alkyne (1.0 equiv.), CoBr$_2$(dppe) (10 mol%), Zn (50 mol%), ZnI$_2$ (50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (1.5 equiv.), CH$_2$Cl$_2$, 16 h, r.t.; [a] isolated yield after DDQ oxidation in benzene at room temperature; [b] decomposition of the starting material; [c] isolated as hydrochloride.

Complete decomposition was unexpectedly observed with the isatine derivative (Table 5, Entry 6). Further simplifications of the amide substructure led to the synthesis of *N*-propargylpyrrolidine (Table 5, Entry 7). After the cycloaddition step the corresponding dihydroaromatic product was detected by GC-MS, but it could not be isolated in a reasonable yield because of its poor distribution coefficient during extraction after DDQ oxidation. However, when the basicity was progressively diminished by inclusion of the nitrogen atom

in an indole or carbazole system (Table 5, Entry 8 and 9) the isolated yields raised to 16% and 47%. In the meantime, an innovative ruthenium-catalysed hydroamidation reaction (Scheme 41) was published by *Goossen*[80a] and the enamide (**154**) was selected as a possible starting material for the cobalt(I)-catalysed *Diels-Alder* reaction.
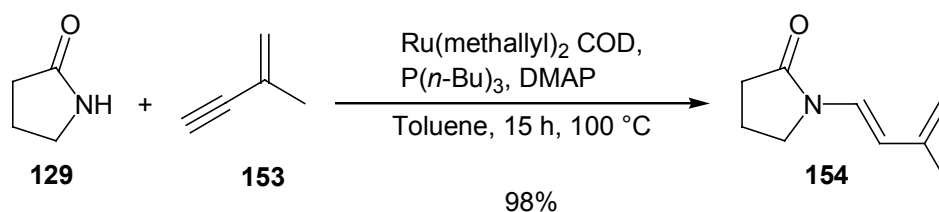
Scheme 41　Ruthenium-catalysed hydroamidation reaction

Unfortunately, when the enamide (**154**) was reacted with phenylacetylene (**24**) and the cobalt catalyst under standard conditions no conversion to (**155**) was observed (GC-MS) (Scheme 42). Rather the products of [2+2+2]-cyclotrimerisation of phenylacetylene were isolated. Further experiments with other terminal and internal alkynes (**156-157**) also resulted in trimer formation (Table 6).
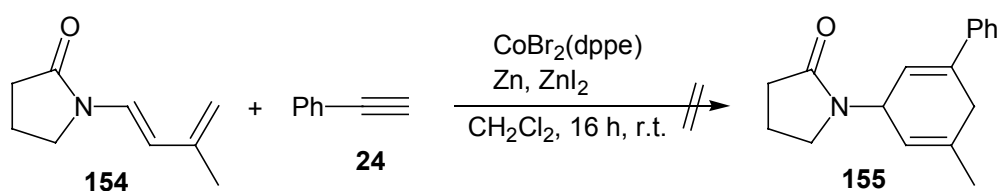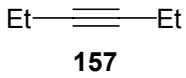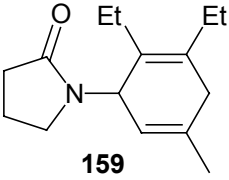
Scheme 42　Attempted *Diels-Alder* reaction on the enamide (**154**)

Table 6　　　Cobalt(I)-catalysed *Diels-Alder* reaction of enamide (**154**) with alkynes

Entry	Alkyne	Desired product	Temp.	Yield (%)
1	Ph—≡ **24**	**155**	25 °C/50 °C	0[a]
2	**156**	**158**	25 °C/50 °C	0[a]

Table 6 Cobalt(I)-catalysed *Diels-Alder* reaction of enamide (**154**) with alkynes *(cont.)*

Entry	Alkyne	Desired product	Temp.	Yield (%)
3	Et———Et **157**	**159**	25 °C/50 °C	0[a]

Reagents and conditions: enamide (**154**) (1.0 equiv.), CoBr$_2$(dppe) (10 mol%), Zn (50 mol%), ZnI$_2$ (50 mol%), alkyne (1.5 equiv.), CH$_2$Cl$_2$, 16 h; [a] no conversion into the desired product, only mixtures of trimers were formed.

The formation of trimers with a diimine cobalt catalyst in acetonitrile has already been reported by *Hilt*[31a,38] (Scheme 22). Since the alkynes had no competitive cycloaddition pathway available, the normally disfavoured trimerisation pathway predominated. The lack of *Diels-Alder* reaction of the enamide (**154**) is also sustaining the hypothesis that the nitrogen atom and the diene or dienophile moieties (Scheme 42 and Table 3, Entry 1) must be separated by at least one carbon atom.

When the sterical demand of the terminal alkyne (**109**) was increased by the synthesis of the phenyl propargylic derivative (**161**) using a standard *Sonogashira*[81] procedure (Scheme 43, eq. 1), a reduction in the reactivity was expected. Surprisingly, the reaction with 2,3-dimethyl-1,3-butadiene (**42**) proceeded under mild conditions (10% catalyst, CH$_2$Cl$_2$, 16 hours, room temperature). The desired product (**162**) could be isolated in 80% yield after DDQ oxidation (Scheme 43, eq. 2).
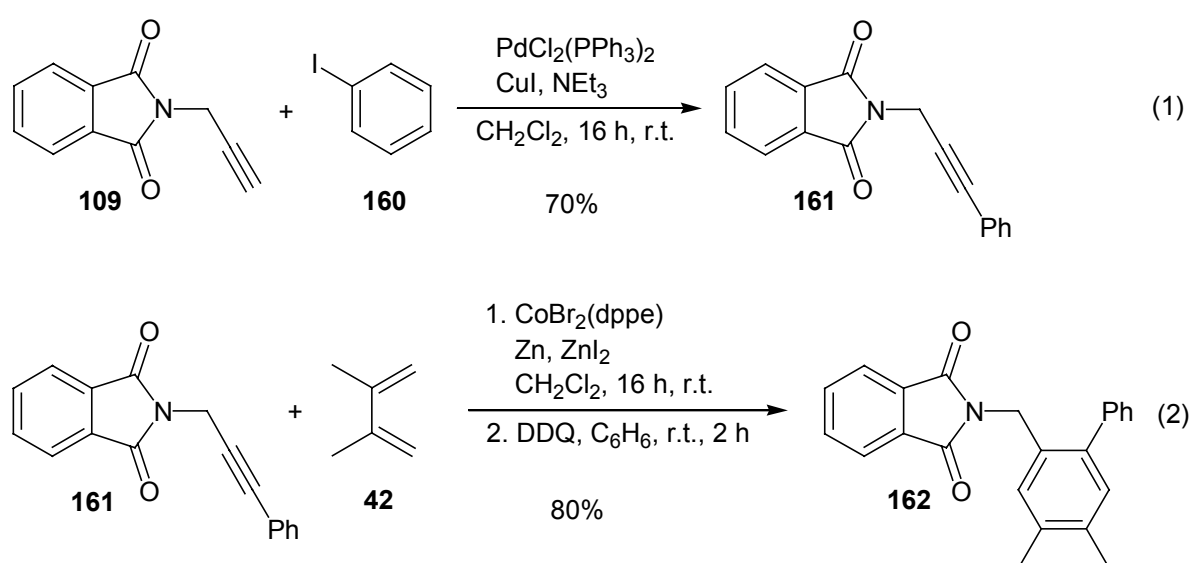
Scheme 43 *Diels-Alder* reaction with internal alkynes

On the basis of this result the imides in Tables 2 and 4 were converted into the corresponding aryl propargylic derivatives by means of the *Sonogashira* reaction. Using catalytic amounts of $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (5 mol%) in the presence of an excess of triethylamine the reactions proceeded smoothly at room temperature and the products were isolated in 46-96% yield after column chromatography, as reported in Table 7.

Table 7   *Sonogashira* coupling with terminal alkynes
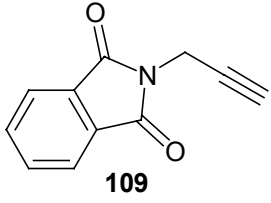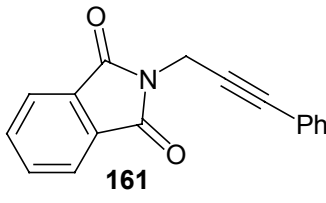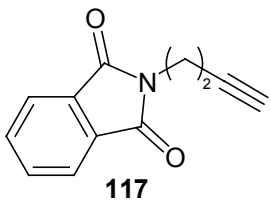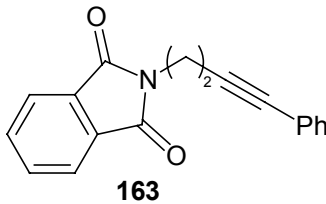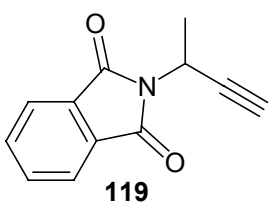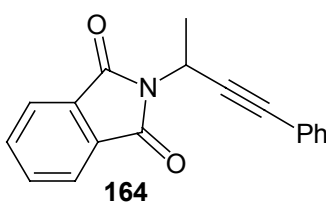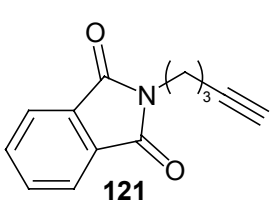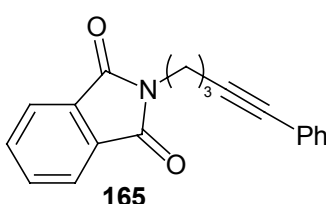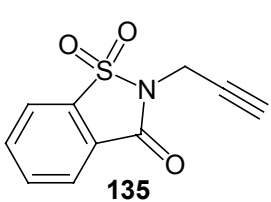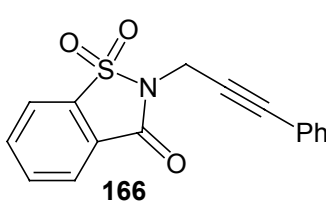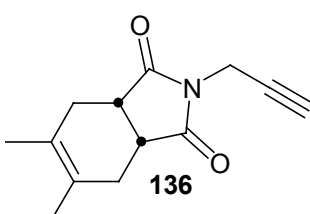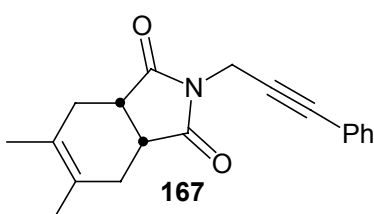
Entry	Terminal alkyne	Product	Yield[a] (%)
1	109	161	70
2	117	163	77
3	119	164	81
4	121	165	86
5	135	166	67
6	136	167	65

Table 7   *Sonogashira* coupling with terminal alkynes *(cont.)*
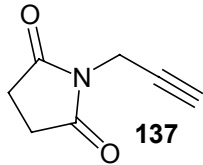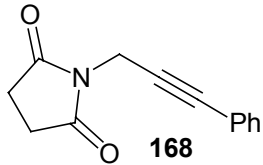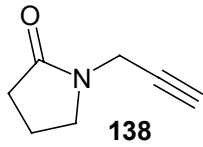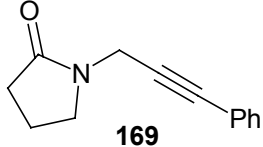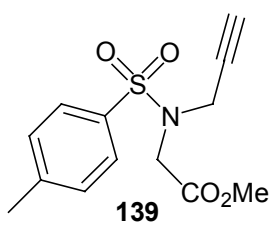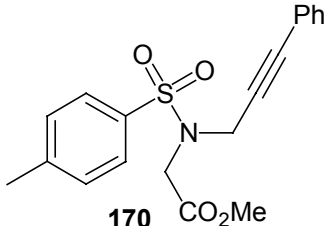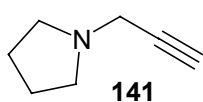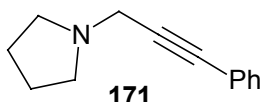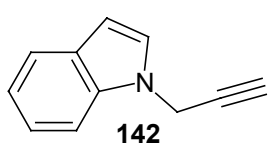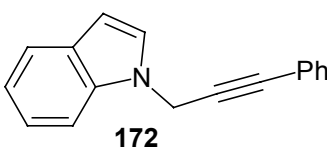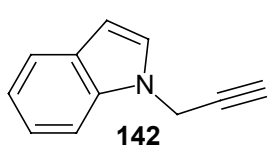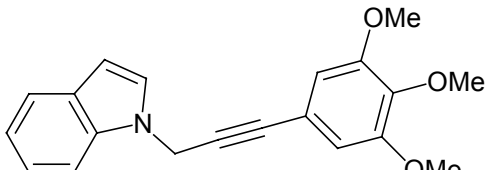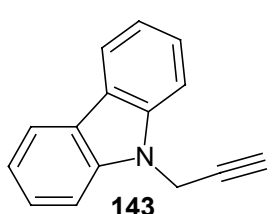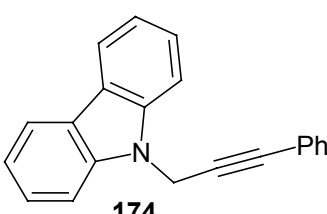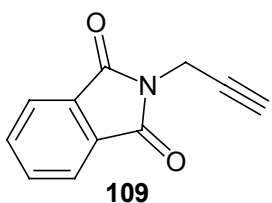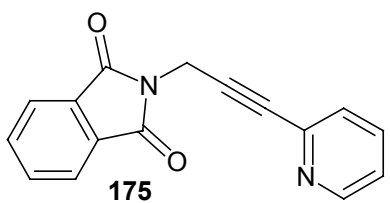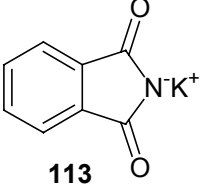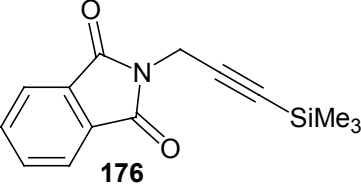
Entry	Terminal alkyne	Product	Yield[a] (%)
7	**137**	**168**	66
8	**138**	**169**	71
9	**139**	**170**	96
10	**141**	**171**	62
11	**142**	**172**	67
12	**142**	**173**	63
13	**143**	**174**	46
14	**109**	**175**	77

Table 7   *Sonogashira* coupling with terminal alkynes *(cont.)*

Entry	Terminal alkyne	Product	Yield[a] (%)
15	**113**	**176**	88

Reagents and conditions: alkyne (1.0 equiv.), iodo-arene or 2-iodo pyridine (Entry 14) (1.2 equiv.), PdCl$_2$(PPh$_3$)$_2$ (5 mol %), CuI (5 mol %), NEt$_3$ (5.0 equiv.), CH$_2$Cl$_2$, 16 h, r.t.; [a] yield not optimised.

The TMS-derivative (**176**) was prepared following a procedure similar to the synthesis of (**109**) (Scheme 44).
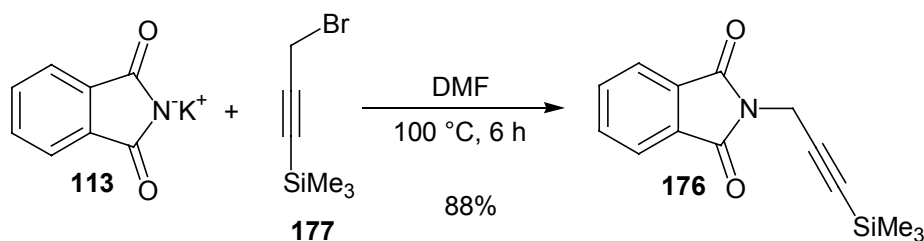
Scheme 44   Synthesis of the TMS-derivative (**176**)

The *Sonogashira* products (**161, 163-176**) were subsequently reacted with 2,3-dimethyl-1,3-butadiene (**42**) under standard conditions and the result are summarised in Table 8.

Table 8   Cobalt(I)-catalysed *Diels-Alder* reaction of internal propargylic amines
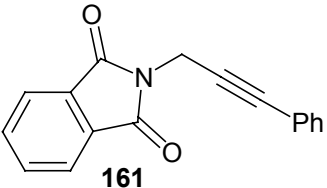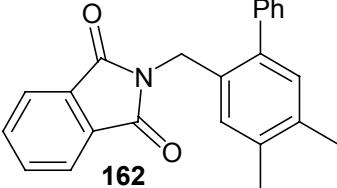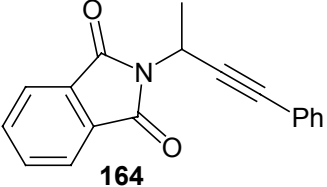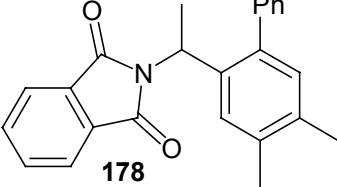
Entry	Protected amine	Product	Yield[a] (%)
1	**161**	**162**	80
2	**164**	**178**	98

Table 8   Cobalt(I)-catalysed *Diels-Alder* reaction of internal propargylic amines *(cont.)*
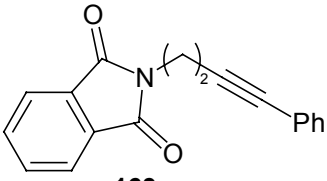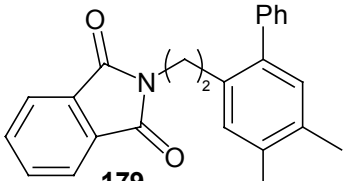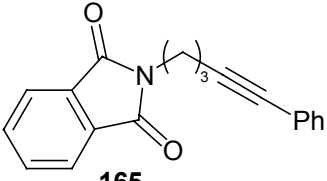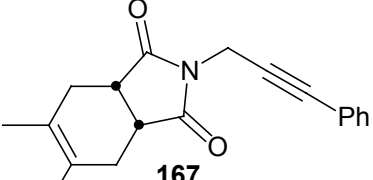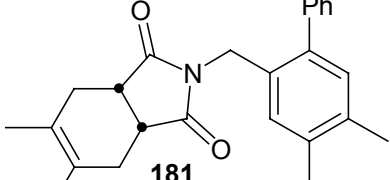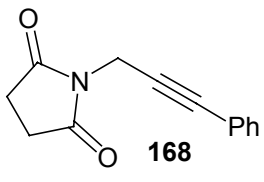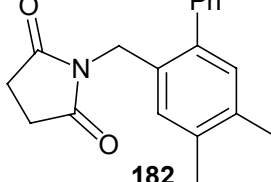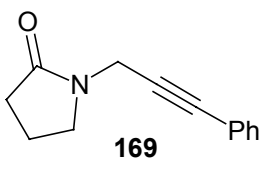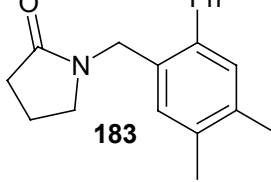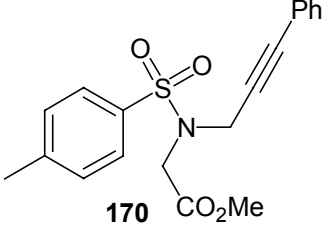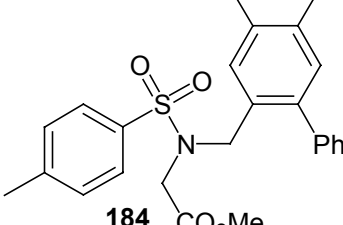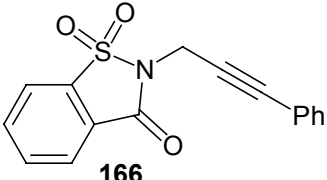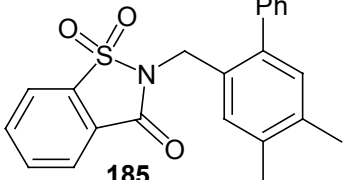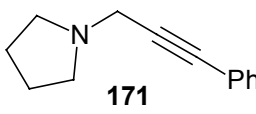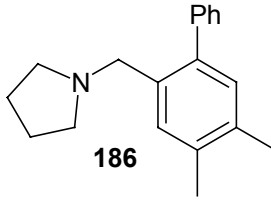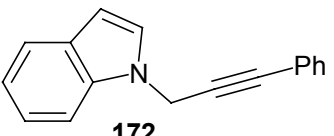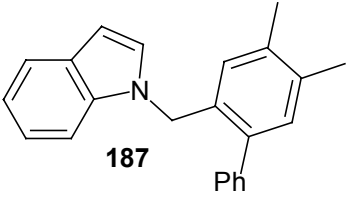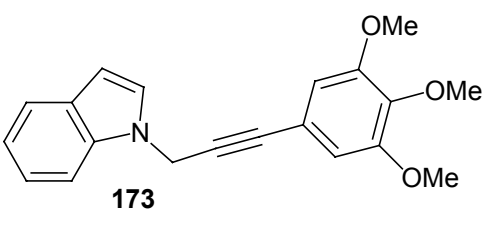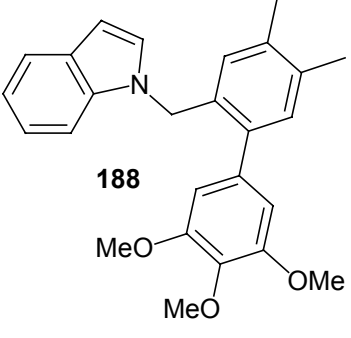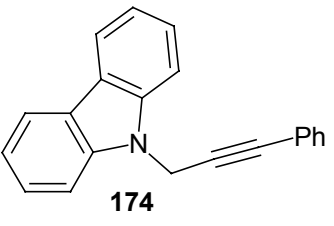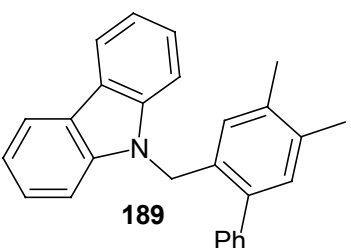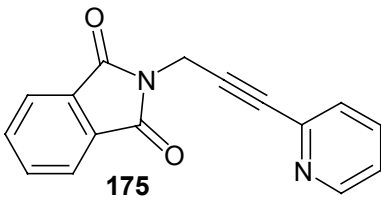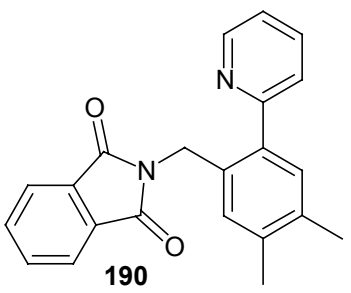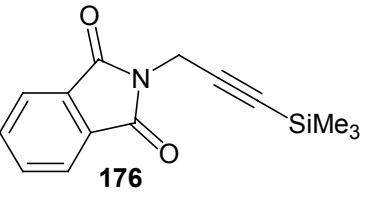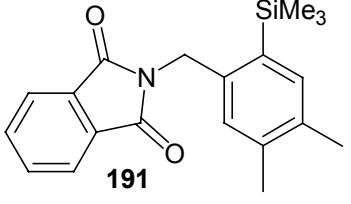
Entry	Protected amine	Product	Yield[a] (%)
3	**163**	**179**	98
4	**165**	**180**	90
5	**167**	**181**	98
6	**168**	**182**	84
7	**169**	**183**	90
8	**170**	**184**	80
9	**166**	**185**	91

Table 8   Cobalt(I)-catalysed *Diels-Alder* reaction of internal propargylic amines *(cont.)*

Entry	Protected amine	Product	Yield[a] (%)
10	**171**	**186**	0[b]
11	**172**	**187**	70
12	**173**	**188**	48
13	**174**	**189**	98
14	**175**	**190**	0[c]
15	**176**	**191**	0[c]

Reagents and conditions: alkyne (1.0 equiv.), CoBr$_2$(dppe) (10 mol%), Zn (50 mol%), ZnI$_2$ (50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (1.5 equiv.), CH$_2$Cl$_2$, 16 h, r.t.; [a] isolated yield after DDQ oxidation in benzene at r.t.; [b] decomposition of the starting material; [c] no conversion.

Excellent yields (up to 98%) were obtained with branched and longer chain imides, as well as with saccharine or saturated imide derivatives (Table 8, Entry 2-4, 5, 9). The glycin-derived starting material (**170**) could be successfully reacted in 80% yield, representing the first example of a non-cyclic nitrogen protecting group and therefore broadens the scope of the reaction considerably (Table 8, Entry 8). Good yields were also obtained from the succinimide and pyrrolidinone derivatives (**168**) and (**169**) (Table 8, Entry 6 and 7), while decomposition was observed with pyrrolidine (Table 8, Entry 10). As previously noted, the inclusion of the nitrogen atom in a indole or carbazole ring system lowered its basicity and the corresponding cycloadducts were isolated in 70% and 98% yield (Table 8, Entry 11 and 13). On the other side, when the polarity of the molecules was increased by the introduction of potentially coordinating heteroatoms a reduction in the yield was observed. The trimethoxy cycloadduct (**188**) was isolated in 48% yield (Table 8, Entry 12), while the pyridine derivative (**175**) gave no conversion probably because of catalyst decomposition (Table 8, Entry 14). To verify this hypothesis a cross-check experiment was conducted. The addition of dry pyridine to a suspension of the catalyst system in dichloromethane, followed by (**161**) and 2,3-dimethyl-1,3-butadiene (**42**) resulted in no conversion to (**162**) (Scheme 45).
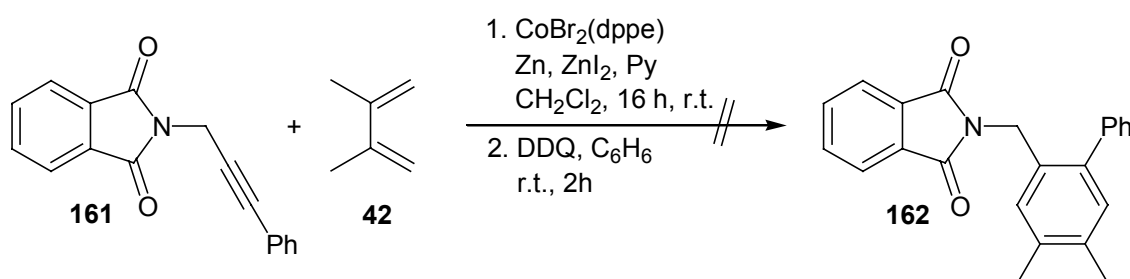
Scheme 45   Attempted *Diels-Alder* reaction in the presence of pyridine

No reaction was also observed when the sterical demand of (**161**) was increased by the exchange of the aromatic ring with a TMS-group (Table 8, Entry 15). This outcome was somewhat surprising, given that trimethylsilyl acetylene (**25**) reacts with 2,3-dimethyl-1,3-butadiene (**42**) under the same conditions affording the dihydroaromatic product (**44**) in 82% yield[31a] (Scheme 46).
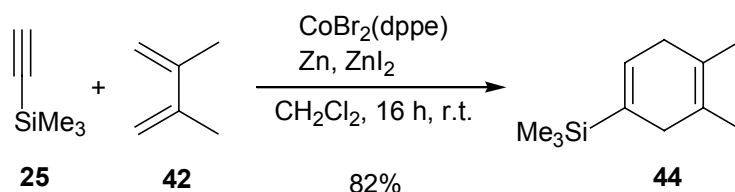
Scheme 46   Synthesis of TMS-substituted 1,4-dienes

These results indicate that the comparatively low yields in the reactions of the internal propargylic amines were probably not based on low reactivity. Further investigations showed that no material was lost during the DDQ oxidation nor during the subsequent purification by column chromatography. However, when (**109**) was added to the catalyst system without addition of 2,3-dimethyl-1,3-butadiene (**42**) decomposition was observed.
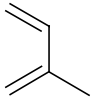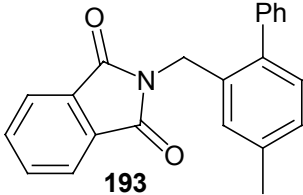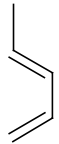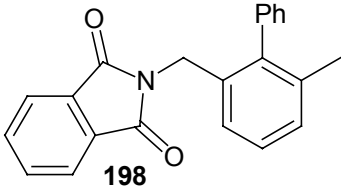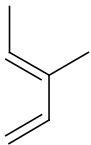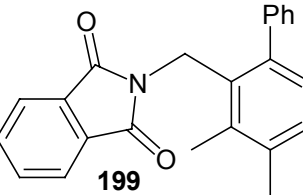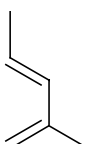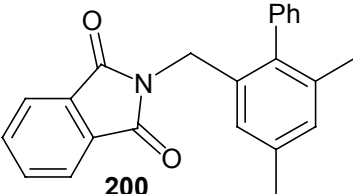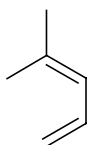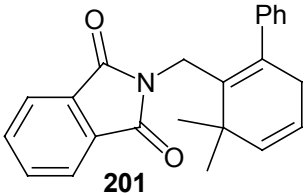
To determine the regiochemical influence of the phthalimide-functionalised alkynes in the reaction with unsymmetrical 1,3-dienes, the internal alkyne (**161**) was reacted with isoprene (**192**) (Scheme 47).
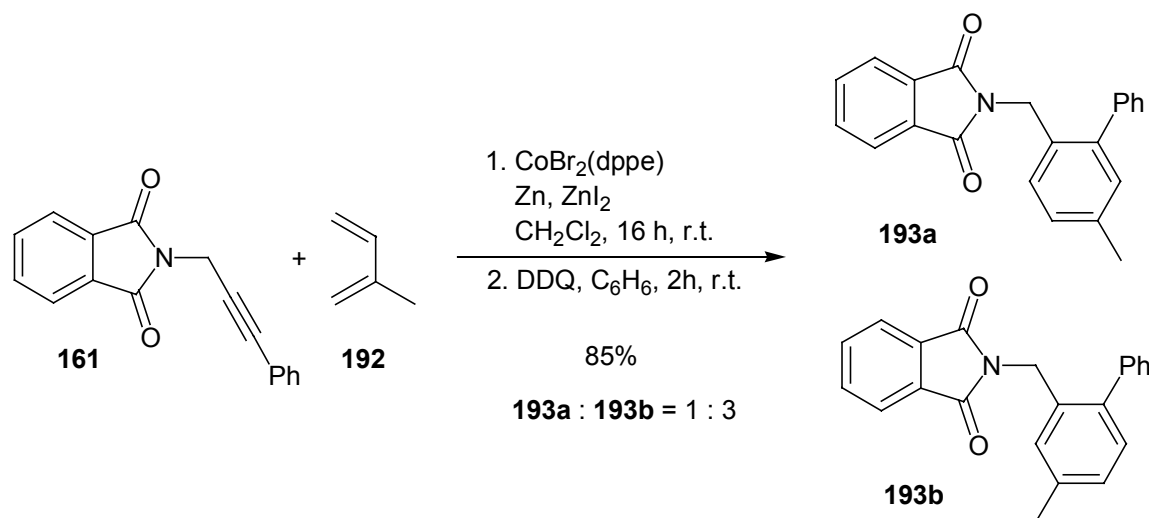
Scheme 47   *Diels-Alder* reaction of (**161**) with isoprene

The two regioisomers (**193a**) and (**193b**) were obtained in 85% yield and in a 1:3 ratio. Since steric hindrance seems to be the major factor in determining the regioselectivity of the reaction[34], the product (**193b**) with the methyl and phenyl substituent in a *para* relationship is favoured over (**193a**). The same principle seems to be applying for other unsymmetrical dienes (Table 9). When the dienes (**194**) and (**195**) were tested in the cobalt(I)-catalysed *Diels-Alder* reaction with 10 mol% of the catalyst at room temperature, the corresponding aromatic products (**198-199**) could be isolated in moderate yields and selectivities after DDQ oxidation (up to 40% yield and 6:1 regioisomeric ratio) (Table 9, Entries 2 and 3). With the sterically more demanding 2-methyl-1,3-pentadiene (**196**) the regioselectivity raised up to 40:1 (Table 9, Entry 4). The higher sterical demand of the diene while coordinated to the cobalt centre could be responsible for the selective formation of one of the two possible regioisomers during the carbon-carbon bond formation step. In all cases no significant improvement in yield nor in regioisomeric ratios were observed by increasing the catalyst loading up to 30% and/or heating up to 60 °C in a sealed tube.

Table 9   *Diels-Alder* reactions of (**161**) with unsymmetrical 1,3-dienes

Entry	Diene	Main product	Ratio[a]	Yield[b](%)
1	**192**	**193**	3:1	85
2	**194**	**198**	6:1	40[c]
3	**195**	**199**	4:1	28
4	**196**	**200**	40:1	41
5	**197**	**201**	—	0[d]

Reagents and conditions: alkyne (1.0 equiv.), CoBr$_2$(dppe) (10 mol%), Zn (50 mol%), ZnI$_2$ (50 mol%), diene (1.5 equiv.), CH$_2$Cl$_2$, 16 h, r.t.; [a] estimated by ^{1}H-NMR; [b] isolated yield after DDQ oxidation in benzene at r.t. except for entry 5; [c] the diene (**194**) contained traces of isoprene (4%, GC), the yield and the ratio were corrected by integration of the ^{1}H-NMR spectrum; [d] no conversion.

No conversion was finally registered with 4-methyl-1,3-pentadiene (**197**) (Table 9, Entry 5), probably because of the high sterical demand of the cobaltacycle intermediate (Scheme 19).

2 Synthesis of heterocyclic compounds *via* cobalt(I)-catalysed *Diels-Alder* reaction

2.1 Dihydropyridine derivatives

In recent years the synthesis of heteroatom substituted dienes and their use in heterocycle synthesis has become an area of major interest[80b]. Following the investigation on cobalt(I)-catalysed *Diels-Alder* reactions, the attention was focused on 2-azadienes[82] of type (**202**) as possible substrates for the synthesis of highly substituted dihydropyridine derivatives (Scheme 48).
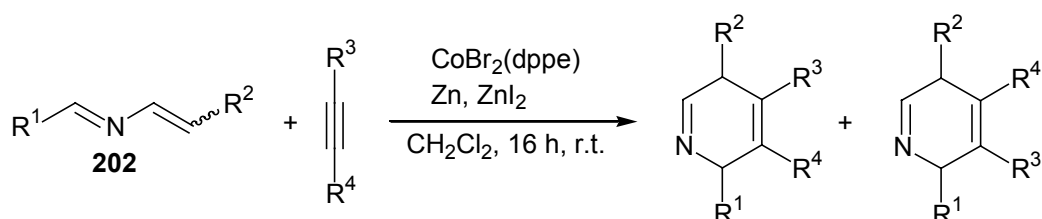
Scheme 48 Azadienes in the cobalt(I)-catalysed *Diels-Alder* reaction

The reaction with (*E*)-2-aza-1-phenyl-1,3-butadiene[83] (**203**) and phenylacetylene (**24**) under standard conditions (10% catalyst, Zn, ZnI_2, 16 h, room temperature) resulted in no conversion to (**204**) (Scheme 49).
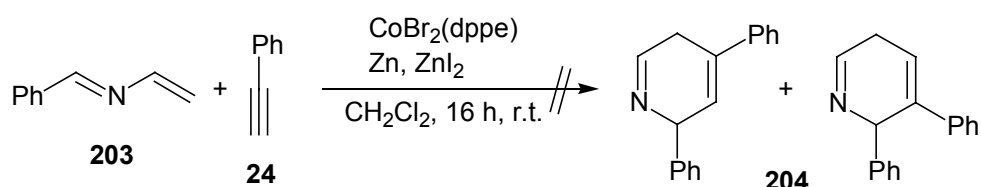
Scheme 49 Attempted synthesis of dihydropyridine derivatives

Further experiments with higher temperatures and catalyst loadings, as well as with Bu_4NBH_4 as reducing agent, were not successful.

2.2 Piperidone and thiopiperidone derivatives

In continuing the research of heterocycle synthesis, phenylisocyanate (**205**) and phenyl isothiocyanate (**206**) were also envisioned as possible starting materials. The cobalt(I)-catalysed *Diels-Alder* reaction with acyclic 1,3-dienes such as 2,3-dimethyl-1,3-butadiene (**42**) should afford piperidone and thiopiperidone derivatives[84] (**207-208**) (Scheme 50). Unfortunately, it was not possible to obtain any product.
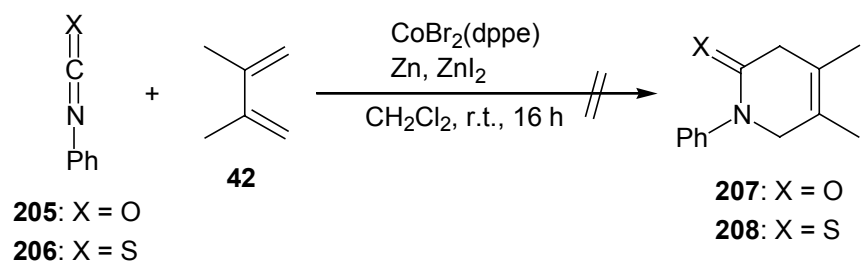
Scheme 50   Attempted synthesis of piperidone and thiopiperidone derivatives

In both cases a combination of catalyst decomposition and unreactivity of the starting materials was believed to be responsible for the negative results.

3 Synthesis of dibenzo-azepine derivatives

Various heterocyclic compounds containing a dihydroisoindolinone skeleton (Figure 4) show important biological activities and many of these exhibit non-nucleosidic HIV-reverse transcriptase inhibitory[85], antihypertensive[86], antipsychotic[87], antiinflammatory[88], anesthetic[89], antiulcer[90] and vasodilatatory[91] properties. Antiviral[92], antileukemic[93a1,b] and platelet aggregation inhibitory[93c] properties have also been reported.
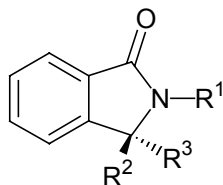
Figure 4 Dihydroisoindolinone skeleton

Isoindolinone derivatives have been widely used as building blocks for the synthesis of various drugs[94] and natural products[95] such as *Lennoxamine* (**209**) and *Chilenine* (**210**), isolated from the Chilean barberries *Berberis darwinii* and *Berberis empetrifolia*, and belonging to the isoindolobenzazepine alkaloids[96] (Figure 5).
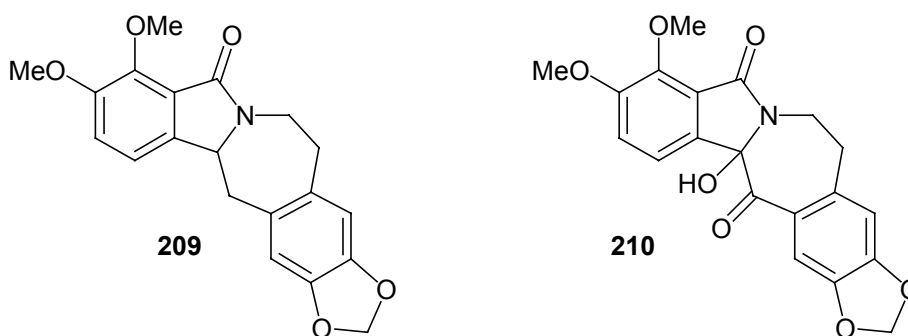
Figure 5 (±)-*Lennoxamine* (**209**) and (±)-*Chilenine* (**210**)

As reported by *Hilt*[97] nitrogen-protected internal alkynes can be successfully employed as starting materials for the cobalt(I)-catalysed *Diels-Alder* reaction with 1,3-dienes. The products of type (**212**) can be used as valuable building blocks for the synthesis of polycyclic heterocyclic compounds with a dihydroisoindolinone skeleton (**214**) *via N*-acyliminium cyclisation, as shown in Scheme 51.
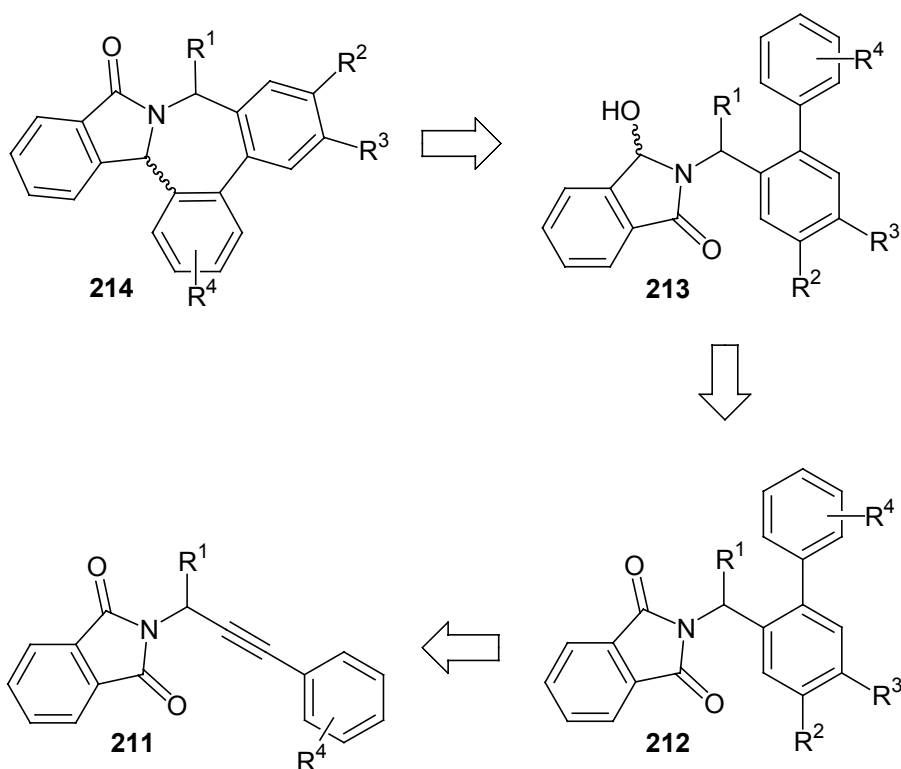
Scheme 51   Retrosynthetic analysis of the isoindolobenzazepine ring system

This approach is well documented by *Decroix*[98] and allows the synthesis of a wide variety of derivatives[99] in a relatively short and efficient synthetic route.

The protected propargylic amines of type (**215**) can be easily prepared[100] from cheap and commercially available starting materials such as phthalimide and propargyl bromide (or longer chain alkynyl halides). The corresponding aryl propargylic derivatives (**217**) were synthesised by the *Sonogashira*[81] reaction with iodoarenes (Scheme 52).
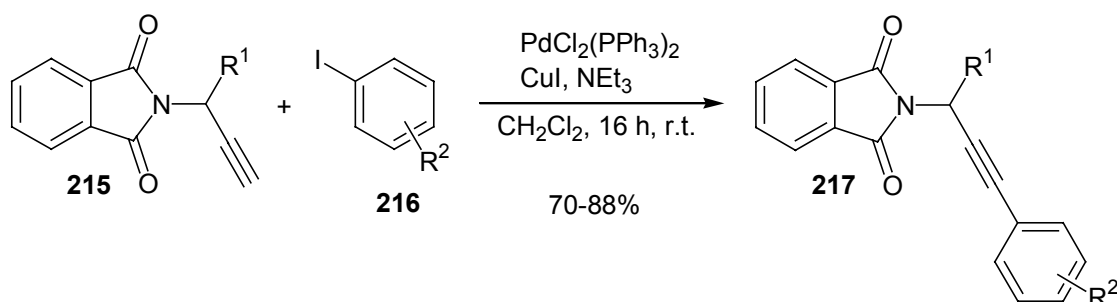
Scheme 52   *Sonogashira* cross-coupling reaction with terminal alkynes

The *Sonogashira* reaction has been extensively used in organic synthesis[101]. Propargylic compounds can be successfully used as reagents in cross-coupling reactions with a variety of functionalised iodo-arene derivatives. Using catalytic amounts of PdCl$_2$(PPh$_3$)$_2$ (5 mol%) and

CuI (5 mol%) in the presence of an excess of triethylamine the reaction proceeded smoothly at room temperature and the corresponding products were obtained in 70-88% yield after column chromatography, as reported in Table 10.

Table 10   *Sonogashira* coupling with terminal alkynes
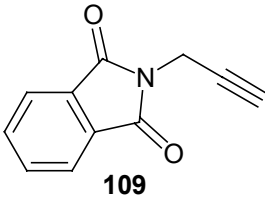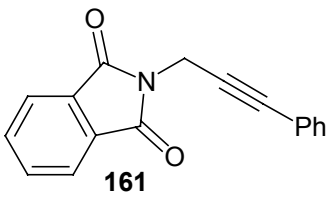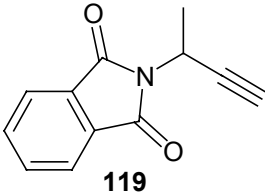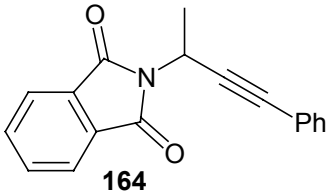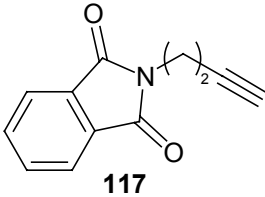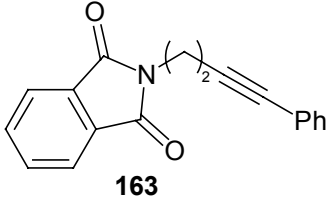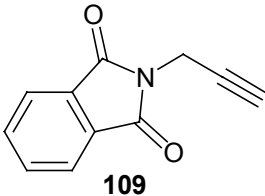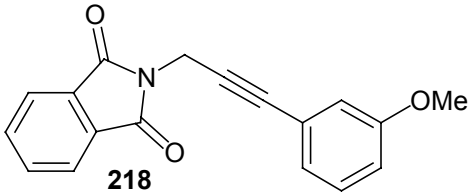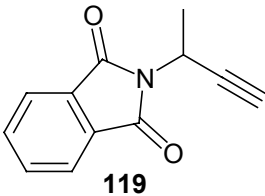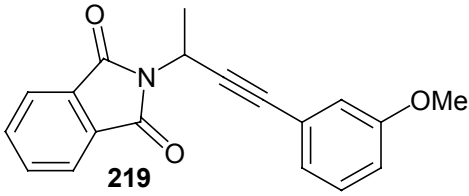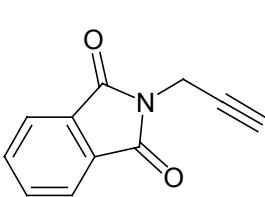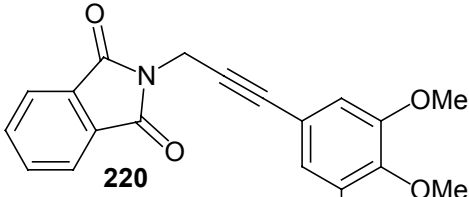
Entry	Protected amine	Product	Yield[a] (%)
1	**109**	**161**	70
2	**119**	**164**	81
3	**117**	**163**	77
4	**109**	**218**	76
5	**119**	**219**	84
6	**109**	**220**	70

Table 10   *Sonogashira* coupling with terminal alkynes *(cont.)*

Entry	Protected amine	Product	Yield[a] (%)
7	**117**	**221**	80
8	**109**	**222**	70
9	**109**	**223**	79
10	**109**	**224**	88

Reagents and conditions: alkyne (1.0 equiv.), iodo-arene (1.2 equiv.), PdCl$_2$(PPh$_3$)$_2$ (5.0 mol%), CuI (5.0 mol%), NEt$_3$ (5.0 equiv.), CH$_2$Cl$_2$, 16 h, r.t.; [a] yield not optimised.

As expected, the cobalt(I)-catalysed reaction with 2,3-dimethyl-1,3-butadiene (**42**) on *Sonogashira* products proceeded under mild conditions and with an acceptable reactivity (10% catalyst, room temperature, 16 h) (Table 11, Entry 1). Moderate increase of the sterical hindrance on both sides of the triple bond did not affect the reactivity and the desired *Diels-Alder* products could be isolated in excellent 90% and 98% yield (Table 11, Entry 5 and 7). However, when the methyl group of (**164**) was substituted with a branched and more sterically demanding side chain[102] no reaction was observed, even with higher catalyst loading and heating up to 60 °C in a sealed tube (Scheme 53).
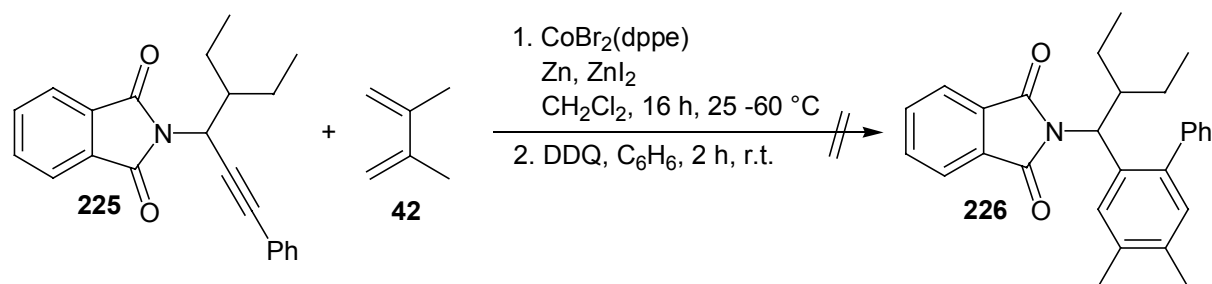
Scheme 53   Attempted *Diels-Alder* reaction with a sterically hindered alkyne

The use of hindered dienes such as 2,3-diphenyl-1,3-butadiene (**227**) resulted in no conversion (Scheme 54), probably because of the steric hindrance of the reagent. The lack of reaction with the electron rich diene (**228**) could instead be rationalised by coordination of the methoxy group to the catalyst and subsequent inactivation.
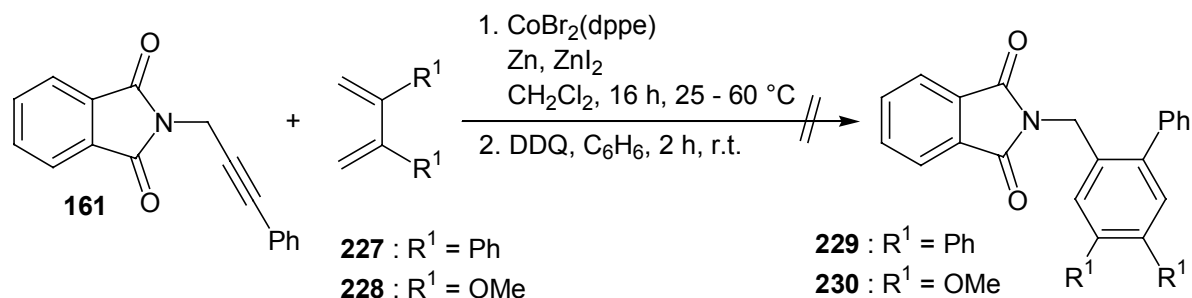
Scheme 54   Attempted *Diels-Alder* reactions with hindered or electron rich dienes

Higher yields were obtained with the corresponding longer chain imides (Table 11, Entry 9 and 10). When isoprene was substituted with 2-methoxy-1,3-butadiene (Table 11, Entry 6) the cycloadduct was isolated in an acceptable 57% yield and in 6:1 regioisomeric ratio (estimated by ^{1}H-NMR). As previously discussed, the phenyl group seems to be the directing group favouring the product (**235**), where the methoxy- and the phenyl-substituents are in a 1,4-relation. On the basis of these considerations a further reduction of the reactivity was expected with 2,5-norbornadiene (**7**). Surprisingly, the reaction proceeded under the usual conditions and the polycyclic product (**238**) was isolated in an excellent 98% yield (Table 11, Entry 11). Electronic effects moderately influenced the cycloaddition. When the aromatic ring introduced with the *Sonogashira* reaction beared an activating substituent such as a methoxy group the yields were higher (Table 11, Entry 1-3). On the other side, only a 76% yield was obtained when a carboxylic ester group was present. (Table 11, Entry 1 and 11). When the polarity of the molecules was increased by the introduction of potentially coordinating heteroatoms a reduction in the yield was observed. The trimethoxy derivative (**233**) was

isolated in 77% yield (Table 11, Entry 4). The same effect was registered for the corresponding longer chain imides (Table 11, Entry 9 and 10).

Table 11   Cobalt(I)-catalysed *Diels-Alder* reaction of internal alkynes
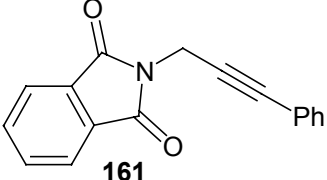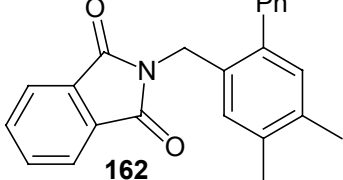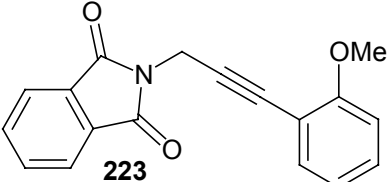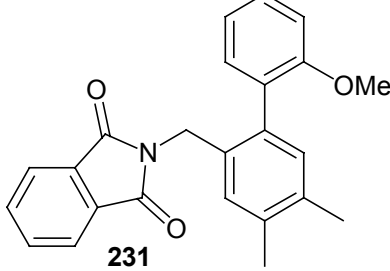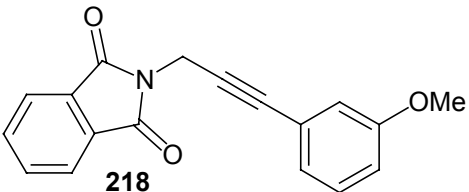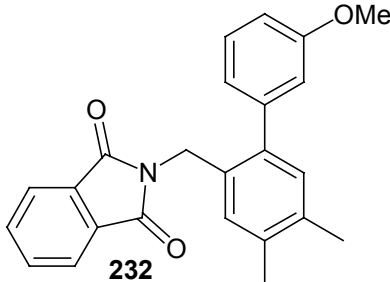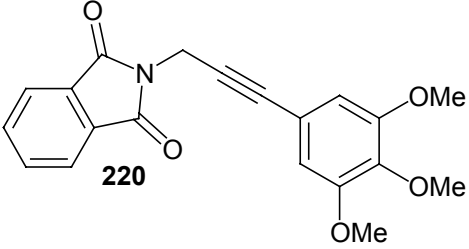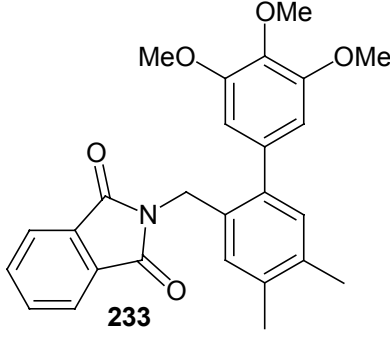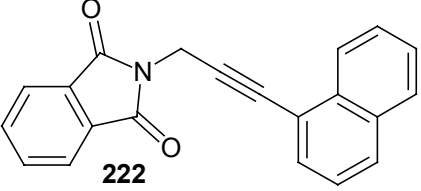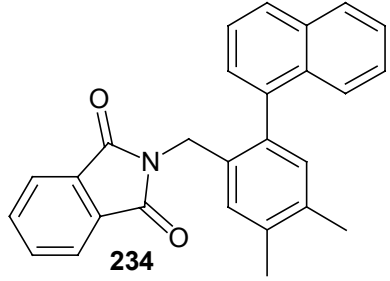
Entry	Protected amine	Product	Yield[a] (%)
1	161	162	80
2	223	231	83
3	218	232	90
4	220	233	77
5	222	234	90

Table 11   Cobalt(I)-catalysed *Diels-Alder* reaction of internal alkynes *(cont.)*
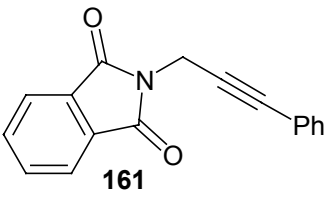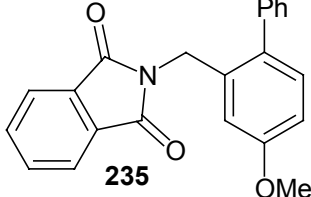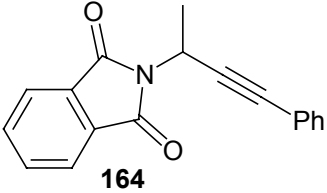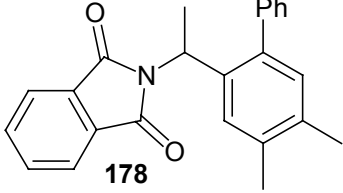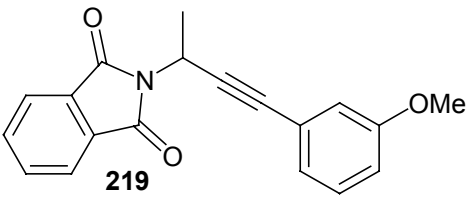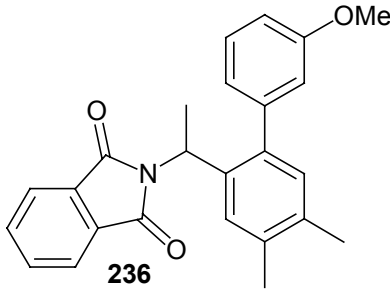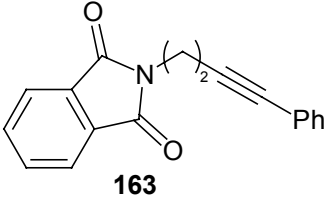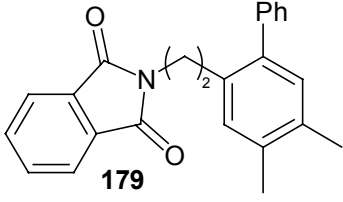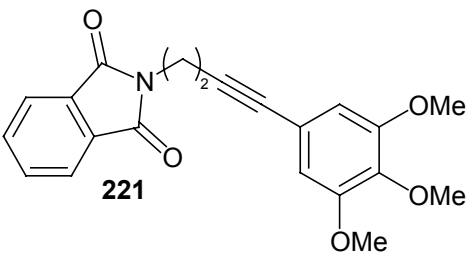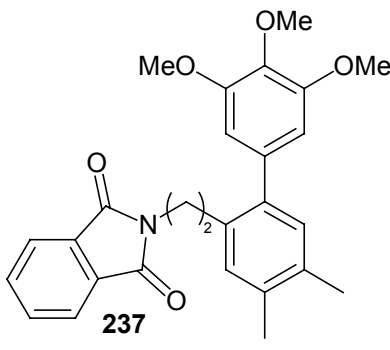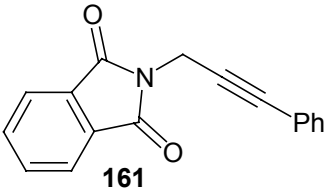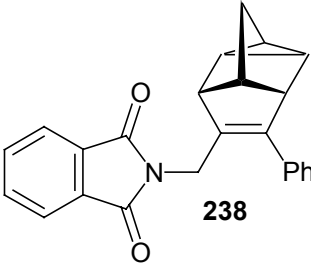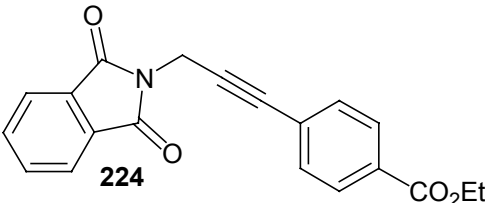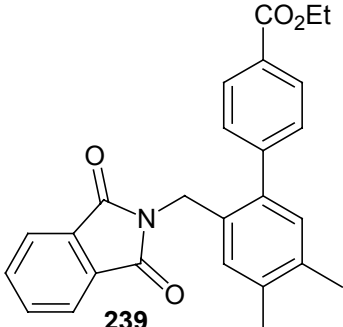
Entry	Protected amine	Product	Yield[a] (%)
6	**161**	**235**	57[b]
7	**164**	**178**	98
8	**219**	**236**	81
9	**163**	**179**	98
10	**221**	**237**	85
11	**161**	**238**	98[c]

Table 11 Cobalt(I)-catalysed *Diels-Alder* reaction of internal alkynes *(cont.)*

Entry	Protected amine	Product	Yield[a] (%)
12	**224**	**239**	76

Reagents and conditions: alkyne (1.0 equiv.), CoBr$_2$(dppe) (10 mol%), Zn (50 mol%), ZnI$_2$ (50 mol%), diene (1.5 equiv.), CH$_2$Cl$_2$, 16 h., r.t.; [a] isolated yield after DDQ oxidation in benzene at r.t., except for entry 11; [b] reaction with 2-methoxy-1,3-butadiene; [c] reaction with 2,5-norbornadiene.
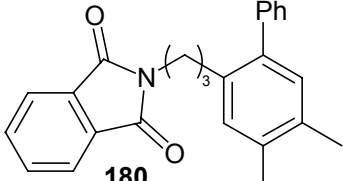
Subsequent chemoselective reduction of the phthalimide functionality furnished the corresponding α-hydroxylactam (**240**) (Scheme 55). All the reactions were performed with an excess of sodium borohydride in mixtures of dry dichloromethane and methanol at 0-5 °C, followed by addition of 0.2 M ethanolic hydrochloric acid solution. In all cases a slow addition was necessary to avoid the formation of side products[103,104]. Although the procedure described by *Decroix* and *Speckamp*[98] had to be slightly modified by the use of mixtures of dichloromethane and methanol, the desired α-hydroxylactams were isolated in excellent yields (up to 98%). A spectroscopic characterisation of the reduction products was not always possible, because they were insoluble in the most common deuterated solvents.

162 → NaBH$_4$, H$^+$ / MeOH/CH$_2$Cl$_2$, 15 min., 0 °C / 98% → **240**
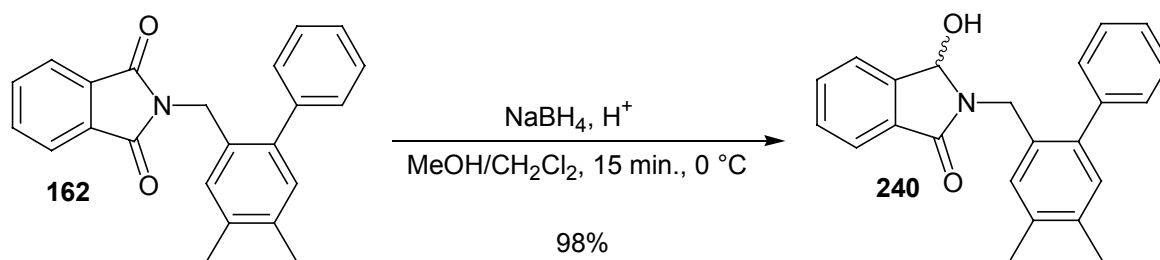
Schema 55 Chemoselective reduction of (**162**) to α-hydroxylactam (**240**)

Therefore they were directly subjected to the cyclization reactions and the yields calculated over two steps. According to *Decroix* and *Speckamp*[98], hydrochloric and trifluoroacetic acid are good catalysts for the intramolecular α-amidoalkylation reaction. Subjection of hydroxylactam (**240**) to trifluoroacetic acid in chloroform for 16 hours at room temperature afforded the cyclised product (**242**) as a racemic mixture, in an excellent 92% yield. The

cyclisation occurred *via* electrophylic attack of the *N*-acyliminium ion[105,106] intermediate (**241**) upon the benzene ring originally introduced by the *Sonogashira* reaction (Scheme 56).
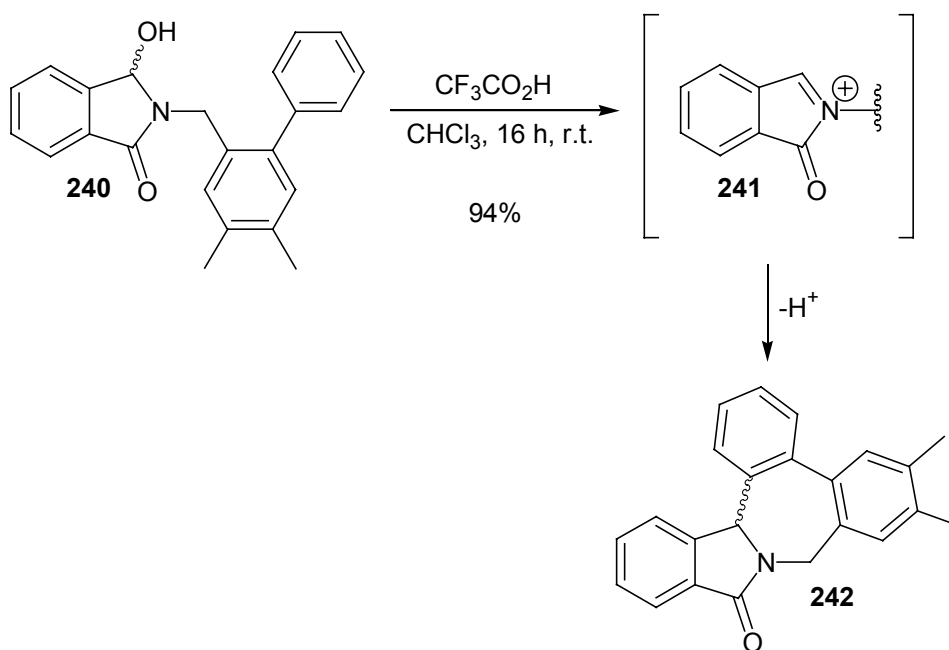
Scheme 56   Acid catalysed cyclisation *via* the *N*-acyliminium ion intermediate (**241**)

This reaction sequence selectively afforded the seven-membered dibenzoazepine (**242**). The formation of alternative cyclisation products derived from the attack of the carbocation (**241**) on the aromatic ring formed during the *Diels-Alder* reaction were not observed, although the electron density is enhanced by the two methyl groups. The corresponding attack from the *para* position (dashed arrow) is unlikely for the formation of highly strained polycyclic compounds (Scheme 57).
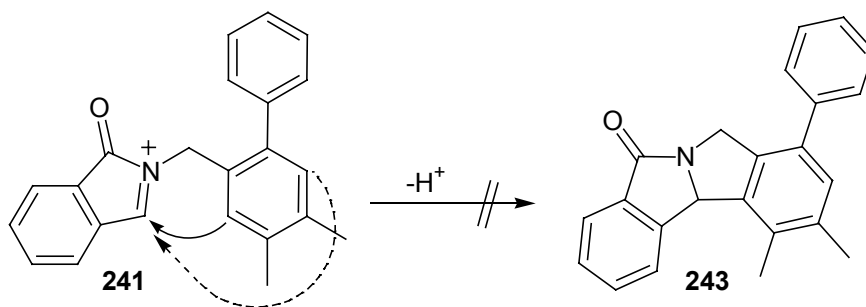
Scheme 57   Alternative cyclisation reactions of the carbocation (241)

No traces of enamide *via* loss of a proton nor degradations were registered. The other α-hydroxylactams were cyclised following the same procedure and the results are summarised in Table 12.

Table 12 Reduction and cyclisation reactions
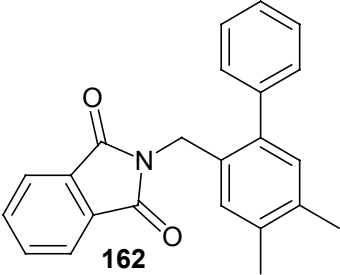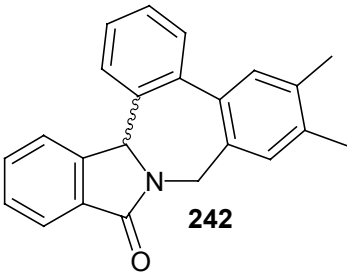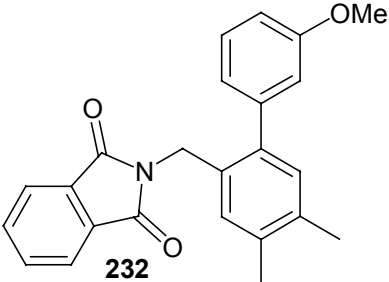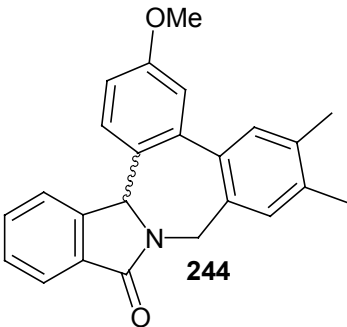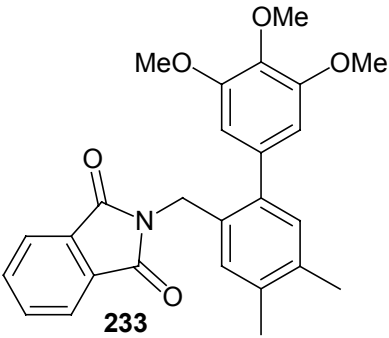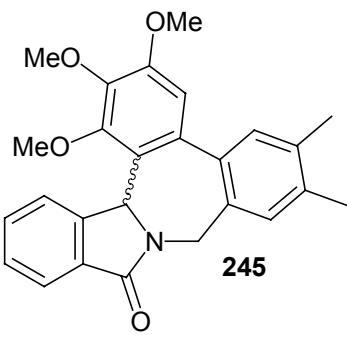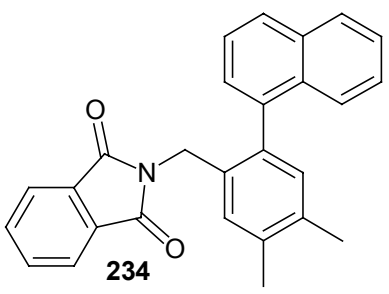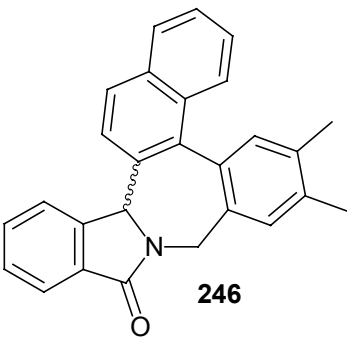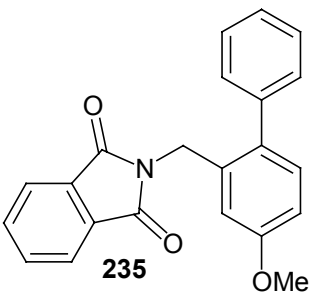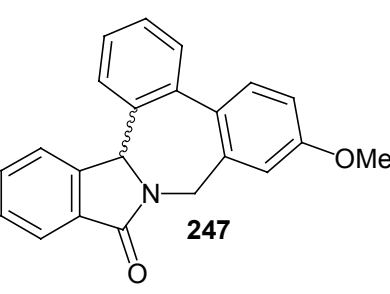
Entry	Substrate	Product	Yield[a] (%)
1	**162**	**242**	92
2	**232**	**244**	92
3	**233**	**245**	96
4	**234**	**246**	91
5	**235**	**247**	83

Table 12   Reduction and cyclisation reactions *(cont.)*
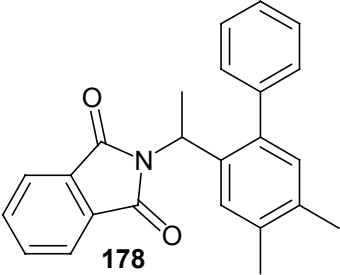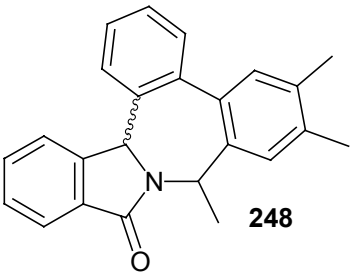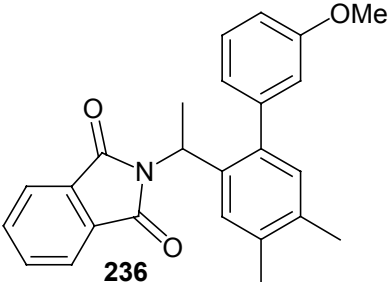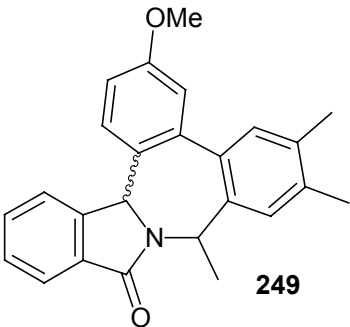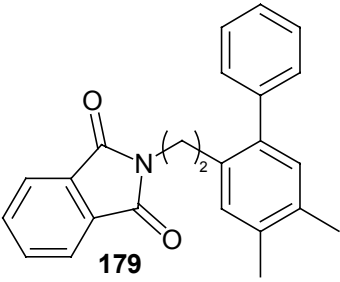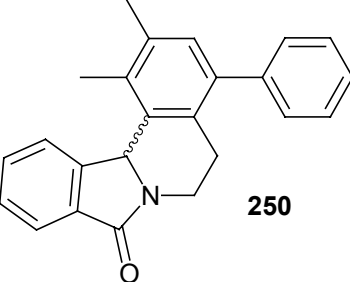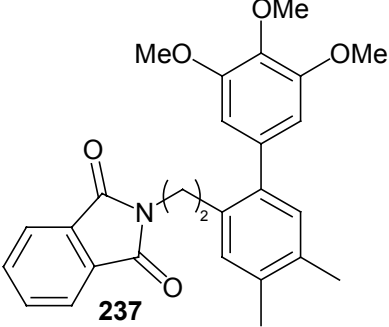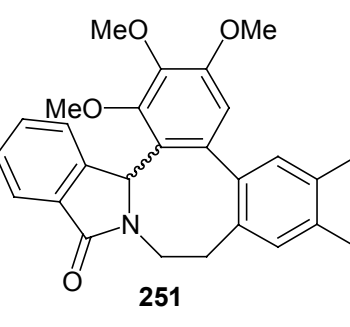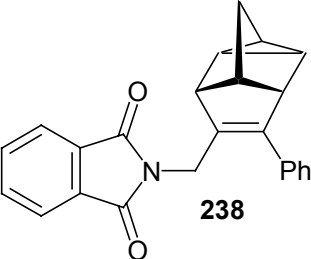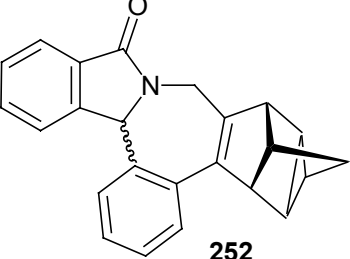
Entry	Substrate	Product	Yield[a] (%)
6	**178**	**248**	87[b]
7	**236**	**249**	90
8	**179**	**250**	60[b]
9	**237**	**251**	85
10	**238**	**252**	97

Table 12   Reduction and cyclisation reactions *(cont.)*

Entry	Substrate	Product	Yield[a] (%)
11	**231**	**253**	0[c]
12	**239**	**254**	0[c]

Reagents and conditions: trifluoroacetic acid, CHCl₃, 16 h; [a] calculated yield over two steps; [b] toluene, 110 °C, reflux; [c] no conversion.

Interestingly, when a catalytic amount of acid was used the starting materials were recovered unreacted. Under strong acidic conditions the cyclisation occurred in excellent yields, even for the less favourable eight membered ring (**251**) (Table 12, Entry 9). The reaction sequence led to the formation of a new stereogenic center inducing a crown conformation and resulting in an axial chirality of the biaryl moiety (Scheme 58).

1. NaBH₄, H⁺
   MeOH/CH₂Cl₂, 15 min., 0 °C
2. CF₃CO₂H, CHCl₃, 16 h, r.t.

85%
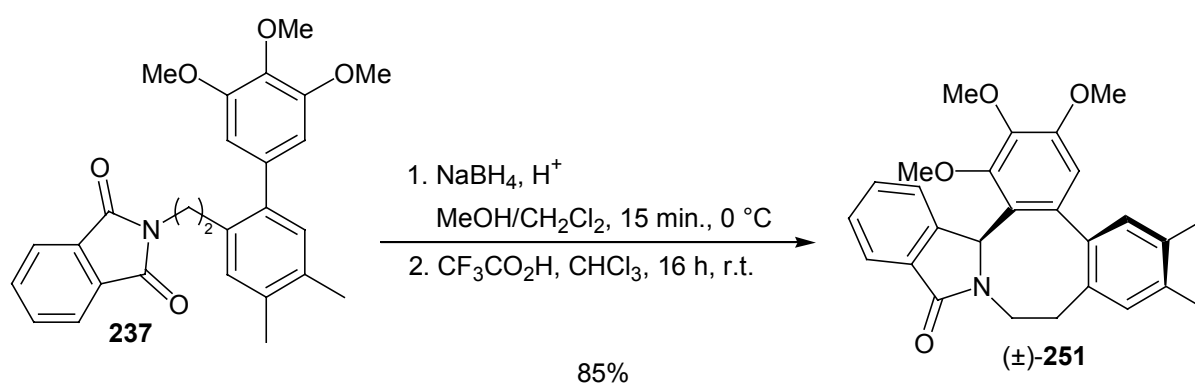
Scheme 58   Ring closure of (**237**) to eight membered ring (±)-(**251**)

Consequently, diastereomeric products can be expected. The crude NMR spectra of (**251**) showed a double set of signals that arised from the mixture of diastereoisomers. Their separation was not possible by column chromatography on silica gel and a single fraction

containg both the diastereoisomers was obtained in 85% yield and in a 3:1 ratio. High temperature ^{1}H-NMR (*d*-DMSO, 100 °C) showed no ring inversion. Diastereoisomers separation could instead be accomplished by preparative HPLC with *n*-Hexan:*i*-PrOH 100:7 as eluent. Two racemic fractions were obtained and characterisation by two dimensional NMR techniques confirmed for both the proposed eight members ring structure. X-ray diffraction of a single crystal from the major portion showed that the eight-membered ring system is locked in a crown-like conformation (Figure 6). Attempted crystallisation of the minor fraction was unsuccessful and furnished only amorphous material.
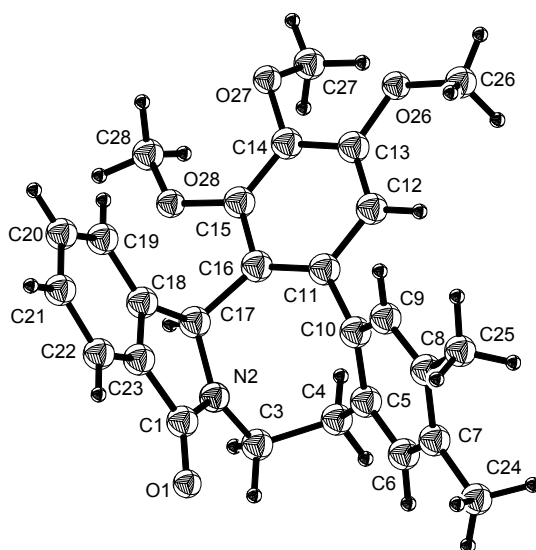
Figure 6   Crystal structure of (±)-(**251**)

The cyclisation at room temperature under standard conditions was unsuccessfull with the α-hydroxylactams derived from (**178**) and (**179**). Hence, they were refluxed in dry toluene with an excess of trifluoroacetic acid. After work-up the cyclised products (**248**) and (**250**) were isolated in 87% and 60% yield (Table 12, Entry 6 and 8). NMR investigation confirmed that the expected seven membered ring was formed from (**178**) as a 7:1 mixture of diastereoisomers, that were successively separated by column chromatography on silica gel. A six membered ring structure was instead proposed for (**250**) (Scheme 59).
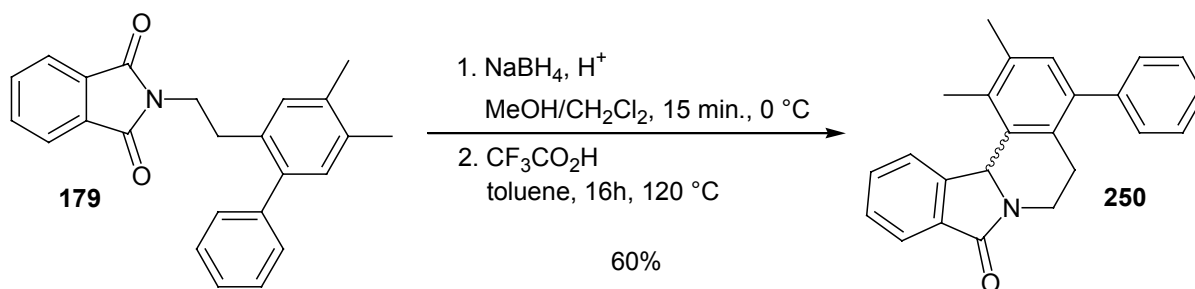
Scheme 59   Thermal ring closure to (**250**)

This result could be explained assuming an intramolecular electrophilic attack of the more electron rich aromatic ring introduced with the *Diels-Alder* reaction on the *N*-acyliminium ion intermediate (Scheme 59). The x-ray analysis subsequently confirmed the proposed structure for (**250**) (Figure 7).
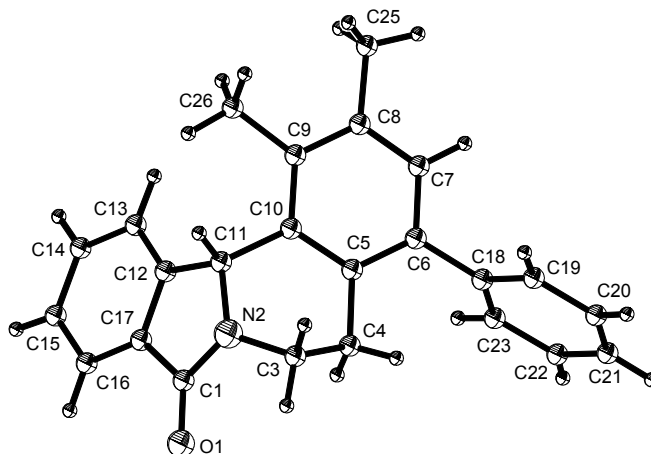
Figure 7   Crystal structure of (**250**)

When the aromatic ring introduced by the *Sonogashira* reaction was activated by electron donating substituents the cyclisations proceeded in yields up to 96% (Table 12, Entry 2, 3 and 7). The structure of the products could be easily predicted following the usual rules for the electrophilic aromatic substitution. When the biaryl system beared a methoxy group in a 3' position two products with a seven membered ring structure became possible. Because of the steric hindrance the *ortho* attack to the *N*-acyliminium ion was in both cases disfavoured and only the products (**244**) and (**249**), derived from *para* attack, were selectively obtained in 92% and 90% yield (Scheme 60 and Figure 8).

232 : R^1 = H
236 : R^1 = Me

1. $NaBH_4$, H^+
   $MeOH/CH_2Cl_2$, 15 min., 0 °C
2. CF_3CO_2H, $CHCl_3$, 16 h, r.t.

244 : R^1 = H : 92%
249 : R^1 = Me : 90%
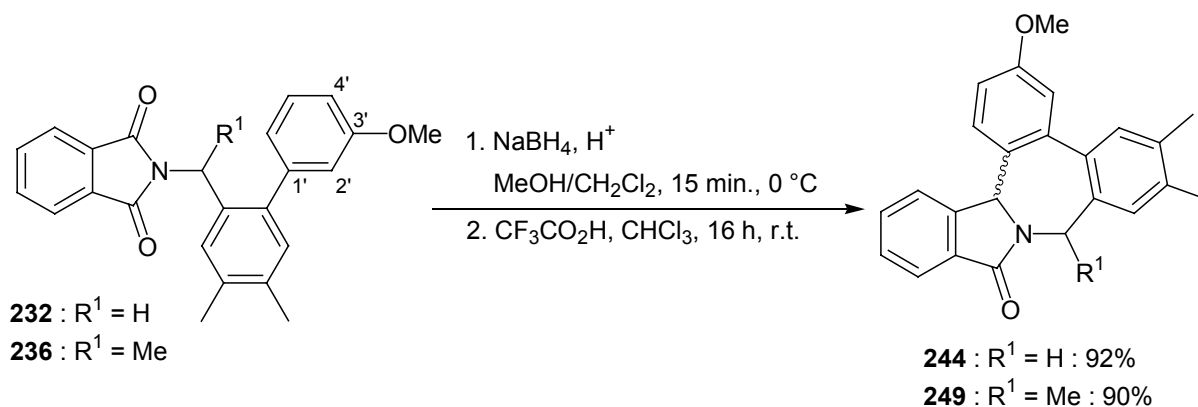
Scheme 60   Selective ring closure of (**232**) and (**236**)
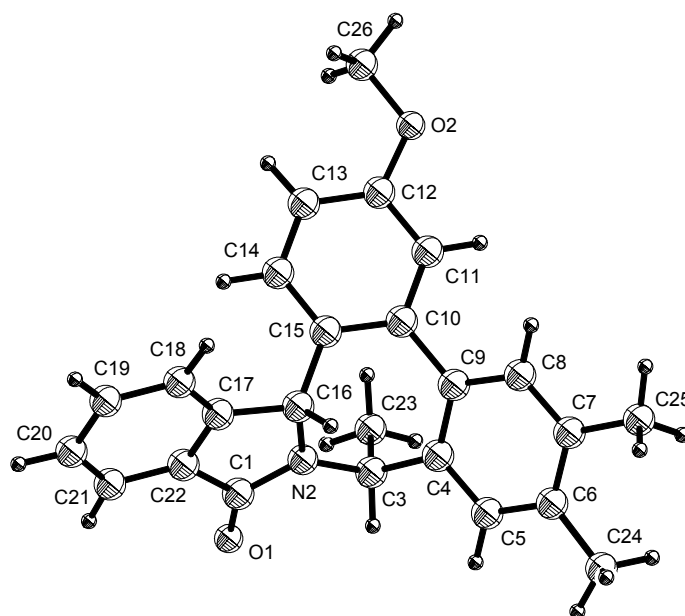
Figure 8   Crystal structure of (**249**)

If the methoxy group was placed in a 2' position the *meta* attack leading to the seven membered ring became not possible, while *ortho* and *para* attack would afford constrained eight membered systems. Under standard acidic conditions no conversion was registered and the corresponding α-hydroxylactam was recovered unreacted (Table 12, Entry 11). No cyclisation occurred when a deactivating group such as a carboxylic ester was present on the 4' position of the biaryl system (Table 12, Entry 12). The introduction of a methoxy group on position 4 of the biaryl system (*via Diels-Alder* reaction of (**161**) with 2-methoxy-1,3-butadiene (**255**)) did not enhance the formation of a five membered ring. Subjection of (**235**) to the standard reduction-cyclisation procedure afforded selectively (**247**) in 83% overall yield (Scheme 61 and Figure 9).
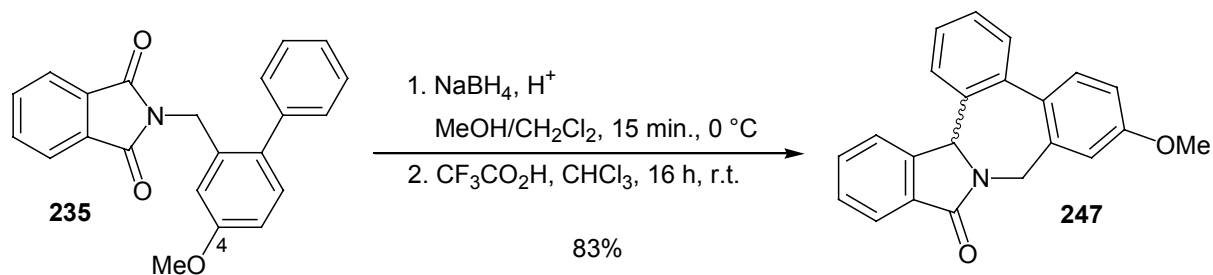
Scheme 61   Acid catalysed cyclisation of (**235**)
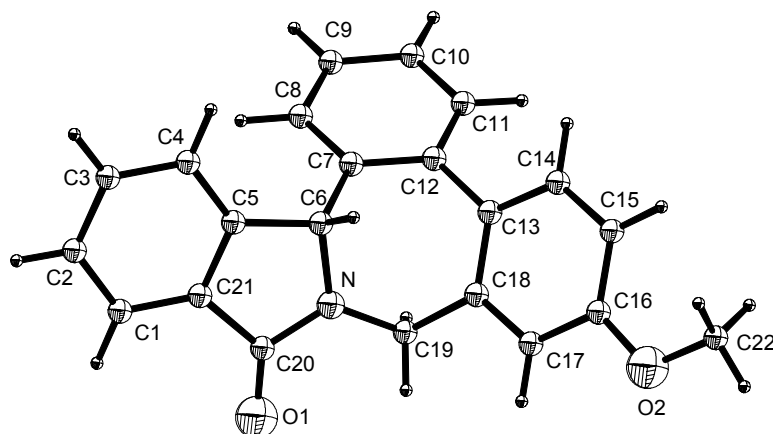
Figure 9 Crystal structure of (**247**)

The number of possible products with a dihydroisoindolinone skeleton could also be enlarged by introducing polycyclic aromatic compounds in the *Sonogashira* cross-coupling reaction. If 1-iodo naphthalene is used as a model for more complex aromatic systems, the *Friedel-Crafts* type cyclisation could lead to a variety of alkylation products. However, among several possibilities, only the product (**246**) was formed in 91% yield (Scheme 62 and Figure 10).
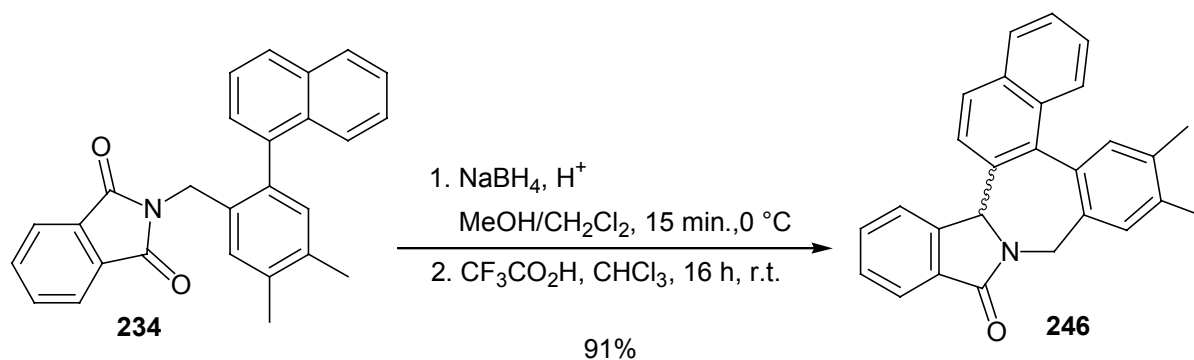
Scheme 62 Ring closure of 1-iodo naphthalene derivatives

The acid-catalysed cyclisation proceded under the usual conditions with the norbornadiene derivative (**238**), and the corresponding seven membered ring product was isolated in an excellent 97% yield (Scheme 63). X-ray diffraction of a single cristal subsequently confirmed the proposed structure of the product (Figure 11).
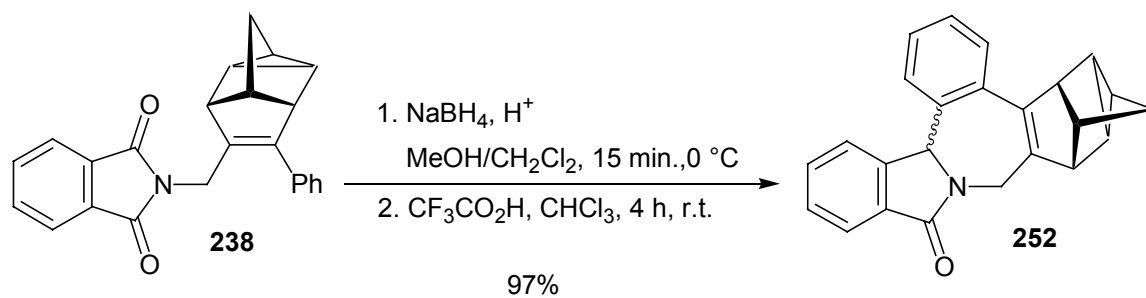
Scheme 63   Cyclisation of the deltacyclene (**252**)
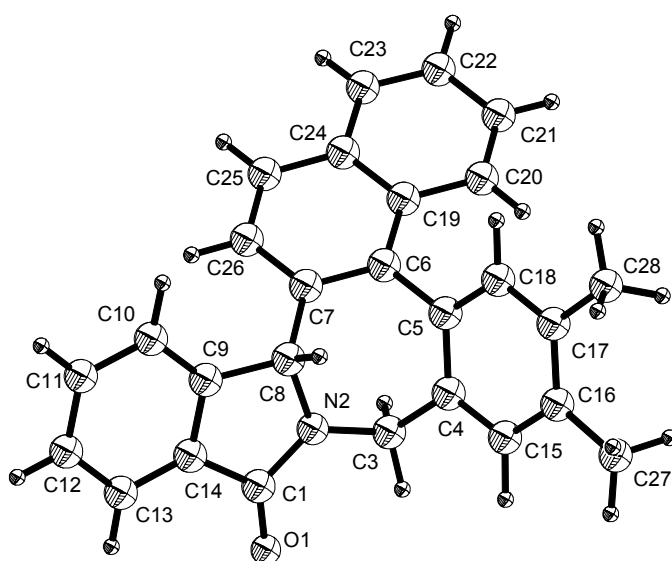
Figure 10   Crystal structure of (**246**)
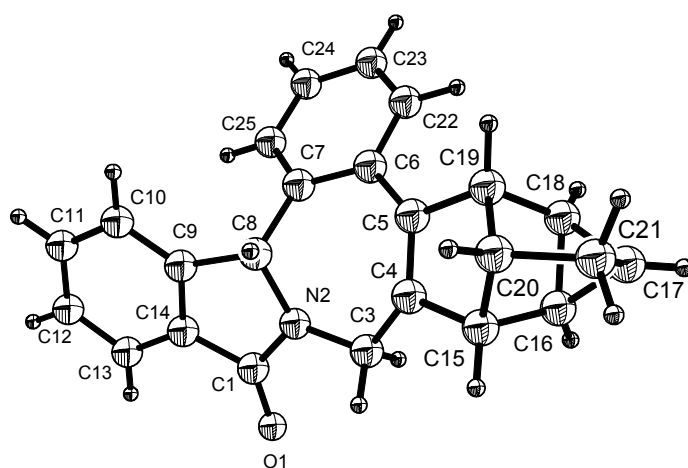
Figure 11   Crystal structure of (**238**)

Since it has been reported that α-chloroalkylamides served as a *N*-acyliminium ion source[107], some reactions were attempted in the presence of thionyl chloride. In contrast to literature results, the yields were often lower and accompanied by degradation products.

Because of the excellent regioselectivity of the cobalt(I)-catalysed *Diels-Alder* reaction with 2-methyl-1,3-pentadiene (Table 9, Entry 4) the cyclisation sequence was also tested on the cycloadduct (**200**). Under standard conditions (excess of trifluoroacetic acid, 16 h, room temperature) the α-hydroxylactam was recovered unreacted. When it was refluxed in toluene overnight no cyclisation occurred. Surprisingly, the tolyl substituted product (**257**) was isolated in 85% yield (Scheme 64).
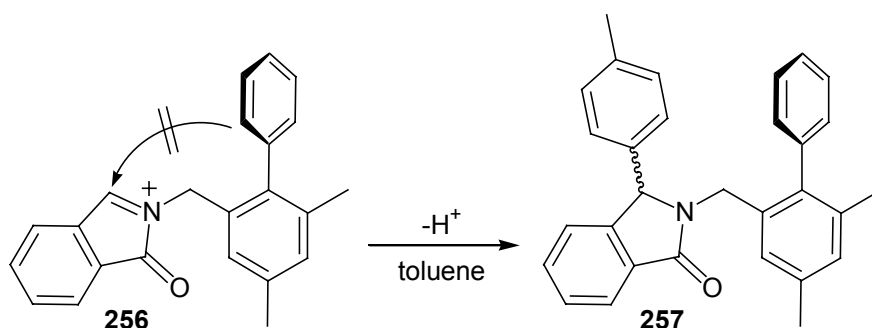
Scheme 64   Unexpected tolyl substituted product formation

This could be explained assuming that the restricted rotation of the biaryl system prevented the adoption of the right angle for the ring closure reaction. Therefore the iminium ion (**256**) reacted with the only nucleophilic molecule available, the solvent.

4 Catalytic C-H activation by means of metal-carbenoid induced C-H insertion

4.1 Rhodium(II)-catalysed C-H activation and cyclopropanation

The research of efficient ways to construct complex chemical structures from readily available starting materials continues unabated. C-H activation by means of rhodium-carbenoid induced C-H insertion represents one of the major progresses in synthetic organic chemistry of the last decades[108]. *Müller* reported that $Rh_2(OAc)_4$ catalyses the decomposition of ethyl 2-diazopropionate (**259**) in the presence of 1,4-cyclohexadiene (**258**) affording the insertion product (**260**) in 82% yield, while the formation of the cyclopropane (**261**) could not be detected[109] (Scheme 65).
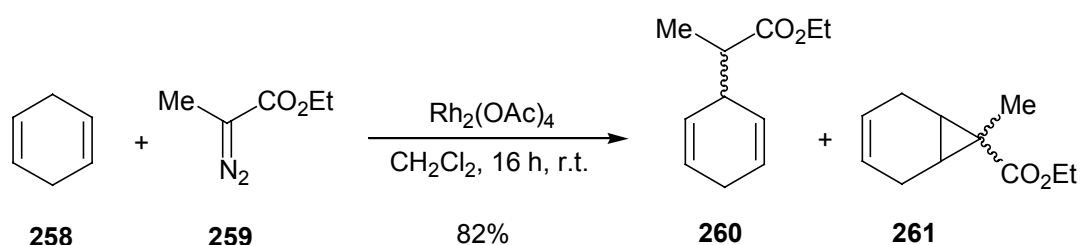
Scheme 65   Rhodium-catalysed C-H activation reaction on 1,4-cyclohexadiene

Since the cobalt(I)-catalysed *Diels-Alder* reaction of alkynes and acyclic 1,3-dienes is a powerful tool for the generation in excellent yields of dihydroaromatic compounds of type (**60**) (Scheme 19), a possible approach to highly substituted benzene derivatives (**262**) was envisioned (Scheme 66).
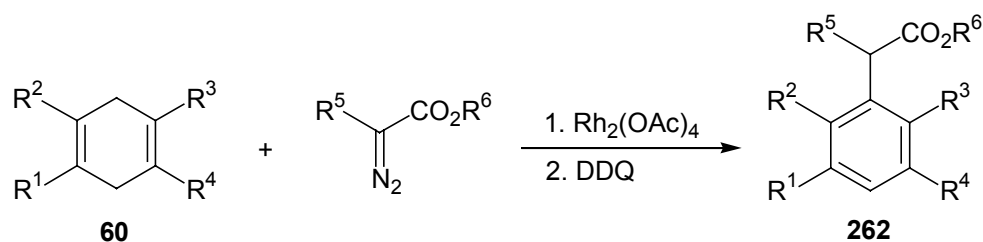
Scheme 66   Synthesis of highly substituted benzene derivatives *via* rhodium-carbenoid induced C-H insertion

Because the experimental procedure described by *Müller*[109] was believed to be not suitable, especially regarding the considerable excess of the reacting 1,4-diene (10 equivalents!), an optimisation process was started first. Preliminary tests with the diene (**43**) and ethyl

diazoacetate (EDA) (**263**) showed that in all cases mixtures of insertion (**264**) and cyclopropanation (**265**) products were formed (GC-MS) (Scheme 67 and Table 13).
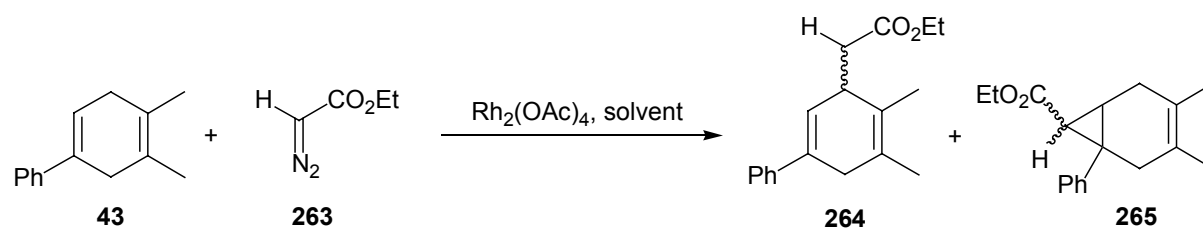
Scheme 67   Preliminary tests with ethyl diazoacetate (**263**)

Table 13   Intermolecular C-H insertion/cyclopropanation of EDA with 1,4-diene (**43**)

Entry	Diene:EDA	Solvent	Rh$_2$(OAc)$_4$ (mol%)	Temp.	Addition time	Conversion to 264 and 265[a]
1	1 : 1	CH$_2$Cl$_2$	10	25 °C	5 min.	Traces
2	1 : 3	CH$_2$Cl$_2$	10	25 °C	5 min.	Complete
3	1 : 1	CH$_2$Cl$_2$	10	25 °C	5 min.	One pot – no conversion
4	1 : 1	CH$_2$Cl$_2$	2	25 °C	5 min.	Traces
5	1 : 3	CH$_2$Cl$_2$	2	25 °C	5 min.	Complete
6	**1 : 3**	**CH$_2$Cl$_2$**	**2**	**0 °C**	**30 min.**	**Complete**
7	1 : 3	Toluene	2	0 °C	30 min.	Traces
8	1 : 3	Et$_2$O	2	0 °C	30 min.	Traces

Reagents and conditions: addition of EDA (**263**) in CH$_2$Cl$_2$ (2 ml) to (**43**) (1.0 equiv.) in CH$_2$Cl$_2$ (3 ml) and Rh$_2$(OAc)$_4$; [a] results after GC-MS control of the crude reaction mixture, products (**264**) and (**265**) were not isolated.

If equimolar ratios of (**43**) and (**263**) were used, traces of cyclopropanation and insertion products were detected, probably because of competing 1,2-hydrogen migration from the rhodium carbenoid[56] (Table 13, Entry 1 and 4). Complete conversion was achieved with an excess of diazoester (**263**) at room temperature as well as at 0 °C (Table 13, Entry 2, 5 and 6). However, because of the strong heat evolution during the reaction, an ice cooling bath is advisable. When EDA (**263**) was added to the crude *Diels-Alder* reaction mixture no conversion was observed (Table 13, Entry 3). The substitution of dichloromethane with toluene or diethyl ether gave only traces of the desired products even with an excess of the diazoester (Table 13, Entry 7 and 8). In a further set of experiments ethyl diazoacetate (**263**) was substituted with ethyl 2-diazopropionate (**259**) and methyl 2-diazophenylacetate (**92**) (Scheme 68 and Table 14).
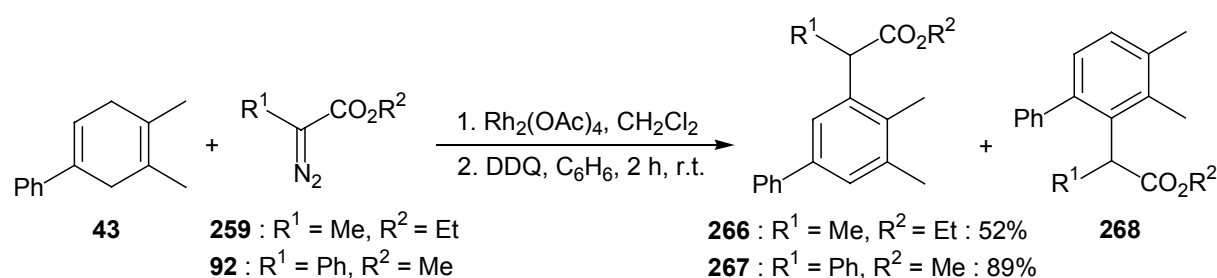
Scheme 68   Intermolecular C-H insertion on diene (**43**)

As reported by *Müller* and *Tohill*[109], the two double bonds in a 1,4-relationship of the 1,4-cyclohexadiene (**258**) are enhancing the reactivity of the allylic positions towards C-H activation with the diazoesters (**259**) (Scheme 65). A similar effect was also expected for the diene (**43**). Indeed, the reactions depicted in Scheme 68 showed remarkable selectivity for C-H activation and no cyclopropanes were detected in the reaction mixtures. The reactions showed also absolute regiocontrol and product of type (**266-267**) were selectively obtained (Figure 12 and 13).

Table 14   Optimisation of the reaction in Scheme 68

Entry	Diazoester	Diene:diazoester	Rh$_2$(OAc)$_4$ (mol%)	Temp.	Addition time	Yield[a] (%)
1	259	1 : 3	2	0 °C	60 min.	58
2	259	1 : 3	2	-18 °C	60 min.	59
3	259	1 : 3	2	-78 °C	60 min.	0
4	259	1 : 2	2	0 °C	5 min.	30
5	**259**	**1 : 2**	**0.5**	**0 °C**	**60 min.**	**52**
6	259	1 : 2	0.5	0 °C	60 min.	30[b]
7	92	1 : 3	2	0 °C	60 min.	70
8	**92**	**1 : 2**	**0.5**	**0 °C**	**60 min.**	**89**
9	92	1 : 2	0.5	0 °C	60 min.	78[b]

Reagents and conditions: syringe pump (1 h) or syringe (5 min) addition of (**259**) or (**92**) in CH$_2$Cl$_2$ (2 ml) to (**43**) (1.0 equiv.) in CH$_2$Cl$_2$ (3 ml) and Rh$_2$(OAc)$_4$; [a] isolated yield after DDQ oxidation in benzene at r.t.; [b] diene (**43**) was stored for 24 hours under argon at 0 °C.

The effect of the temperature was examined first. No substantial improvement in the yield was obtained lowering the temperature up to −18 °C, while at −78 °C no reaction occurred (Table 14, Entry 1-3). A fast addition of the diazoester (**259**) favoured the carbene dimerisation[56] with consequently low yield of the desired C-H activation product (Table 14, Entry 4). When the ratio diene:diazoester was reduced to 1:2 and the equivalents of the

catalyst to 0.5 mol% the isolated yield was 52% (Table 14, Entry 1 and 5). A similar trend was also observed with the diazoester (**92**) (Table 14, Entry 7 and 8) and the corresponding insertion product (**267**) was isolated in excellent 89% yield after DDQ oxidation. As expected, the diene (**43**) underwent slowly oxidation upon standing and the yields after the C-H activation reactions were lower (Table 14, Entry 6 and 9). The optimisation process was subsequently extended to the TMS-derivative (**44**) (Scheme 69 and Table 15).

44

259 : R^1 = Me, R^2 = Et
92 : R^1 = Ph, R^2 = Me

269 : R^1 = Me, R^2 = Et : 55%
270 : R^1 = Ph, R^2 = Me : 77%

271
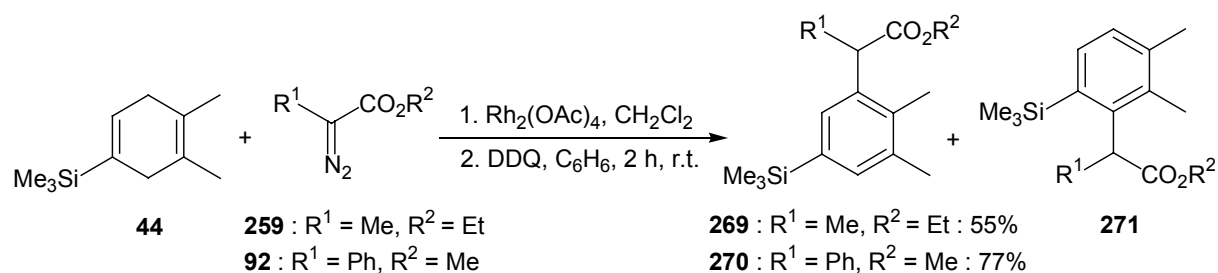
Scheme 69   Intermolecular C-H insertion on diene (**44**)

Table 15   Optimisation of the reaction in Scheme 69

Entry	Diazoester	Diene:diazoester	Rh$_2$(OAc)$_4$ (mol%)	Temp.	Addition time	Yield[a] (%)
1	259	1 : 2	4	0 °C	30 min.	20
2	259	1 : 2	2	0 °C	30 min.	35
3	**259**	**1 : 2**	**0.5**	**0 °C**	**60 min.**	**55**
4	259	1 : 2	0.5	0 °C	120 min.	33
5	259	1 : 2	0.5	25 °C	60 min.	21
6	92	1 : 2	2	0 °C	30 min.	44
7	92	1 : 2	1	0 °C	45 min.	52
8	92	1 : 2	0.5	0 °C	45 min.	54
9	**92**	**1 : 2**	**0.5**	**0 °C**	**60 min.**	**77**

Reagents and conditions: syringe pump addition of (**259**) or (**92**) (2.0 equiv.) in CH$_2$Cl$_2$ (2 ml) to (**44**) (1.0 equiv.) in CH$_2$Cl$_2$ (3 ml) and Rh$_2$(OAc)$_4$; [a] isolated yield after DDQ oxidation in benzene at r.t.

The right combination of addition time and catalyst equivalent proved to be the crucial factors. Higher catalyst loading with a short addition time gave only 20% yield (Table 15, Entry 1). When the addition time was extended over two hours with 0.5 mol% of Rh$_2$(OAc)$_4$ the desired product was also isolated in lower yield (Table 15, Entry 4). As in the case of the diene (**43**) the best results were obtained with 0.5 mol% of the catalyst and 60 minutes addition time at 0 °C (Table 15, Entry 3 and 7). These conditions were subsequently used for

all the other C-H activation reactions. Due to the asymmetry of the dienes (**43**) and (**44**) an additional question involved the regioselectivity of the reactions, which could afford products of type (**269**) or (**271**) (Scheme 69). However, as outlined in Figure 12, the steric hindrance should promote the carbene attack on side (a) of the dienes favouring products of type (**269**) over the products of type (**271**).

side a

43 : R = Ph
44 : R = SiMe$_3$

side b
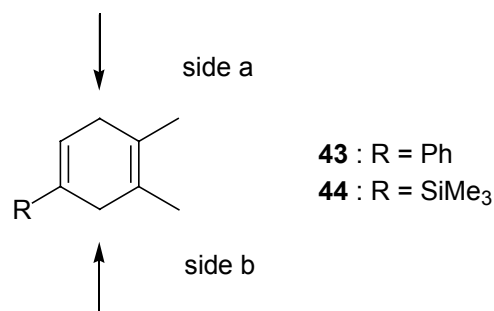
Figure 12   Possible points of C-H activation on 1,4-dienes (**43**) and (**44**)

NOE analysis of (**270**) confirmed this hypothesis (Figure 13). The existence of a NOE effect between hydrogens (abbreviated as Hs in the picture) on C7 and C8 and between C4 and C9 is clearly demonstrating the regioselectivity of the reaction. Such a coupling would not have been possible with products of type (**271**).

Having set the reaction conditions, the diene (**43**) (generated from the cobalt(I)-catalysed *Diels-Alder* reaction between phenylacetylene (**24**) and 2,3-dimethyl-1,3-butadiene (**42**)) was tested as a substrate in reactions with different acceptor, acceptor/acceptor and donor/acceptor carbenoid precursors (Scheme 70 and Table 16).

43

259 : R^1 = Me, R^2 = Et
272 : R^1 = ^{i}Pr, R^2 = Et
273 : R^1 = CH$_3$CO, R^2 = Et
274 : R^1 = PhCH=CH, R^2 = Et
92 : R^1 = Ph, R^2 = Me

266 : R^1 = Me, R^2 = Et
275 : R^1 = ^{i}Pr, R^2 = Et
276 : R^1 = CH$_3$CO, R^2 = Et
277 : R^1 = PhCH=CH, R^2 = Et
267 : R^1 = Ph, R^2 = Me
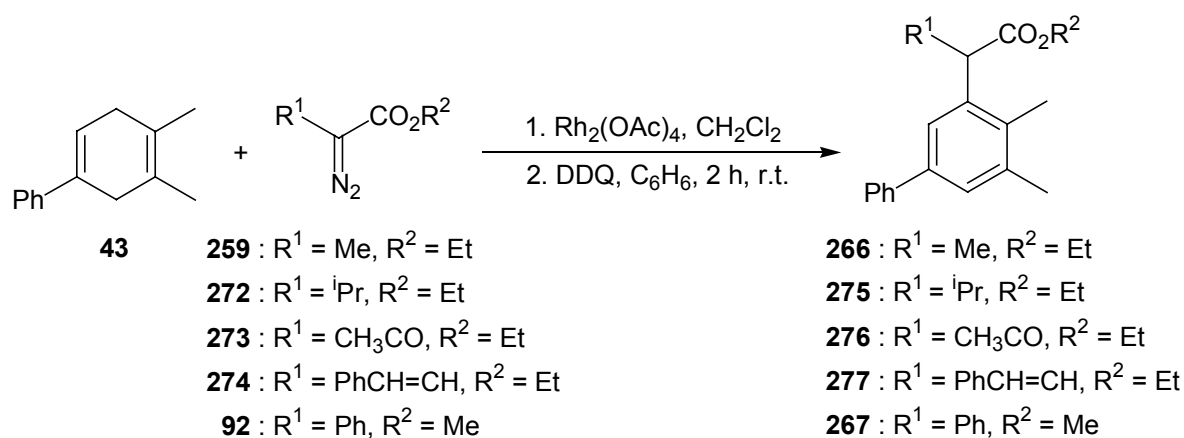
Scheme 70   Intermolecular C-H insertion on diene (**43**)
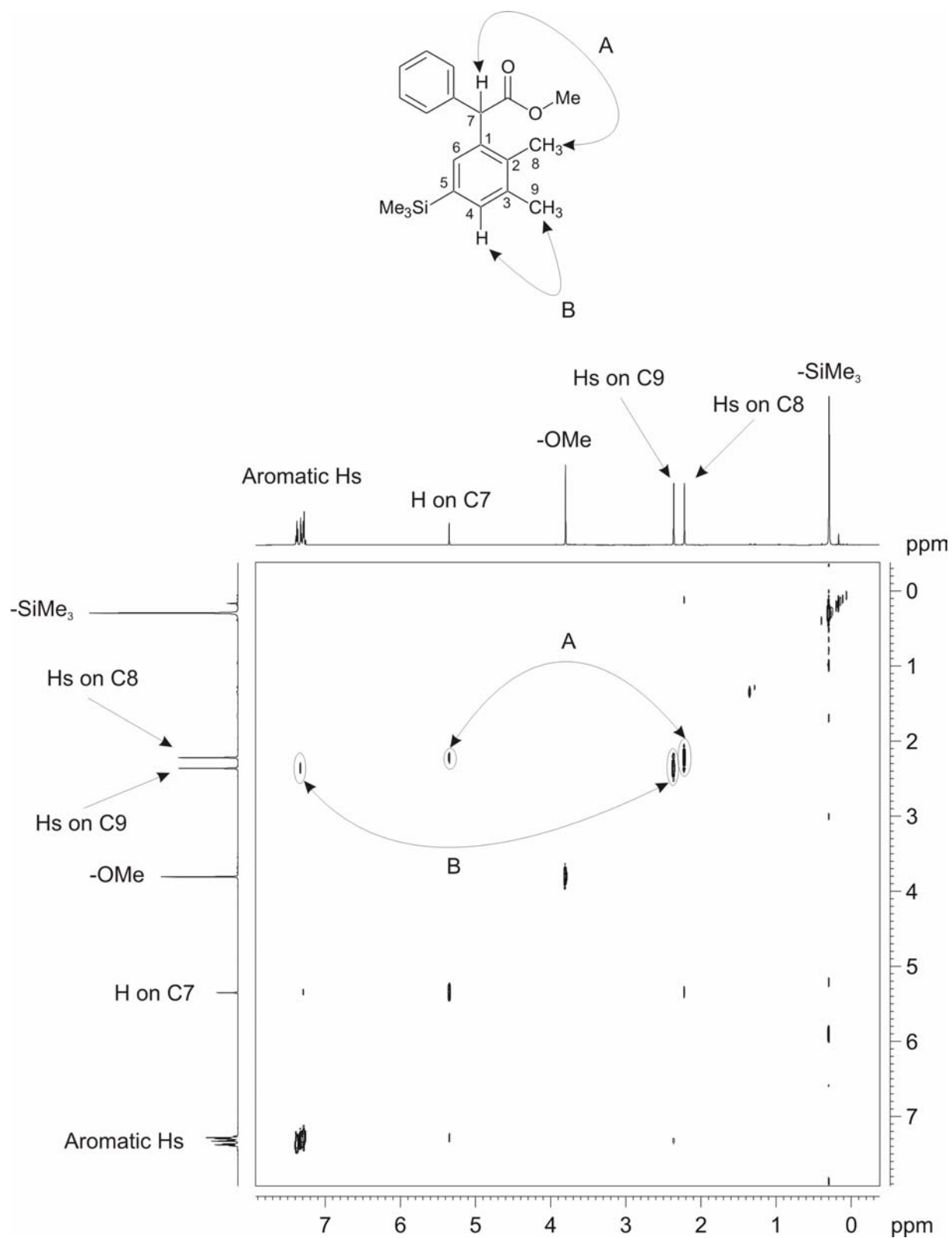
Figure 13   Significative NOE correlations for (**270**)

Table 16   Intermolecular C-H insertions of diazoesters in Scheme 70 with diene (**43**)

Entry	R^1	R^2	Yield[a] (%)
1	Me	Et	52
2	^{i}Pr	Et	0[b]
3	CH$_3$CO	Et	0[b]
4	Ph-CH=CH	Et	60[c]
5	Ph	Me	89

Reagents and conditions: syringe pump addition (1 h) of diazoesters (2.0 equiv.) in CH$_2$Cl$_2$ (2 ml) to (**43**) (1.0 equiv.) in CH$_2$Cl$_2$ (3 ml) and 0.5 mol% of Rh$_2$(OAc)$_4$ at 0 °C; [a] isolated yield after DDQ oxidation in benzene at r.t.; [b] no conversion; [c] reaction at room temperature.

Acceptor[41] substituted carbenoid precursors resulted in low yields or no reaction. Ethyl 2-diazopropionate (**259**) reacted by insertion to afford (**266**) in 52% yield (Table 16, Entry 1). The poor result could be ascribed to the competing carbene dimerisation process[56]. GC-MS control of the crude reaction mixture showed unreacted starting material as well as dimerisation products. No conversion was registered with the more sterical demanding diazoester (**272**) (Table 16, Entry 2). Acceptor/acceptor[41] substituted diazo compounds derived from 1,3-dicarbonyls such as (**273**) are more stable due to the presence of the second electron withdrawing group. Therefore, very active catalysts are required to decompose them and no product formation was detected even after prolonged reflux in dichloromethane (Table 16, Entry 3). Donor/acceptor[64] substituted carbenoids are less susceptible to dimer formation[110] and the corresponding C-H insertion aromatic products could be isolated in good to excellent yields after DDQ oxidation (Table 16, Entry 4 and 5). The tendency of acceptor-substituted carbenoids to dimerise was also confirmed by reaction of ethyl 2-diazopropionate (**259**) with other dienes, as reported in Table 17.

Table 17   Intermolecular C-H insertions of diazoester (**259**) with 1,4-dienes
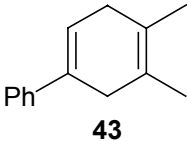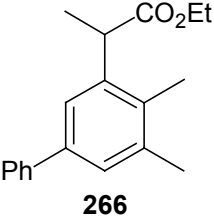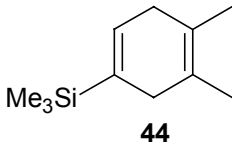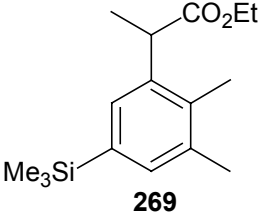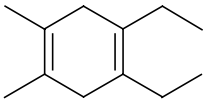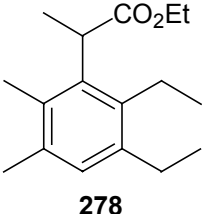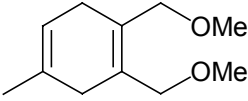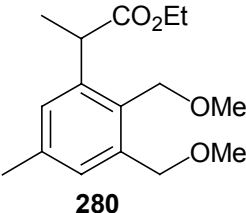
Entry	1,4-Diene	Product	Yield[a] (%)
1	**43**	**266**	52

Table 17   Intermolecular C-H insertions of diazoester (**259**) with 1,4-dienes *(cont.)*

Entry	1,4-Diene	Product	Yield[a] (%)
2	**44**	**269**	55
3	**45**	**278**	9
4	**279**	**280**	traces

Reagents and conditions: syringe pump addition (1 h) of diazoester (**259**) (2.0 equiv.) in CH_2Cl_2 (2 ml) to the diene (1.0 equiv.) in CH_2Cl_2 (3 ml) and 0.5 mol% of $Rh_2(OAc)_4$ at 0 °C; [a] isolated yield after DDQ oxidation in benzene at r.t.

Hindered dienes such as (**45**) and (**279**) made the carbene attack to the allylic system more difficult and the dimerisation pathway further on favoured. Consequently, low yields of the desired insertion products were obtained (Table 17, Entry 3 and 4). Because of the instability[111] of the vinyldiazoester (**274**), that should be synthesised and immediately reacted, the phenyldiazoacetate (**92**) was used as the only carbenoid precursor in reactions with other 1,4-dienes (Table 18).

Table 18   Intermolecular C-H insertions of diazoester (**92**) with 1,4-dienes
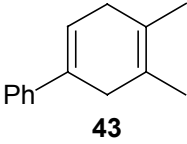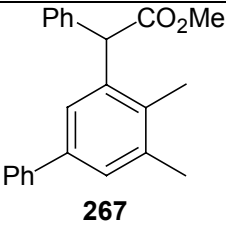
Entry	1,4-Diene	Product	Yield[a] (%)
1	**43**	**267**	89

Table 18   Intermolecular C-H insertions of diazoester (**92**) with 1,4-dienes *(cont.)*
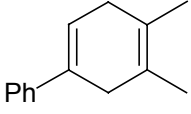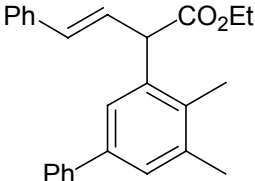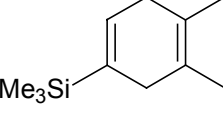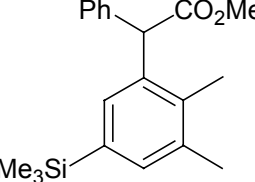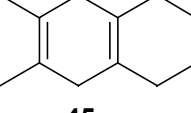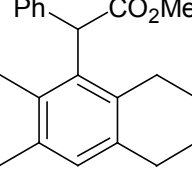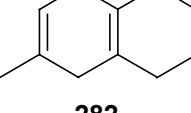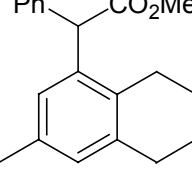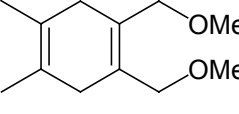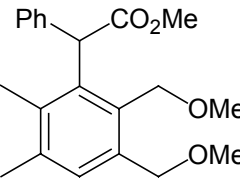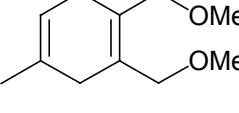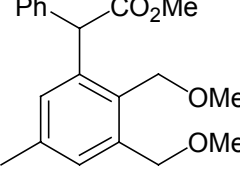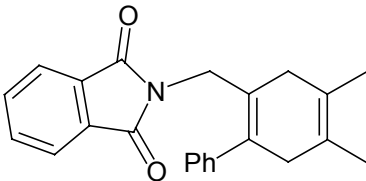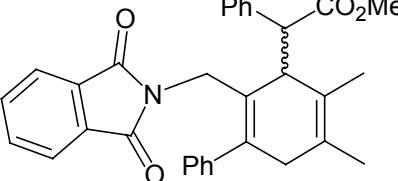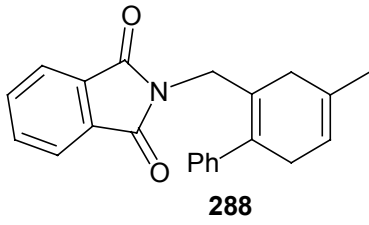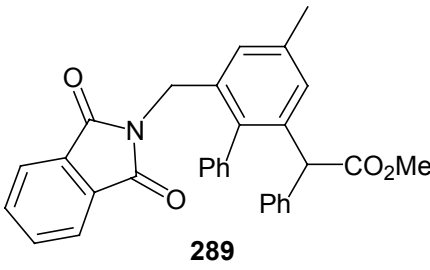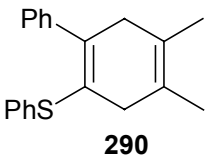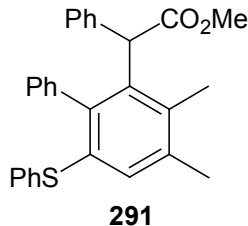
Entry	1,4-Diene	Product	Yield[a] (%)
2	**43**	**277**	60[b]
3	**44**	**270**	77
4	**45**	**281**	44
5	**282**	**283**	60
6	**52**	**284**	62
7	**279**	**285**	74
8	**286**	**287**	45[c]

Table 18 Intermolecular C-H insertions of diazoester (**92**) with 1,4-dienes *(cont.)*

Entry	1,4-Diene	Product	Yield[a] (%)
9	**288**	**289**	68[d]
10	**290**	**291**	0[e]

Reagents and conditions: syringe pump addition (1 h) of diazoester (**92**) (2.0 equiv.) in CH_2Cl_2 (2 ml) to the diene (1.0 equiv.) in CH_2Cl_2 (3 ml) and 0.5 mol% of $Rh_2(OAc)_4$ at 0 °C; [a] isolated yield after DDQ oxidation in benzene at r.t.; [b] reaction at r.t.; [c] DDQ oxidation was not possible; [d] the diene (**288**) is a 3:1 mixture of regioisomers, only the main regioisomer is reported. See Scheme 47 and Table 9; [e] no conversion.

Electronic[112] and steric[113] effects are the two major factors in determining the site of C-H activation. As all the 1,4-dienes listed in Table 18 were obtained from the cobalt(I)-catalysed *Diels-Alder* reaction of non activated starting materials, electronic effects are expected to be outweighed by steric factors. Indeed, the substitution of the phenyl group of (**43**) with a bulky TMS group resulted in a decreased yield of (**270**) (Table 18, Entry 1 and 3). When the more sterical challenging dienes (**45**) and (**52**) were tested, the desired pentasubstituted benzene derivatives were isolated in 44% and 62% yield (Table 18, Entry 4 and 6). A further analysis of the results also showed that the yields for the di-methoxy derivatives (**284**) and (**285**) were always higher than the corresponding products obtained from aliphatic dienes (Table 18, Entry 3-7). $Rh_2(OAc)_4$ is a binuclear compound and possesses one vacant axial coordination site per metal atom. *Nakamura*[114] and *Pirrung*[115] suggested that only one of the two rhodium atoms acts as a carbene binding site. The other metal center assists the C-H insertion reaction by acting as an electron sink. The coordination of one methoxy group to the free metal center could be responsible for an additional stabilisation of the carbene moiety. Such a mechanism is not possible for aliphatic dienes such as (**45**) and (**282**). The nitrogen-functionalised diene[97] (**286**) could also be successfully reacted under standard conditions, although only in 45% yield (Scheme 71). Unexpectedly, the dihydroaromatic insertion product (**287**) could not be oxidised by DDQ at room temperature. It also showed a remarkable resistance to air oxidation which allowed to grow crystals for x-ray diffraction (Figure 14). Attempted DDQ oxidation in

refluxing benzene resulted in decomposition. As it is evident from the crystal structure of (**287**) (Figure 14), the substituents of the dihydroaromatic ring are preventing the approach of the DDQ molecules and the subsequent oxidation of the aromatic ring.
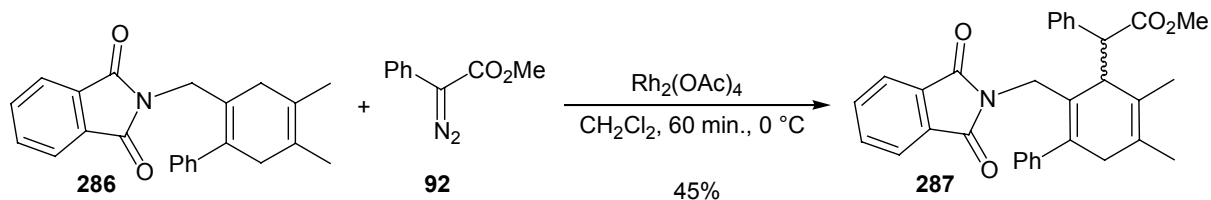
Scheme 71   Rhodium-catalysed C-H activation on nitrogen-functionalised alkynes
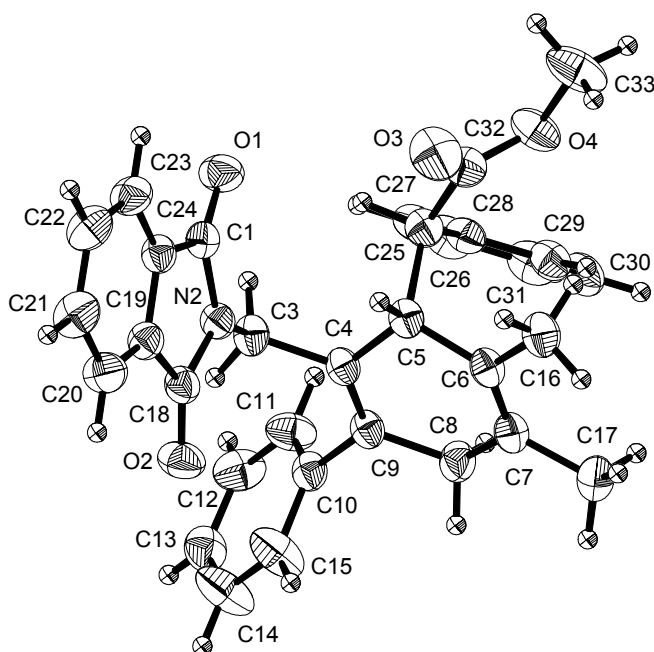
Figure 14   Crystal structure of (**287**)

When isoprene (**193**) was used in the cobalt(I)-catalysed *Diels-Alder* reaction instead of 2,3-dimethyl-1,3-butadiene (**42**), a less hindered nitrogen-functionalised diene was obtained as a non separable mixture of regioisomers (**288a**) and (**288b**) and in a 3:1 ratio[97] (Scheme 72). Due to the asymmetry of the dienes (**288a**) and (**288b**) a complex mixture of products was expected from the reaction with phenyldiazoacetate (**92**) and Rh$_2$(OAc)$_4$.
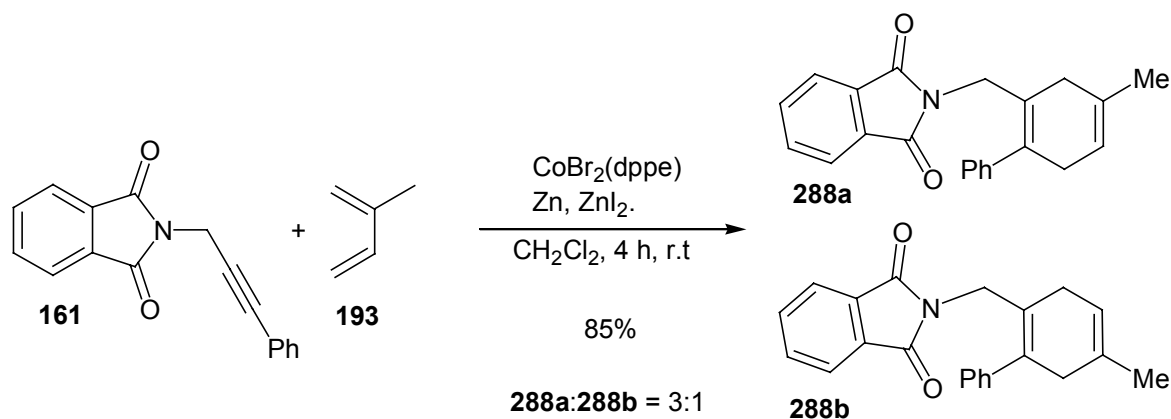
Scheme 72   Cobalt(I)-catalysed *Diels-Alder* reaction of (**161**) with isoprene

Under standard conditions the expected C-H insertion took place. Subsequent DDQ oxidation at room temperature was successful and, after the work-up, a product (**289**) was isolated in 68% yield (Scheme 73).
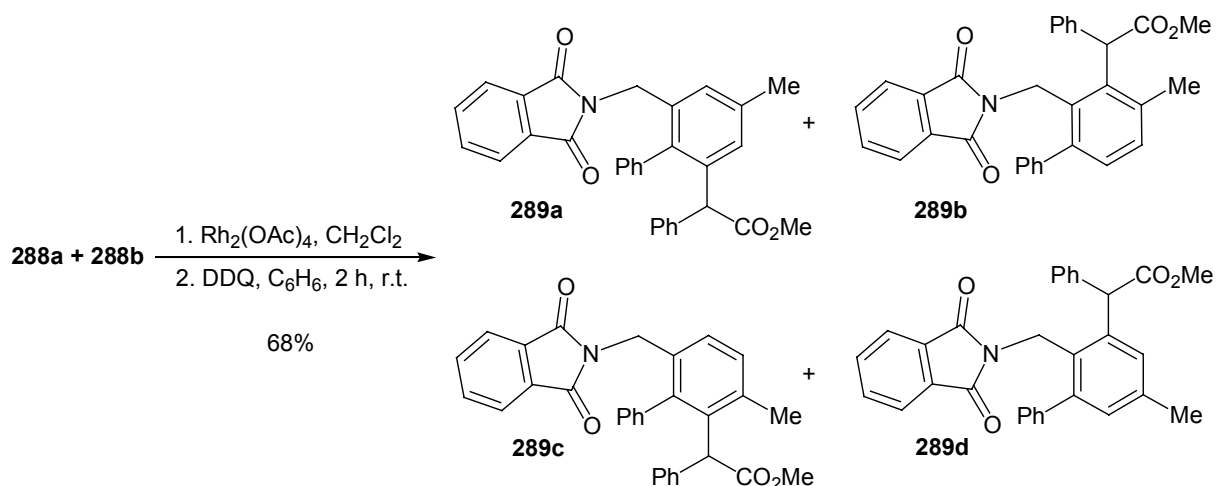
Scheme 73   Possible products of C-H insertion on dienes (**288a**) and (**288b**)

The ^{1}H-NMR spectra of a pure sample of (**289**) showed the presence of three compounds, in a ratio of 85:11:4. A review of the results so far obtained with asymmetric 1,4-dienes showed that the C-H activation always took place at the less hindered side. On the base of this consideration the products (**289b**) and (**289c**) were believed to be less probable, while (**289a**) and (**289d**) could both have been possible. Two dimensional NMR analysis (HMBC and NOESY) showed undoubtedly that (**289a**) was the main product (Figure 15), while the structure of the other compounds could not be assigned because of the low intensity of the signals.
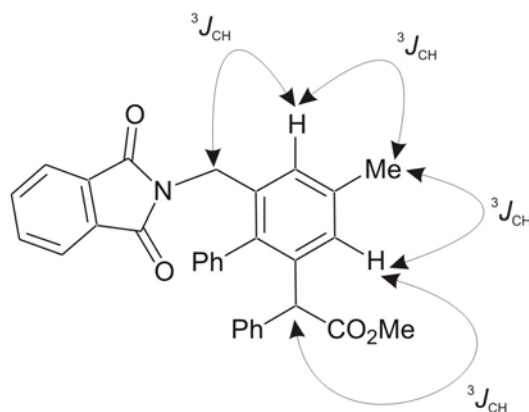
Figure 15   Significative HMBC correlations for (**289**)

These results are noteworthy because they show how deep is the effect of the steric hindrance of the 1,4-diene on the regioselectivity of the reaction. Sulfur-functionalised dienes[33] of type (**290**) were also tested in the rhodium-catalysed C-H activation (Scheme 74).
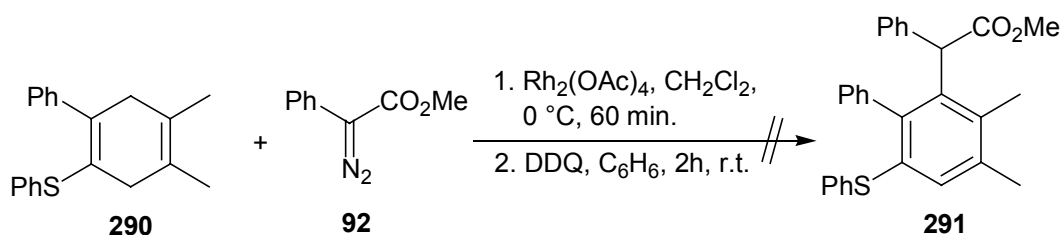
Scheme 74   Attempted rhodium-catalysed C-H activation on sulfur-functionalised alkynes

Unfortunately no reaction was observed. A cross-check experiment with 1,4-cyclohexadiene (**258**) and one equivalent of thioanisole under the same conditions also resulted in no conversion, probably because of catalyst decomposition.

An alternative approach was envisioned by the use of oxygen-functionalised acyclic 1,3-dienes[35] such as 2-(trimethylsiloxy)-1,3-butadiene (**51**) and terminal or internal alkynes in the *Diels-Alder* reaction (Scheme 75).
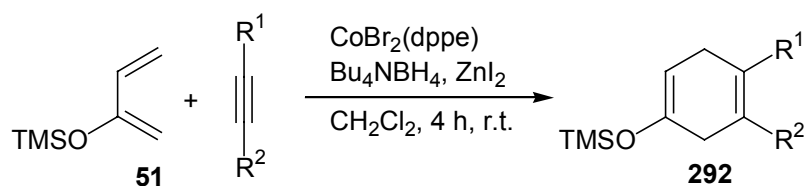
Scheme 75   Cobalt(I)-catalysed *Diels-Alder* reaction with oxygen-functionalised dienes

The resulting dihydroaromatic products of type (**292**) are useful intermediates for a wide variety of chemical transformations such as the synthesis of the bis-acetoxylated product[116] (**294**) from (**293**) (Scheme 76).
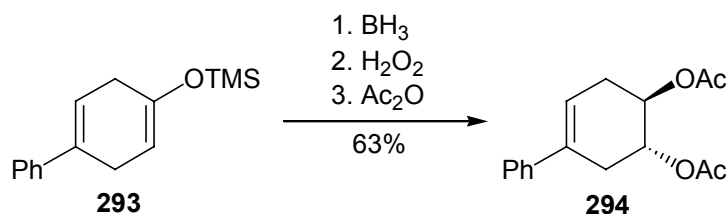
Scheme 76   Products of type (**292**) as intermediates in organic synthesis

Rhodium-catalysed C-H activation reaction followed by *in situ* hydrolysis with diluted acids or TBAF could give access to β,γ-unsaturated cyclohexanones of type (**295**) (Scheme 77), which are interesting building blocks for further manipulations.
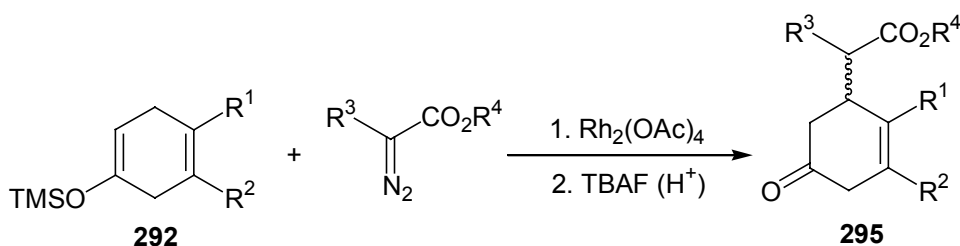
Scheme 77   Rhodium-catalysed C-H activation on oxygen-functionalised 1,4-dienes

Preliminary tests with the diene (**296**) and methyl-2-diazophenylacetate (**92**) as carbenoid precursor confirmed the validity of this pathway, although the desired product (**297**) could be isolated in only 35% yield as a racemic mixture (Scheme 78).
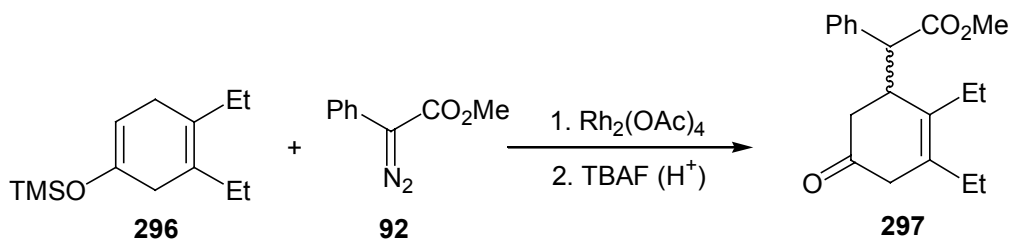
Scheme 78   Synthesis of the β,γ-unsaturated cyclohexanone (**297**)

The β,γ-unsaturated cyclohexanone (**297**) showed a remarkable tendence to interconvert into the α,β-unsaturated derivative (**298**) in the presence of traces of acid or base[117] (Scheme 79) *via* the corresponding enol or enolate ion.
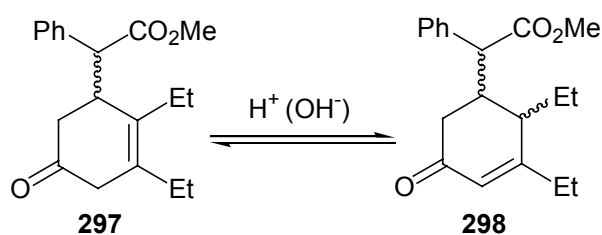
Scheme 79   Acid-catalysed isomerisation of (**297**) to the α,β-unsaturated derivative (**298**)

Although the reaction was not further on investigated it could represent a new synthetic pathway for the synthesis of polysubstituted α,β-unsaturated cyclic ketones.

Substrates of type (**299**) were of particular interest because of the contemporary presence in the molecule of a *exo*-chain double bond and of a 1,4-dihydroaromatic system. They were synthesised *via* cobalt(I)-catalysed *Diels-Alder* reaction of 2,3-dimethyl-1,3-butadiene (**42**) and 3-methylbut-3-en-1-in (**153**) (Scheme 80).
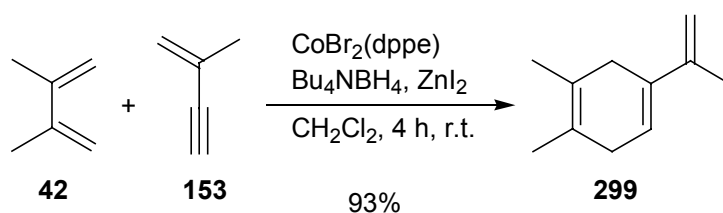
Scheme 80   Synthesis of the substrate (**299**)

The isopropenyl moiety and the 1,4-dihydroaromatic ring are competing targets for the intermediate rhodium carbenoid. Unfortunately, it was not possible to modulate the reactivity of the carbenes and mixtures of cyclopropanation and C-H insertion products were always obtained. When ethyl 2-diazopropionate (**259**) was used the cyclopropanes fraction could be separated (40% yield) from the cyclopropanation plus insertion products (22% yield) by column chromatography (Scheme 81).
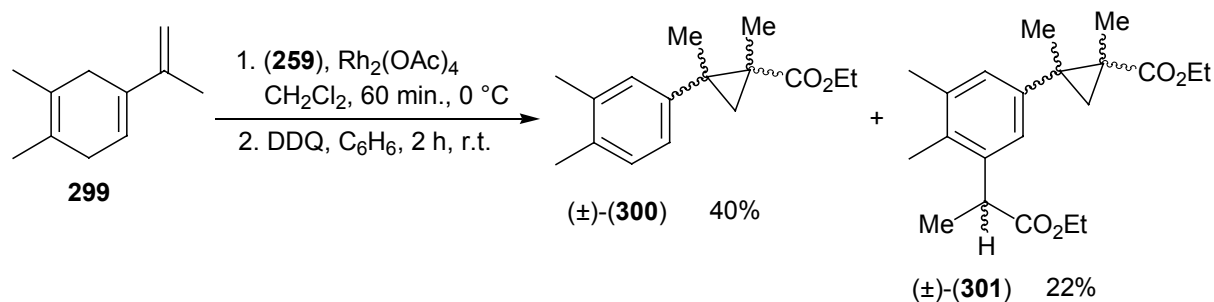
Scheme 81   Rhodium-catalysed C-H activation/cyclopropanation on (**299**)

Subsequent chromatography of the cyclopropanes fraction allowed the isolation of the two couple of diastereoisomers (**300a**) and (**300b**) as racemic mixtures (Scheme 82).
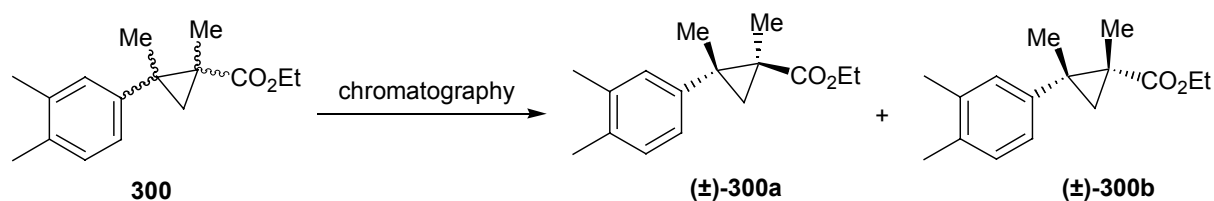
Scheme 82   Separation of the cyclopropanes diastereoisomers *via* chromatography

The relative configuration of (±)-(**300a**) and (±)-(**300b**) was assigned by NOE analysis. The *trans* position of the two methyl groups on C1 and C3 of the cyclopropane ring in (±)-(**300a**) was confirmed by the existence of a NOE effect between hydrogens (abbreviated as Hs in the figures) on C5 and C2 and between C4 and C2 (Figure 16). The *cis* position of the two methyl groups in (±)-(**300b**) was instead undoubtedly assigned by the existence of a NOE effect between H_A and the hydrogens on C4 and C5. An additional proof is also the absence of NOE effect between H_B and the hydrogens on C4 and C5 (Figure 17). Attempted separation by column chromatography of the cyclopropanation plus insertion products (**301**) furnished only two main fractions, each containing complex mixtures of diastereoisomers. An exact structure determination by means of two dimensional NMR techniques was not possible. With phenyldiazoacetate (**92**) as carbenoid precursor an inseparable mixture of diastereoisomers (**303**) was obtained in 76% yield (Scheme 83) while no cyclopropanation product (**302**) could be isolated.
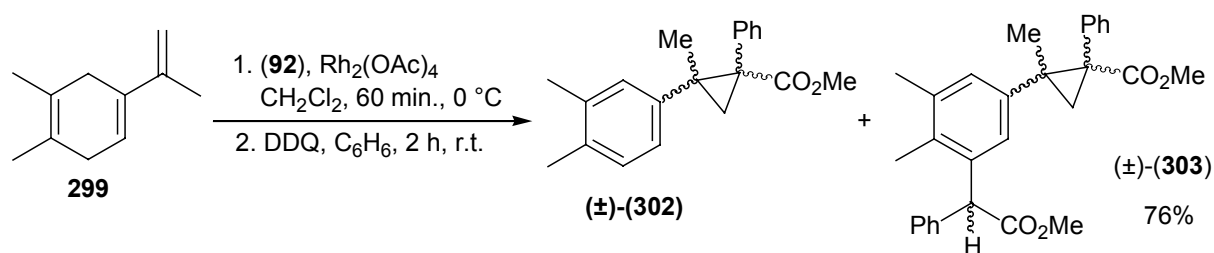
Scheme 83   Rhodium-catalysed C-H activation/cyclopropanation on (**299**)
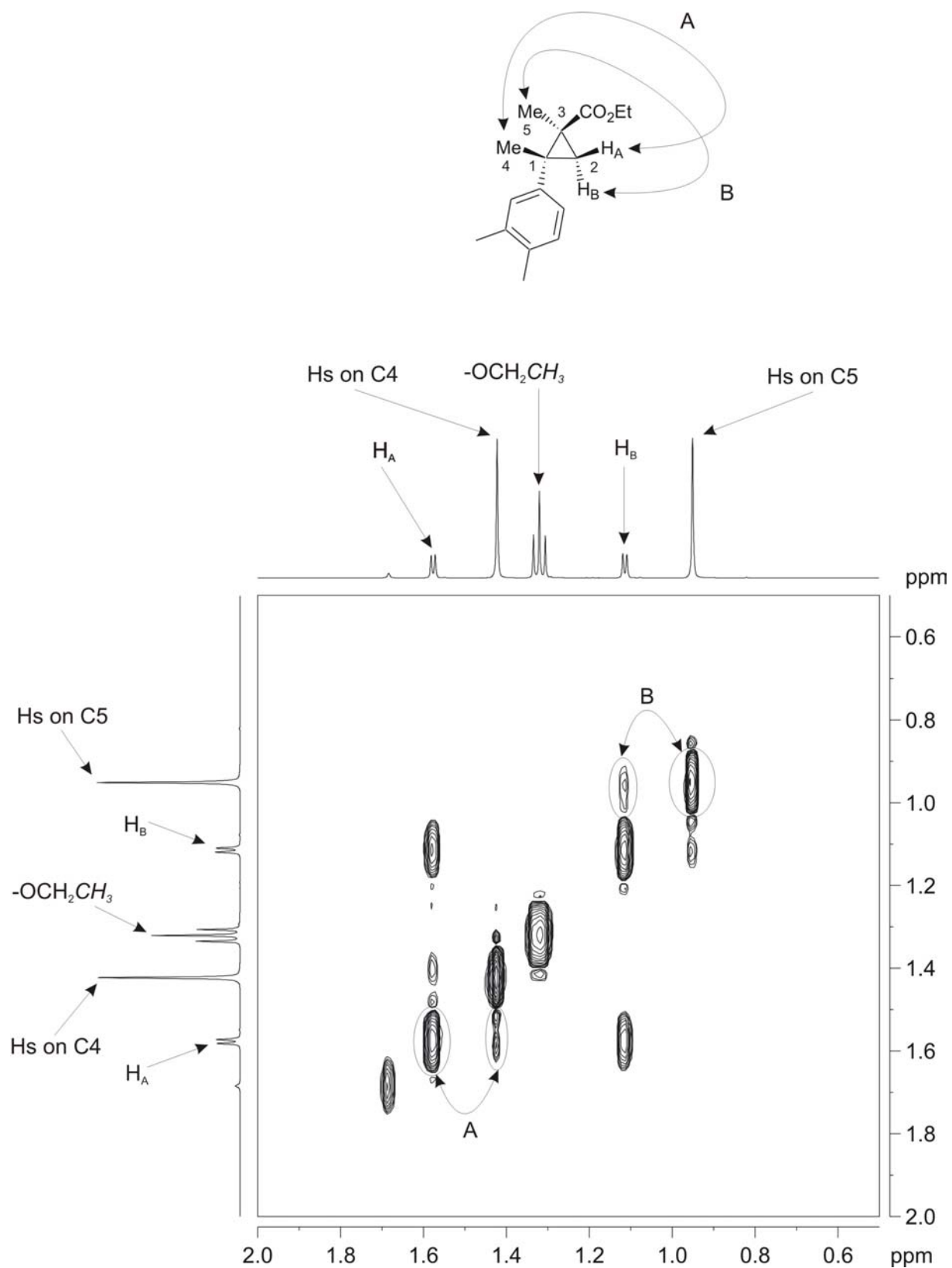
Figure 16   Significant NOE correlations for (±)-(**300a**) (partial spectra)
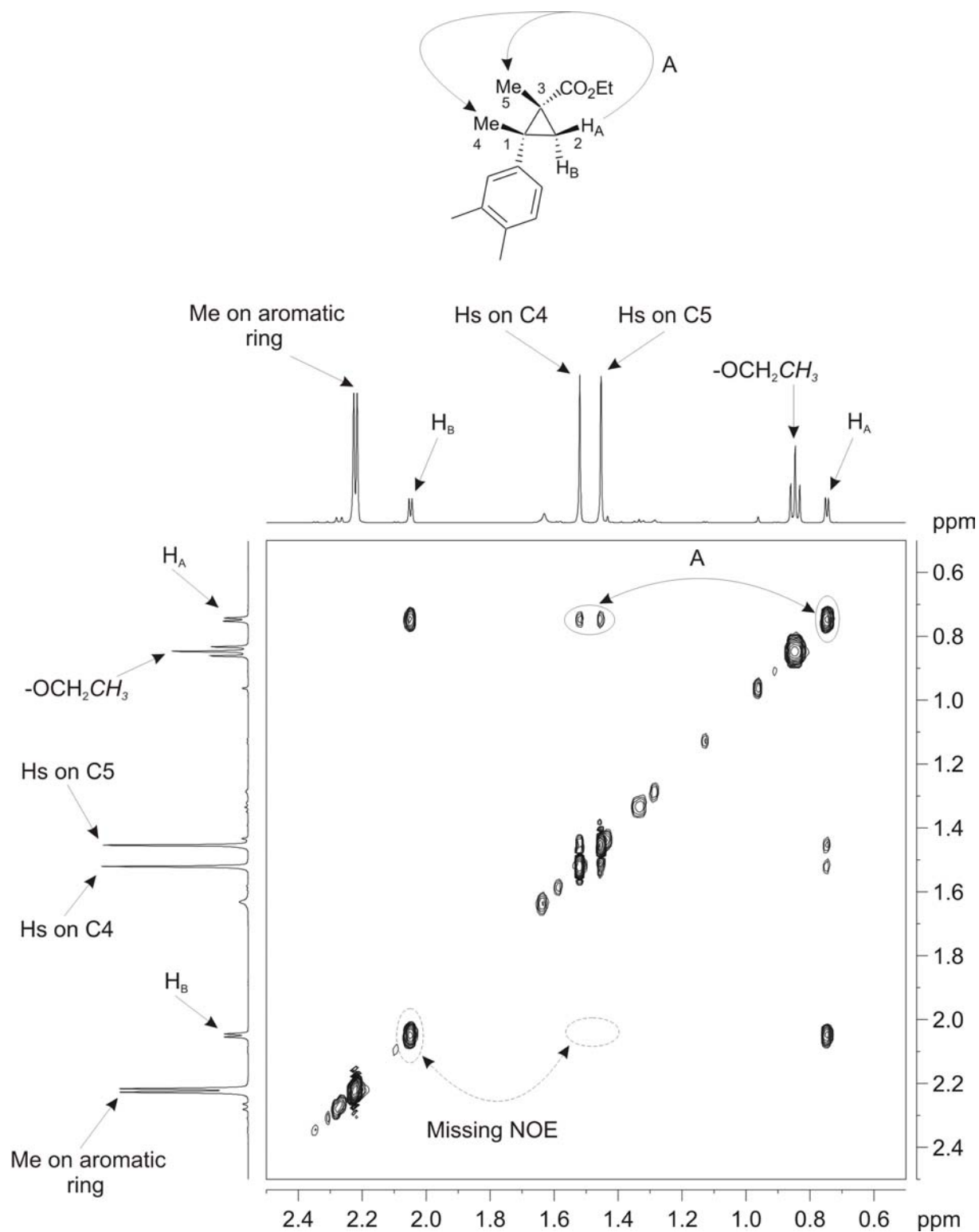
Figure 17   Significant NOE correlations for (±)-(**300b**) (partial spectra)

In a different set of experiments, the reactivity of non-cyclic olefines with a 1,4-diene subunit such as (62) and (64) was tested (Figure 18).
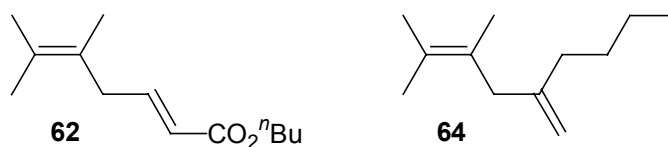
Figure 18   Acyclic and *exo*-chain olefines

As already mentioned in the introduction, the cobalt-catalysed 1,4-hydrovinylation process[36] leads with very high selectivity to linear products of type (62) when electron-poor alkenes such as *n*-butyl acrylate (61) are used (Scheme 20, eq. 1). Branched products (64) with an *exo*-chain double bond are instead obtained with neutral alkenes such as 1-hexene (63) (Scheme 20, eq. 2). A common feature of both hydrovinylation products (62) and (64) is the 1,4-diene subunit, which makes them interesting substrates for the rhodium-carbenoid C-H activation chemistry. Rhodium-based catalysts are also known for being used in cyclopropanation reactions[118]. Therefore an alternative reaction pathway is possible. When the acrylate derivative (62) was tested with ethyl 2-diazopropionate (259) and 0.5 mol% of $Rh_2(OAc)_4$ under standard conditions, no cyclopropanation (304) nor insertion (305) products were detected (Scheme 84).
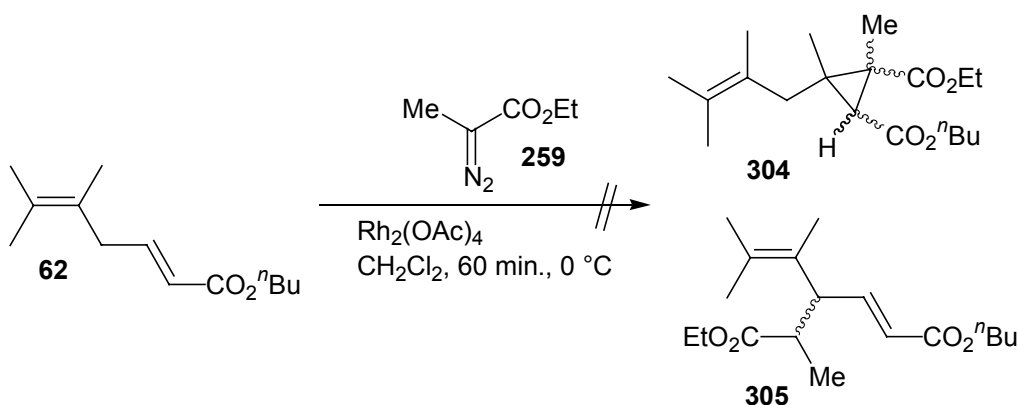
Scheme 84   Attempted cyclopropanation or C-H activation on (62)

While the cyclopropanation at the tetrasubstituted double bond was believed to be disfavoured because of the steric hindrance, the lack of reaction on the other functionalities was disappointing. The branched hydrovinylation product (64) gave only cyclopropanation at the *exo*-chain double bond with both diazoesters (259) and (92) in 58% and 70% yield and no C-H insertion (Scheme 85 and 86).

These results are in accordance with the well documented tendency of olefins to undergo metal-carbenoid cyclopropanation, particularly for mono- or *cis*-disubstituted double bonds[119]. The lack of C-H activation, despite the high number of allylic sites available in both starting materials, indicates the preference of the C-H activation to occur at the double allylic methylene positions of cyclic 1,4-dienes.
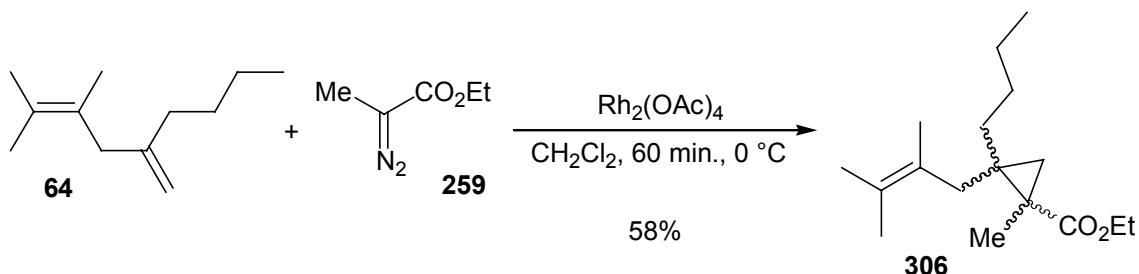
Scheme 85   Rhodium catalysed cyclopropanation of (**64**) with (**259**)
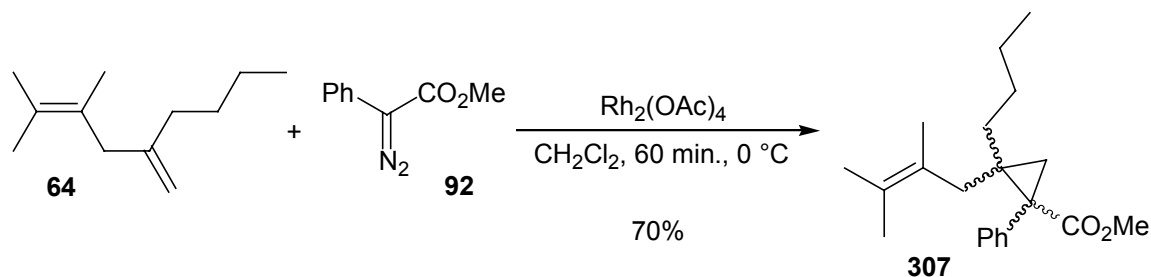
Scheme 86   Rhodium catalysed cyclopropanation of (**64**) with (**92**)

4.2   Copper(II)-catalysed C-H activation reactions

Transition-metal catalysed decomposition of diazo compounds is a general method to prepare metal-stabilised carbenoids, which are versatile intermediates for organic synthesis. The copper-catalysed asymmetric cyclopropanation is probably one of the most popular applications of the carbenoid chemistry[68]. In addition, Cu-catalysed decomposition of diazo compounds may also lead to C-H bond insertion, although Rh(II) catalysts are usually more appropriate. Copper-catalysts are highly electrophilic and tend to generate carbenoids that are too reactive to undergo selective C-H activation reactions. However, *Müller* and *Boléa* recently reported an example of intramolecular copper-catalysed C-H insertion[57a] (Scheme 87). On the basis of this report a possible application of intermolecular copper-catalysed C-H insertion on cyclic 1,4-dienes was envisioned.
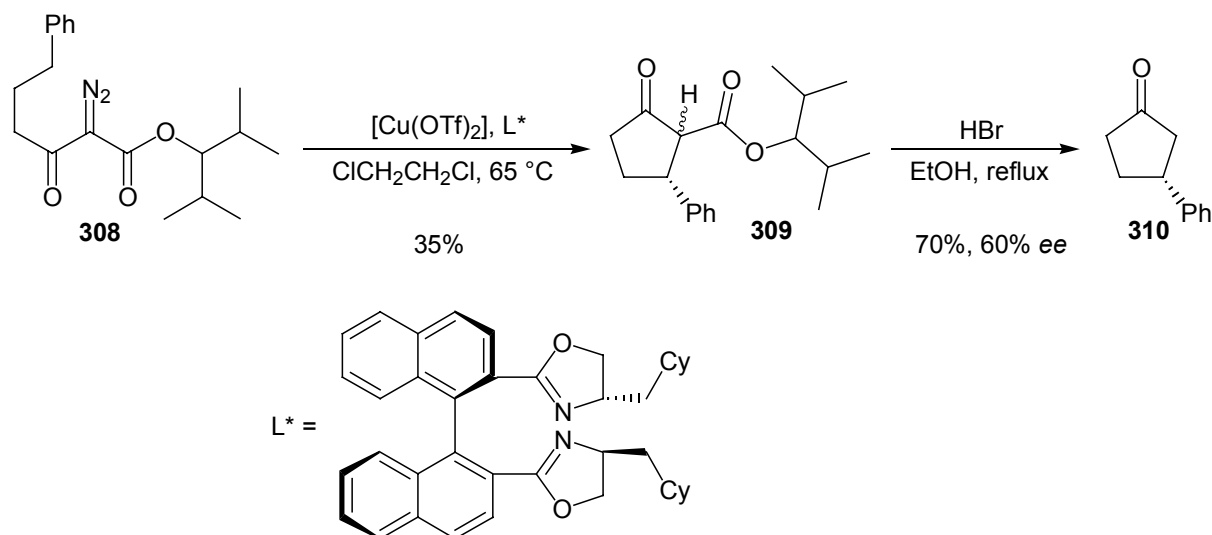
Scheme 87   Copper-catalysed intramolecular C-H insertion

Three different copper complexes were tested, namely Cu(II)-acetylacetonate (**311**), Cu(II)-hexafluoroacetylacetonate (Cu(hfacac)$_2$) (**312**) and Cu(II)-bis(*N*-benzyl-salicylaldiminato) (**313**) (Figure 18). The last is an achiral version of the cyclopropanation catalyst originally developed by *Nozaki* in 1966[120]. During his research he found that the reaction of styrene and ethyl diazoacetate (**263**) catalysed by (**314**) gave the cyclopropane adducts in less than 10% *ee*. This was the first reported example of transition metal catalysed enantioselective reaction.
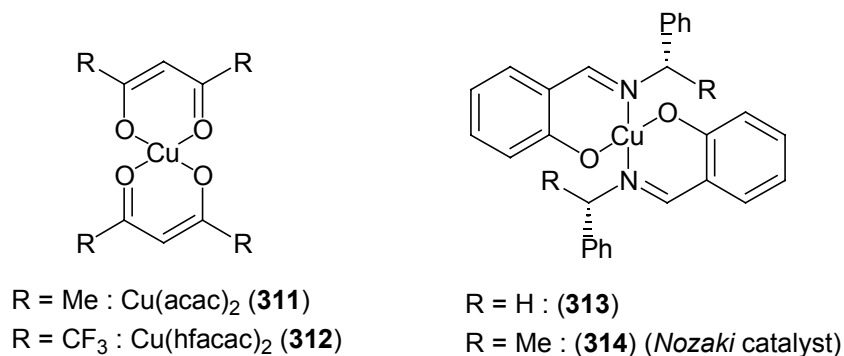
Figure 18   Copper-based catalysts

Initially, Cu(acac)$_2$ (**311**) was tested in reactions with different acceptor, acceptor/acceptor, donor/acceptor carbenoid precursors in the presence of (4,5-dimethyl-cyclohexa-1,4-dienyl)-benzene (**43**) (Scheme 88 and Table 19).
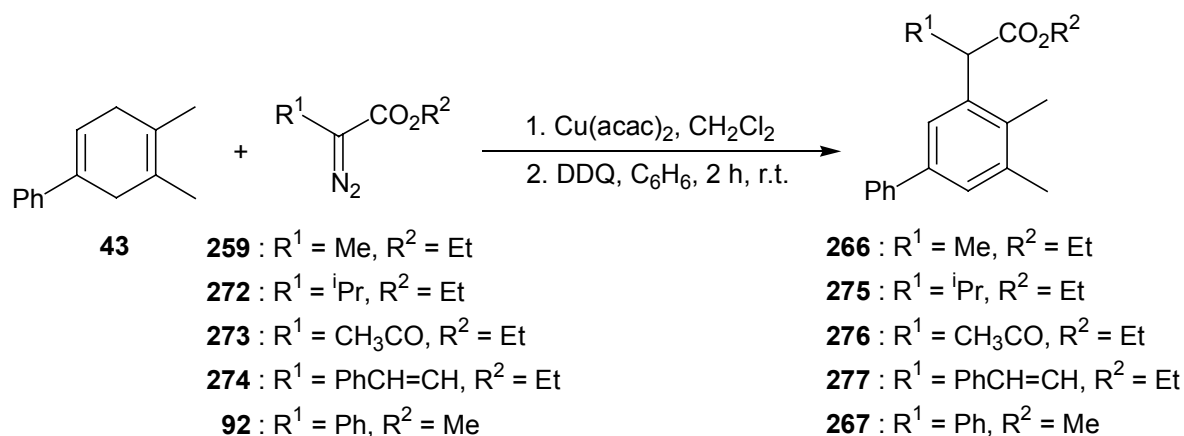
Scheme 88 Intermolecular copper-catalysed C-H insertion of diazoesters with diene (**43**)

Table 19 Intermolecular C-H insertions of diazoesters with 1,4-diene (**43**)

Entry	R^1	R^2	Catalyst	Yield[a] (%)
1	Me	Et	Cu(acac)$_2$	0[b]
2	^{i}Pr	Et	Cu(acac)$_2$	0[b]
3	CH$_3$CO	Et	Cu(acac)$_2$	0[b]
4	Ph-CH=CH	Et	Cu(acac)$_2$	0[b]
5	Ph	Me	Cu(acac)$_2$	70
6	Ph	Me	Rh$_2$(OAc)$_4$	89

Reagents and conditions: syringe pump addition (1 h) of diazoesters (2.0 equiv.) in CH$_2$Cl$_2$ (2 ml) to (**43**) (1.0 equiv.) in CH$_2$Cl$_2$ (3 ml) and 1 mol% of catalyst at 0 °C; [a] isolated yield after DDQ oxidation in benzene at r.t.; [b] no conversion.

Since (**43**) has no competitive cyclopropanation pathway available, the normally disfavoured insertion pathway should predominate also with copper catalysts. Unfortunately, the diazoesters (**259**, **272-274**) failed to give C-H insertion and only phenyldiazoacetate (**92**) gave the desired product (**267**) in 70% yield after DDQ oxidation. ^{1}H-NMR analysis showed that the regioselectivity was the same as for the corresponding Rh(II) catalysed reaction. These results were not surprising because copper-catalysts are highly electrophilic and tend to generate carbenoids that are too reactive and prone to dimerisation. In addition, the previously described supporting role of the second rhodium atom in the binuclear complex Rh$_2$(OAc)$_4$ is not available for single metallic complexes such as Cu(acac)$_2$. However, due to the enhanced stability provided by the α-substituents to the carbene derived from (**92**), the C-H insertion pathway becomes possible. The solely reaction with donor/acceptor carbenoid precursors is the main limitation of copper-based catalysts, while rhodium(II) catalysts are catalytically active across the entire spectrum of carbenoid precursors. In a further set of experiments the

influence of the ligand, addition rate and temperature for were examined (Scheme 89). The results are summarised in Table 20.
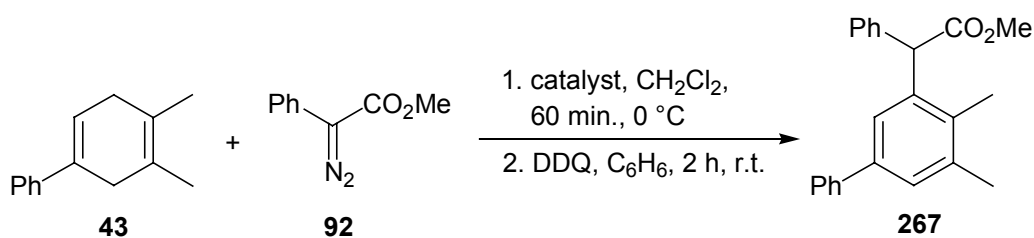
Scheme 89   Optimisation of the copper-catalysed C-H insertions of diazoester (**92**) with 1,4-diene (**43**)

Table 20   Intermolecular C-H insertions of diazoester (**92**) with 1,4-diene (**43**)

Entry	Catalyst	Cat. Equiv. (%)	Temperature	Addition time	Yield[a] (%)
1	Cu(acac)$_2$	1	25 °C	5 min.	52
2	Cu(acac)$_2$	1	25 °C	60 min.	55
3	Cu(acac)$_2$	1	0 °C	5 min.	70
4	Cu(acac)$_2$	1	0 °C	60 min.	63
5	Cu(acac)$_2$	5	0 °C	5 min.	68
6	Cu(hfacac)$_2$	1	0 °C	5 min.	85
7	Cu(hfacac)$_2$	1	25 °C	60 min.	83
8	314	1	25 °C	5 min.	traces
9	Rh$_2$(OAc)$_4$	0.5	0 °C	60 min.	89

Reagents and conditions: syringe pump (1 h) or syringe (5 min) addition of (**92**) (2.0 equiv.) in CH$_2$Cl$_2$ (2 ml) to (**43**) (1.0 equiv.) in CH$_2$Cl$_2$ (3 ml) and the catalyst at 0 °C or 25 °C; [a] isolated yield after DDQ oxidation in benzene at r.t.

As expected, the exchange of the acetylacetonate with the hexafluoroacetylacetonate ligand increased the electrophilicity and therefore the reactivity of the metallocarbenoid intermediate. The yield raised from 55% to 83% for the reactions at room temperature (Table 20, Entry 2 and 7) and from 70% to 85% for the reactions at 0 °C (Table 20, Entry 3 and 6). Interestingly, the rate of the diazoester addition proved to be not so important like in the rhodium-catalysed reactions (Table 20, Entry 1-4). Nonetheless, because of the quick evolution of nitrogen in case of fast addition (which could result in overpressure in the reaction flask) a slow addition and an ice-cooling bath are advisable. Higher loadings of catalyst showed no effect on the conversion (Table 20, Entry 3 and 5). The copper-catalysed C-H activation procedure was subsequently extended to some of the dienes previously used in the rhodium-catalysed reaction. All the experiments were performed with 1 mol% of

Cu(hfacac)$_2$. The diazoester was added by means of a syringe pump over one hour in CH$_2$Cl$_2$ at 0 °C. As reported in Table 21 the yields with Cu(hfacac)$_2$ and Rh$_2$(OAc)$_4$ were comparable, and only the nitrogen- and sulfur functionalised dienes (**286**) and (**290**) failed to react. For the phthalimide-derived diene (**286**) the combination of a difficult access to the dihydroaromatic system and of the high reactivity of the copper carbenoid were assumed to favour the dimerisation pathway. As already reported by *Nozaki*[120], strongly coordinating heteroatoms are able to destroy the catalytic activity of the copper complexes. Such a coordination mechanism is believed to be applicable also to the dihydroaromatic vinyl sulfide (**290**). Cross-check experiments with 1,4-cyclohexadiene (**258**) and one equivalent of thioanisole as additive resulted in no conversion.

Table 21   Intermolecular C-H insertions of diazoester (**92**) with 1,4-dienes
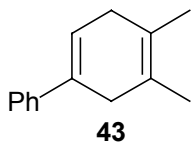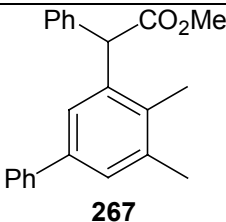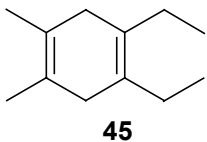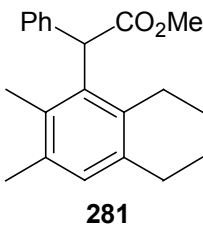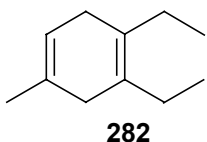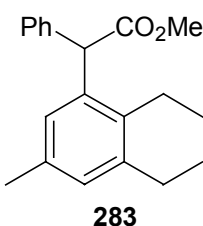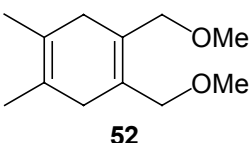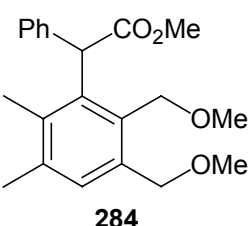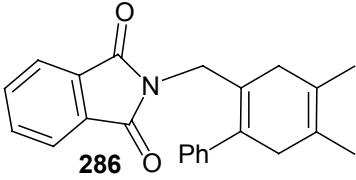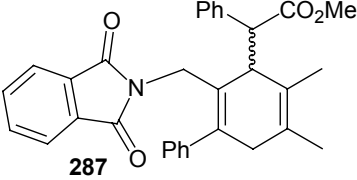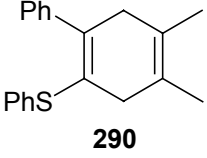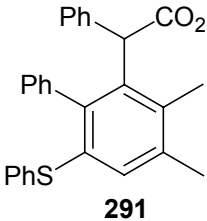
Entry	1,4-Diene	Product	Yield[a] (%)	
			Cu(hfacac)$_2$	Rh$_2$(OAc)$_4$
1	**43**	**267**	83	89
2	**45**	**281**	55	44
3	**282**	**283**	58	60
4	**52**	**284**	51	62

Table 21   Intermolecular C-H insertions of diazoester (**92**) with 1,4-dienes *(cont.)*

Entry	1,4-Diene	Product	Yield[a] (%)	
			Cu(hfacac)$_2$	Rh$_2$(OAc)$_4$
5	**286**	**287**	0[b]	45
6	**290**	**291**	0[b]	0[b]

Reagents and conditions: syringe pump addition (1 h) of (**92**) (2.0 equiv.) in CH$_2$Cl$_2$ (2 ml) to the diene solution (1.0 equiv.) in CH$_2$Cl$_2$ (3 ml) and 1 mol% of Cu(hfacac)$_2$ at 0 °C; [a] isolated yield after DDQ oxidation in benzene at r.t.; [b] no conversion.

Although only donor/acceptor carbenoid precursors were accepted by the catalyst, these results show that copper could represent a valid alternative to the expensive rhodium-based catalysts.

5   Summary

As demonstrated in the last years, cobalt(I)-catalysed *Diels-Alder* reactions can be performed with several starting materials bearing various functional group. While boron, silicon, oxygen and sulfur containing functionalities were accepted by the catalyst, nitrogen-functionalised starting materials could not employed so far.

The objectives of this investigation were the development of a cobalt(I)-catalysed *Diels-Alder* reaction on nitrogen functionalised alkynes and the synthesis of dibenzoazepine derivatives. Starting from the discovery that the phthalimido group is a suitable protecting group for the reaction of propargylic amines with 1,3-dienes several modifications were tested and sulfimides and amides proved to be effective, although the yields were moderate (up to 48%). When aryl propargylic amines, synthesised *via Sonogashira* coupling, were tested the desired *Diels-Alder* adducts were obtained in excellent yields (up to 98%) (Scheme IV).
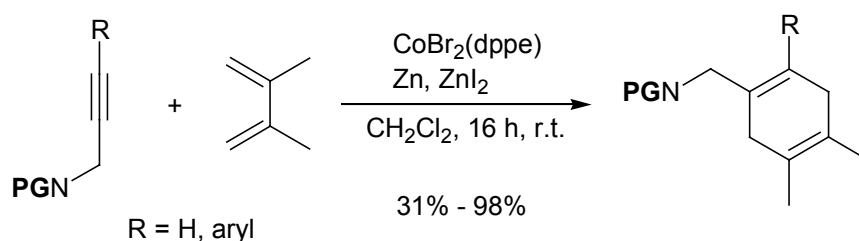
Scheme IV

Glycin derived starting materials could also be reacted in excellent yields, representing the first example of a non-cyclic protecting group moiety on the nitrogen functionality. However, a free NH-group on the amide protected nitrogen was not accepted by the cobalt catalyst. The cycloadducts were converted to the corresponding biaryl derivatives by DDQ oxidation. The phthalimido-protected oxidised cycloadducts are valuable building blocks for the synthesis of polycyclic polyfunctionalised heterocyclic compounds. A reaction sequence consisting of a chemoselective sodium borohydride reduction and an acid induced *Friedel-Crafts* type cyclisation led to polyfunctionalised seven-membered dibenzo-azepine derivatives in excellent yields (Scheme V).
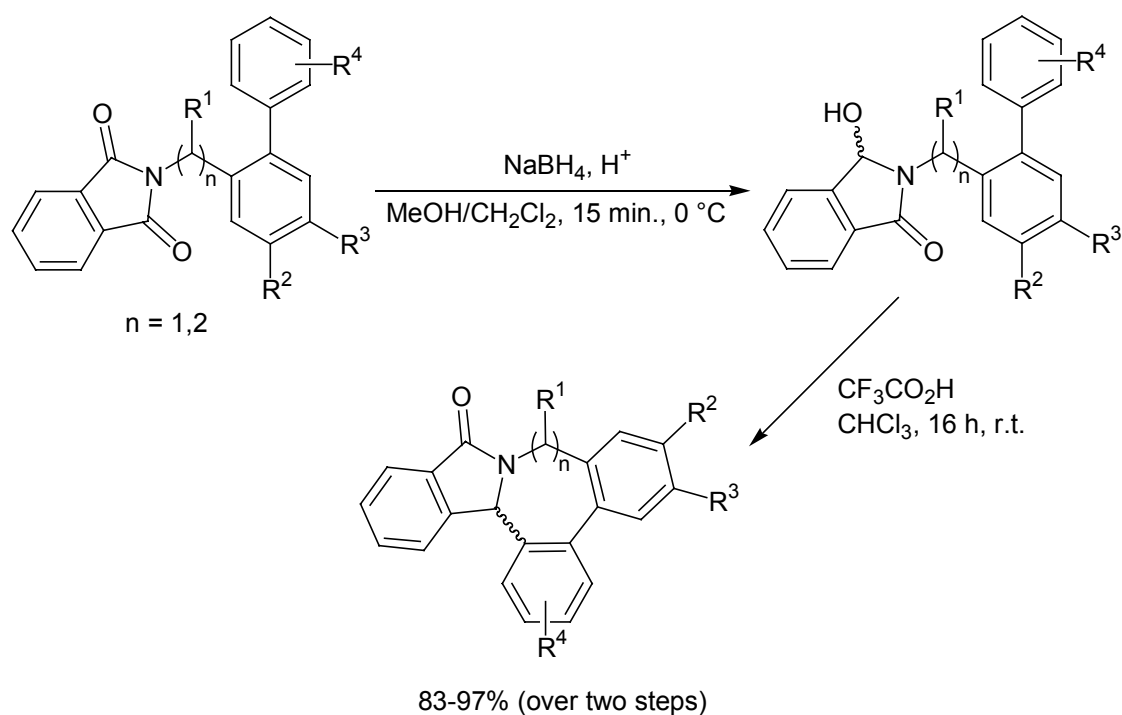
Scheme V

This sequence can also be used to generate six- and eight-membered isoindolinone derivatives when appropriate electronic and structural preconditions are fulfilled.

Alternatively, the dihydroaromatic compounds can be used as substrates for rhodium(II)-catalysed C-H activation reaction with a variety of diazo compounds as carbenoid precursors. Nitrogen, silicon and oxygen-functionalysed dienes were also accepted by the catalyst, while sulfur functionalysed dienes failed to react. The corresponding polysubstituted benzene derivatives were obtained in excellent yields (up to 89%) and as single regioisomers (Scheme VI).
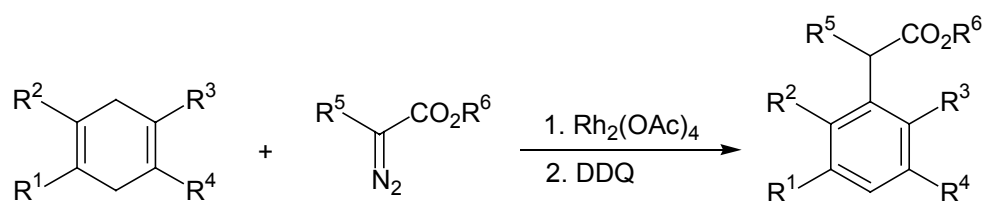
Scheme VI

A copper-catalysed C-H activation reaction was also developed and, although limited to stabilised carbenes, the yields were comparable with the rhodium(II)-catalysed reaction.

5   Zusammenfassung

Wie in den letzten Jahren gezeigt werden konnte toleriert die Kobalt(I)-katalysierte *Diels-Alder*-Reaktion eine große Bandbreite an Substraten mit diversen funktionellen Gruppen. Während Bor, Silizium, Sauerstoff und Schwefel enthaltene funktionelle Gruppen bereitwillig von dem Katalysator akzeptiert werden, konnten Stickstoff-funktionalisierte Startmaterialien bisher nicht eingesetzt werden.

Ziel dieser Untersuchung war die Entwicklung der Kobalt(I) katalysierten Diels-Alder Reaktion von Stickstoff-funktionalisierten Alkinen und die Synthese von Dibenzoazepinen. Ausgehend von der Entdeckung, daß sich Phthalimid als Schutzgruppe für die Reaktion propargylischer Amine mit 1,3-Dienen eignet, wurden weitere Modifikationen vorgenommen. In deren Verlauf stellten sich Sulfimide und einfache Amide als ebenso geeignete Schutzgruppen heraus, obwohl mit diesen nur moderate Ausbeuten erzielt werden konnten (bis zu 48%).

Der Einsatz von Arylpropargylaminen, welche leicht durch die *Sonogashira*-Reaktion zugänglich sind, lieferte die entsprechenden *Diels-Alder*-Produkte in exzellenten Ausbeuten (bis zu 98%) (Schema IV).
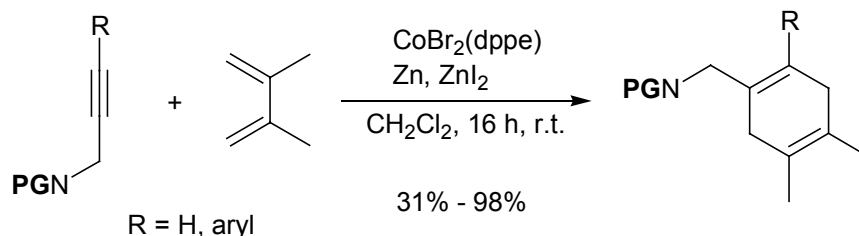
Schema IV

Ebenso konnten erstmals von Glycin abgeleitete Startmaterialien eingesetzt werden wodurch die Verwendung azyklischer Schutzgruppen am Stickstoff demonstriert werden konnten. Trotzdem werden Startmaterialien mit einer freien NH-Gruppierung nicht von dem Kobalt-Katalysator toleriert.

Die Cycloaddukte wurden anschließend mittels DDQ Oxidation in die entsprechenden Biaryle überführt. Die Phthalimid-geschützen, oxidierten Cycloaddukt sind wertvolle Bausteine für die Synthese polyzyklischer, hochfunktionalisierter heterozyklischer Verbindungen.

Eine Reaktionssequenz bestehend aus einer chemoselektiven Natriumborhydridreduktion und einer säureinduzierten *Friedel-Crafts*-artigen Zyklisierung führte in exzellenten Ausbeuten zu polyfunktionalisierten Dibenzoazepinen (Schema V).

83-97% (over two steps)
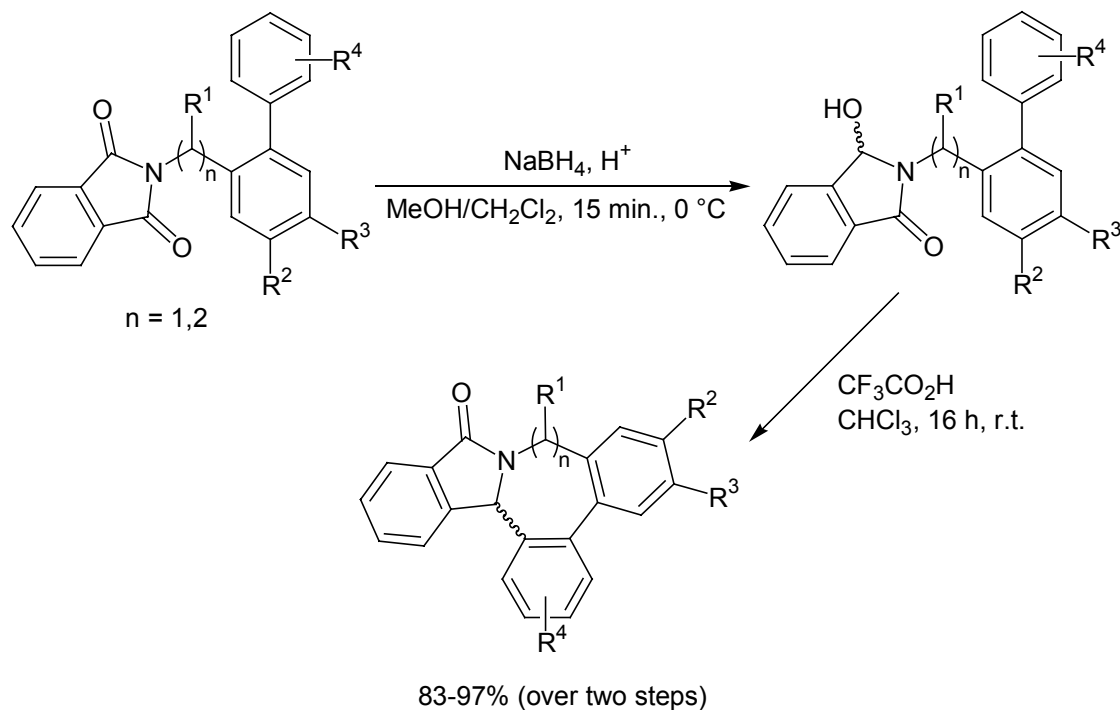
Schema V

Diese Reaktionssequenz kann ebenso zur Darstellung von Sechs- und Achtring Isoindolinonen verwendet werden, wenn entsprechende elektronische und strukturelle Bedingungen eingehalten werden.

Alternativ können die dihydroaromatischen Verbindungen als Substrate für Rhodium(II)-katalysierte C-H-Aktivierung mit einer großen Bandbreite an Diazoverbindungen, als Carbenoid-Vorläufer, verwendet werden.

Stickstoff-, Silizium- und Sauerstoff-funktionalisierte Diene konnten im Gegensatz zu Schwefel-funktionalisierten Dienen ebenfalls mit dem Katalysator umgesetzt werden. Die entsprechenden polysubstituierten Benzolderivate konnten in Form eines einzigen Regioisomers in exzellenten Ausbeuten (bis zu 89%) erhalten werden (Schema VI).
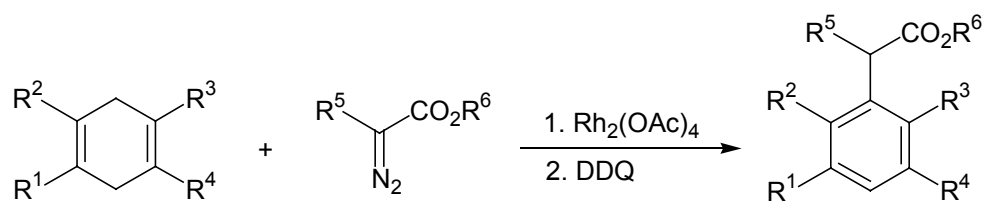
Schema VI

Desweiteren wurde eine Kupfer-katalysierte C-H-Aktivierung entwickelt, welche jedoch, trotz ihrer Beschränkung auf stabilisierte Carbene, der Rhodium(II)-katalysierten Reaktionen vergleichbare Ausbeuten lieferte.

C   Experimental part

1   General

All reactions were performed in heat gun-dried glassware under argon atmosphere. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe, syringe pump or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation and then at vacuum pump. All yields given refer to as isolated yields.

1.1   Solvents

All the solvents were pre-dried over Na_2SO_4 or $MgSO_4$. Subsequently they were dried by refluxing 48 hours over drying agents, distilled and stored under argon atmosphere. CH_2Cl_2 and acetone were dried over P_2O_5, THF over KOH, CaH_2 and then potassium, diethyl ether and petroleum ether (40-60 °C) over sodium/potassium, toluene over potassium, methanol over magnesium, ethanol over sodium/phthalic acid ethyl ester, dimethylformamide over CaH_2. Solvents for column chromatography were distilled by rotary evaporation.

1.2   Materials

- Commercial grade reagents were used and eventually purified by distillation or recrystallisation.
- *Catalysts*: bis-(2-methallyl)-COD-ruthenium(II), $PdCl_2(PPh_3)_2$, $Rh_2(OAc)_4$, $Cu(acac)_2$ and $Cu(hfacac)_2$ are commercially available. Cu(II)-bis(*N*-benzyl-salicylaldiminato) (**313**) was synthesised according to the procedure of *Sacconi* and *Ciampolini*[121]. $CoBr_2(dppe)$ was synthesised according to the procedure of *Hilt*[77].
- ZnI_2 was dried at 120 °C for 16 hours at vacuum pump and stored under argon.
- *Dienes*: Because of the tendency of the dienes to aromatise even if stored at low temperatures under argon, they were prepared immediately before use with a short reaction time (4 hours) and higher loadings of catalyst (up to 10%). Large scale *Diels-Alder* reactions (>5 mmol) sometimes results in an uncontrollable heat evolution after a variable induction period in which the color of the mixture changes from green to deep brown. A water or ice cooling bath is therefore advisable. In order to minimize air exposure, purification of the *Diels-Alder* products by Kugelrohr distillation under argon or vacuum was preferred to column chromatography. Even so, a small amount of aromatic product could always be detected in ^{1}H-NMR and estimated by integration between 2% and 5%. Although all the dienes are known compounds no spectroscopical characterisation was found in the literature. Therefore ^{1}H-NMR and ^{13}C-NMR spectra were measured and the data are reported together with the corresponding synthetic procedure.
- *Diazoesters*: Ethyldiazoacetate (**263**), commercially available, was distilled before use. The other diazo compounds were synthesised according to literature procedures. Ethyl 2-diazopropionate[122] (**259**), ethyl 2-diazo *iso*-propylacetate[122] (**272**), 2-diazo-3-oxobutyric acid ethyl ester[481] (**273**) and methyl 2-diazophenylacetate[53] (**92**) are stable and can be stored without any particular precaution at 0-5 °C for months, while ethyl (*E*)-2-diazo-4-phenylbutenoate[123] (**274**) is rather unstable and should be prepared and used immediately. Because of the diazoester excess and especially in the case of large scale preparations (>5 mmol of diene) special care should be taken in order to avoid overpressure in the reaction flask during the reaction.

- The following starting materials were prepared according to literature procedures: 2-prop-2-ynyl-isoindole-1,3-dione[100] (**109**), phenethyl-carbamic acid methyl ester[124] (**111**), *N*-methoxycarbonyl-*N*-(2-phenylethyl)-2-phenylethynylamine[78] (**112**), 2-but-3-

ynyl-isondole-1,3-dione[125] (**117**), toluene-4-sulfonic acid 1-methyl-prop-2-ynyl ester[126] (**118**), 2-(1-methyl-prop-2-ynyl)-isoindole-1,3-dione[127] (**119**), 2-pent-4-ynyl-isoindole-1,3-dione[128] (**121**), 1,1-dioxo-2-prop-2-ynyl-1,2-dihydro-1-λ^6-benzo[*d*]isothiazol-3-one[100] (**135**), 5,6-dimethyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione[129] (**315**), 1-prop-2-ynyl-pyrrolidine-2,5-dione[130] (**137**), 1-prop-2-ynyl-pyrrolidin-2-one[131] (**138**), (benzenesulfonyl-prop-2-ynyl-amino)-acetic acid methyl ester[132] (**139**), 1-prop-2-ynyl-1*H*-indole-2,3-dione[133] (**140**), 1-prop-2-ynyl-pyrrolidine[134] (**141**), 1-prop-2-ynyl-1*H*-indole[135] (**142**), 9-prop-2-ynyl-9*H*-carbazole[135] (**143**), 1-((*E*)-3-methylbuta-1,3-dienyl)-pyrrolidin-2-one[80a] (**154**), 2-methylbut-1-en-3-yne[136] (**153**), 2-(3-pyridin-2-yl-prop-2-ynyl)-isoindole-1,3-dione[137] (**175**), (*E*)-2-aza-1-phenyl-1,3-butadiene[138] (**203**), 2-methoxy-1,3-butadiene[139] (**255**), (4,5-dimethyl-cyclohexa-1,4-dienyl)-benzene[31a] (**43**), (4,5-dimethyl-cyclohexa-1,4-dienyl)-trimethyl-silane[31a] (**44**), 1,2-diethyl-4,5-dimethyl-cyclohexa-1,4-diene[34] (**45**), 1,2-bis-methoxymethyl-4,5-dimethyl-cyclohexa-1,4-diene[34] (**52**), 1,2-diethyl-4-methyl-cyclohexa-1,4-diene[34] (**282**), 1,2-bis-methoxymethyl-4-methyl-cyclohexa-1,4-diene[34] (**279**), 1,2-dimethyl-4-phenyl-5-phenylsulfanyl-1,4-cyclohexadiene[33] (**290**), (4,5-diethyl-cyclohexa-1,4-dienyloxy)-trimethyl-silane[35] (**296**), butyl-5,6-dimethyl-2,5-heptadienoate[36,77] (**62**), 2-butyl-4,5-dimethyl-hexa-1,4-diene[36,77] (**64**), 4-isopropenyl-1,2-dimethyl-cyclohexa-1,4-diene[140] (**299**).

- 2-[1-(1-ethyl-propyl)-3-phenyl-prop-2-ynyl]-isoindole-1,3-dione (**225**) was donated from Prof. Paul Knochel (LMU München).

1.3 Chromatography

- Thin layer chromatography (TLC) was performed on Merck precoated aluminium silica gel 60 F-254 plates. Visualisation of TLC plates was accomplished with one or more of the following: 254 nm UV light; phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), concentrated sulfuric acid (60 ml) in water (940 ml); $KMnO_4$ (1.5 g), $NaHCO_3$ (5 g) in water (400 ml).
- Column chromatography was performed on Merck silica gel (230-400 mesh) under pressure of nitrogen.
- Gaschromatography: GC were measured with a Hewlett & Packard HP 5890 GC System equipped with a Optima-5-MS (30 m · 0.25 mm · 0.25 μm) column and with a FID detector. GC-MS were measured with a Hewlett & Packard HP 6890 GC System equipped with a Hewlett & Packard column, HP-1 Methylpolysiloxane (30 m · 0.32 mm · 0.25 μm), and Hewlett & Packard MSD 5973 Mass Selective Detector (70 eV).
- Preparative HPLC was performed on Dynamax SD-1 equipped with a Dynamax Si60 column at 25 °C, UV detector 254 nm.

2 Instrumental analysis

- **NMR**: ^{1}H-NMR and ^{13}C-NMR spectra were measured with a Bruker ARX-300, ARX-400, ARX-500 or ARX-600. ^{1}H-NMR chemical shift are expressed in parts per million (δ) from the $CDCl_3$ peak at 7.26 ppm, C_6D_6 at 7.16 ppm and D_2O at 4.79 ppm. ^{13}C-NMR chemical shift are expressed in parts per million (δ) from the $CDCl_3$ peak at 77.0 ppm and C_6D_6 at 128.0 ppm. Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants, *J*, are reported in Hz.
- **Mass Spectrometry**: mass spectra samples were measured on a CH7 (EI-MS) (70 eV) Spectrometer, (Varian MAT). High Resolution Mass Spectra (HRMS) were measured with a Finnigan-MAT 95 Q spectrometer.

- **Infrared Spectroscopy**: the samples were measured as KBr-pellets or as thin films on NaCl plates and the spectra were recorded on Interferometer IFS 88 (Bruker) from 4000 to 400 cm^{-1}.
- **Crystal Structure Analysis**: x-ray diffraction data were collected on a IPDS2 diffractometer equipped with a liquid nitrogen Oxford-Cryostream device. Crystal date and details of measurements are summarised in Tables. Common to all compounds: MoKα radiation, λ= 0.71073 Å, monochromator graphite, psi-scan absorption correction.
  SHELXL97 was used for structure solution and refinement based on F^2.
  DIAMOND 3.0 was used for all graphical representations.

3　　General procedures

Unless otherwise stated the following procedures were used.

General procedure for the cobalt-catalysed *Diels-Alder* reaction, Method A

To a solution of the alkyne in dry CH$_2$Cl$_2$ were subsequently added CoBr$_2$(dppe) (10 mol%), Zn dust (50 mol%), ZnI$_2$ (50 mol%) and the diene (1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered with the appropriate eluent over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give a residue that was dissolved in benzene and oxidised by DDQ (1.2 equiv.) at room temperature. After 2 hours the reaction mixture was filtered with the appropriate eluent over a short pad of silica gel or washed with an aqueous solution containing 10% NaOH and 10% Na$_2$S$_2$O$_3$, concentrated under reduced pressure and purified by column chromatography on silica gel.

General procedure for the cobalt-catalysed *Diels-Alder* reaction, Method B

To a solution of the alkyne in dry CH$_2$Cl$_2$ were subsequently added CoBr$_2$(dppe) (5-10 mol%), anhydrous ZnI$_2$ (50 mol%), Zn dust (50 mol%) or NBu$_4$BH$_4$ (1.1 equiv.) and the diene (1.2 equiv.) The resulting mixture was stirred 4 hours at room temperature, then filtered with the appropriate eluent over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation under vacuum or column chromatography on silica gel.

General procedure for the *Sonogashira* reaction

To a stirred solution of the alkyne in dry CH$_2$Cl$_2$ were subsequently added dry triethylamine (5.0 equiv.), iodo-arene (1.2 equiv.), CuI (5 mol%), PdCl$_2$(PPh$_3$)$_2$ (5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO$_3$ solution, the layers were separated and the water phase was extracted by CH$_2$Cl$_2$. The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel.

General procedure for the cyclisation reaction

A solution of the starting material in a 1:1 mixture of dry CH$_2$Cl$_2$ and MeOH was cooled at 0 °C, then NaBH$_4$ (5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been

consumed the excess of $NaBH_4$ was carefully quenched by 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residual white solid was dissolved in 3 ml of chloroform, 1 ml of TFA (trifluoroacetic acid) was added and the mixture was stirred overnight at room temperature. The excess of TFA was carefully quenched by 10% NaOH. The layers were separated and the water phase extracted by $CHCl_3$ (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel.

General procedure for the rhodium-catalysed C-H activation reaction
A solution of the diazoester (2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour *via* syringe pump to a 0 °C solution of freshly made diene and $Rh_2(OAc)_4$ (0.5 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel with the appropriate eluent. The filtrate was concentrated under reduced pressure to give a residue that was dissolved in benzene and oxidised by DDQ (1.2 equiv.) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel with the appropriate eluent, concentrated under reduced pressure and purified by column chromatography on silica gel.

General procedure for the copper-catalysed C-H activation reaction
A solution of the diazoester (2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour *via* syringe pump to a 0 °C solution of freshly made diene and $Cu(hfacac)_2$ (1 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel with the appropriate eluent. The filtrate was concentrated under reduced pressure to give a residue that was dissolved in benzene and oxidised by DDQ (1.2 equiv.) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel with the appropriate eluent, concentrated under reduced pressure and purified by column chromatography on silica gel.

4 Cobalt-catalysed neutral Diels-Alder reactions on nitrogen-functionalised alkynes

Synthesis of 2-(3,4-dimethyl-benzyl)-isoindole-1,3-dione (110)
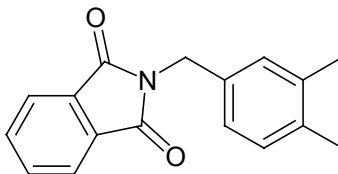
To a stirred solution of 2-prop-2-ynyl-isoindole-1,3-dione (**109**) (150 mg, 0.81 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (50 mg, 0.081 mmol, 10 mol%), Zn dust (26.5 mg, 0.40 mmol, 50 mol%), ZnI$_2$ (129 mg, 0.40 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.14 ml, 1.21 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (221 mg, 0.97 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 77 mg (36%) of (**110**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.88-7.78 (m, 2H), 7.74-7.64 (m, 2H), 7.25-7.14 (m, 2H), 7.07 (d, 1H, J = 7.6 Hz), 4.78 (s, 2H), 2.23 (s, 3H), 2.21 (m, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.9, 136.8, 136.1, 133.8, 132.2, 129.9, 129.8, 126.0, 123.2, 41.3, 19.6, 19.3.
IR (KBr): 3025, 2921, 1705, 1427, 1393, 1110, 956, 794, 729, 706, 530 cm^{-1}.
MS (EI): m/z 265 (M$^+$), 250, 222, 160, 118, 77.
HRMS (EI): m/z calcd. for C$_{17}$H$_{15}$NO$_2$: 265.1103, found 265.1102.

Synthesis of 2-[2-(3,4-dimethyl-phenyl)-ethyl]-isoindole-1,3-dione (123)
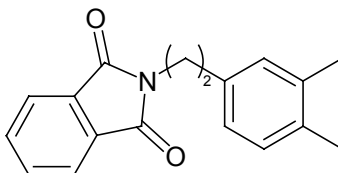
To a stirred solution of 2-but-3-ynyl-isoindole-1,3-dione (**117**) (150 mg, 0.75 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (46.5 mg, 0.075 mmol, 10 mol%), Zn dust (25 mg, 0.38 mmol, 50 mol%), ZnI$_2$ (120 mg, 0.38 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.13 ml, 1.13 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (205 mg, 0.90 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1),

concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 94 mg (45%) of (**123**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.89-7.79 (m, 2H), 7.76-7.65 (m, 2H), 7.11-6.96 (m, 3H), 3.96-3.83 (m, 2H), 2.99-2.86 (m, 2H), 2.22 (s, 6H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.1, 136.6, 135.3, 134.6, 133.7, 132.0, 130.1, 129.7, 126.0, 123.1, 39.4, 34.1, 19.5, 19.2.
IR (KBr): 2934, 1720, 1434, 1392, 1350, 717 cm^{-1}.
MS (EI): *m/z* 279 (M$^+$), 160, 132, 119, 77.
HRMS (EI): *m/z* calcd. for C$_{18}$H$_{17}$NO$_2$: 279.1259, found 279.1262.

Synthesis of 2-[1-(3,4-dimethyl-phenyl)-ethyl]-isoindole-1,3-dione (124)
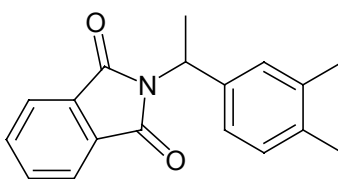
To a stirred solution of 2-(1-methyl-prop-2-ynyl)-isoindole-1,3-dione (**119**) (123 mg, 0.62 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (38 mg, 0.062 mmol, 10 mol%), Zn dust (20 mg, 0.31 mmol, 50 mol%), ZnI$_2$ (100 mg, 0.31 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.10 ml, 0.93 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel and concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (169 mg, 0.74 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 61 mg (35%) of (**124**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.75-7.66 (m, 2H), 7.63-7.53 (m, 2H), 7.22-7.15 (m, 2H), 7.04-6.96 (m, 1H), 5.43 (q, 1H, *J* = 7.3 Hz), 2.16 (s, 3H), 2.13 (s, 3H), 1.82 (d, 3H, *J* = 7.3 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.1, 137.7, 136.5, 135.9, 133.8, 131.9, 129.6, 128.7, 124.7, 123.1, 49.3, 19.8, 19.4, 17.5.
IR (KBr): 2938, 1703, 1385, 1357, 1329, 1043, 716 cm^{-1}.
MS (EI): *m/z* 279 (M$^+$), 264, 132, 77, 41.
HRMS (EI): *m/z* calcd. for C$_{18}$H$_{17}$NO$_2$: 279.1259, found 279.1263.

Synthesis of 2-[3-(3,4-dimethyl-phenyl)-propyl]-isoindole-1,3-dione (125)
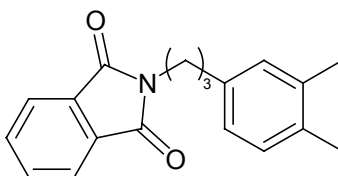
To a stirred solution of 2-pent-4-ynyl-isoindole-1,3-dione (**121**) (150 mg, 0.70 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (44 mg, 0.070 mmol, 10 mol%), Zn dust (23 mg, 0.35 mmol, 50 mol%), ZnI$_2$ (112 mg, 0.35 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.12 ml, 1.05 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (191 mg, 0.84 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 73 mg (36%) of (**125**) as a yellowish oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.88-7.77 (m, 2H), 7.75-7.65 (m, 2H), 7.05-6.87 (m, 3H), 3.74 (t, 2H, J = 7.1 Hz), 2.68-2.57 (m, 2H), 2.19 (s, 3H), 2.17 (s, 3H), 2.10-1.94 (m, 2H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.3, 138.3, 136.3, 133.9, 133.7, 132.0, 129.5, 125.5, 123.0, 37.8, 34.6, 32.7, 29.7, 19.6, 19.2.
IR (KBr): 2938, 1712, 1396, 1028, 720 cm^{-1}.
MS (EI): m/z 293 (M$^+$), 161, 146, 133, 120, 91, 77.
HRMS (EI): m/z calcd. for C$_{19}$H$_{19}$NO$_2$: 293.1416, found 293.1422.

Synthesis of 2-(3,4-dimethyl-benzyl)-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one (144)
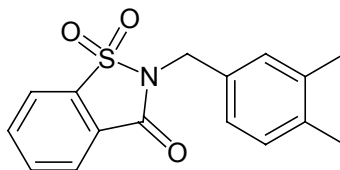
To a stirred solution of 1,1-dioxo-2-prop-2-ynyl-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one (**135**) (150 mg, 0.68 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (42 mg, 0.068 mmol, 10 mol%), Zn dust (22 mg, 0.34 mmol, 50 mol%), ZnI$_2$ (108 mg, 0.34 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.11 ml, 1.02 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (185 mg, 0.81 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 85 mg (41%) of (**144**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.10-8.00 (m, 1H), 7.97-7.77 (m, 3H), 7.33-7.33 (m, 2H), 7.13 (d, 1H, J = 7.7 Hz), 4.87 (s, 2H), 2.27 (s 3H), 2.25 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 158.8, 137.7, 136.8, 136.6, 134.6, 134.2, 131.8, 129.9, 129.8, 127.3, 126.2, 125.1, 120.9, 42.4, 19.7, 19.4.
IR (KBr): 2964, 1732, 1462, 1328, 1250, 1178, 760, 676, 596 cm^{-1}.
MS (EI): m/z 301 (M$^+$), 237, 222, 132, 106, 77.
HRMS (EI): m/z calcd. for C$_{16}$H$_{15}$NO$_3$S: 301.0773, found 301.0763.

Synthesis of 5,6-dimethyl-2-prop-2-ynyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (136)
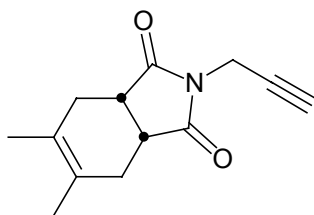
To a 0 °C solution of 5,6-dimethyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (**315**) (150 mg, 0.84 mmol) in 3 ml of dry DMF were successively added NaH (1 mmol, 24 mg, 1.2 equiv.) and freshly distilled propargyl bromide (**114**) (119 mg, 1 mmol, 1.2 equiv.) . The course of the reaction was monitored by GC-MS. After 3 hours the excess of NaH was carefully quenched by ice water and diethyl ether was added. The organic layer was separated and the aqueous phase extracted by diethyl ether (3x20 ml). The combined organic phases were dried over Na$_2$SO$_4$, filtered, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:3) to give 139 mg (76%) of (**136**) as a yellowish oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 4.12 (d, 2H, J = 2.4 Hz), 3.07-2.95 (m, 2H), 2.38 (m, 2H), 2.25-2.04 (m, 3H), 1.59 (s, 6H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 178.7, 126.7, 76.7, 70.7, 39.9, 30.5, 27.6, 18.9.
IR (film): 3265, 2912, 1708, 1426, 1396, 1331, 1181, 994, 709 cm^{-1}.
MS (EI): m/z 217 (M$^+$), 174, 147, 136, 107, 93, 77.
HRMS (EI): m/z calcd. for C$_{13}$H$_{15}$NO$_2$: 217.1103, found 217.1100.

Synthesis of 2-(3,4-dimethyl-benzyl)-5,6-dimethyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (145)
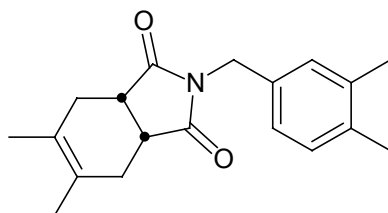
To a stirred solution of 5,6-dimethyl-2-prop-2-ynyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (**136**) (150 mg, 0.69 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (43 mg, 0.07 mmol, 10 mol%), Zn dust (23 mg, 0.345 mmol, 50 mol%), ZnI$_2$ (110 mg, 0.475 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.12 ml, 1.03 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:3) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (188 mg, 0.83 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:3), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:3) to give 94 mg (46%) of (**145**) as a yellowish oil.

¹H-NMR (300 MHz, CDCl₃): δ = 7.05-6.90 (m, 3H), 4.53 (s, 2H), 3.05-2.97 (m, 2H), 2.48-2.36 (m, 2H), 2.27-2.12 (m, 2H), 2.19 (s, 6H), 1.56 (s, 3H), 1.55 (s, 3H).
¹³C-NMR (75 MHz, CDCl₃): δ = 179.8, 136.5, 135.7, 133.3, 129.5, 129.0, 126.9, 125.3, 42.0, 39.9, 30.7, 19.6, 19.3, 18.9.
IR (film): 2973, 2927, 1702, 1425, 1400, 1340, 1186, 995, 802, 777, 613 cm⁻¹.
MS (EI): *m/z* 297 (M⁺), 191, 119, 107, 91, 77.
HRMS (EI): *m/z* calcd. for C₁₉H₂₃NO₂: 297.1729, found 297.1730.

Synthesis of 1-(3,4-dimethyl-benzyl)-pyrrolidine-2,5-dione (146)
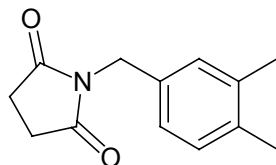
To a stirred solution of 1-prop-2-ynyl-pyrrolidine-2,5-dione (**137**) (150 mg, 1.09 mmol) in dry CH₂Cl₂ (4 ml) were subsequently added CoBr₂(dppe) (67.5 mg, 0.11 mmol, 10 mol%), Zn dust (36 mg, 0.55 mmol, 50 mol%), ZnI₂ (174.5 mg, 0.55 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.19 ml, 1.64 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered with diethyl ether over a short pad of silica gel and concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (298 mg, 1.31 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was washed with an aqueous solution containing 10% NaOH and 10% Na₂S₂O₃, the water phase was separated and extracted by CH₂Cl₂ (2x20 ml). The combined organic phases were dried over Na₂SO₄, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:3) to give 75 mg (31%) of (**146**) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ = 7.20-7.02 (m, 3H), 4.58 (s, 2H), 2.67 (m, 4H), 2.23 (s, 3H), 2.22 (s, 3H).
¹³C-NMR (75 MHz, CDCl₃): δ = 176.8, 136.7, 136.3, 133.2, 130.0, 129.7, 126.3, 42.0, 28.1, 19.6, 19.3.
IR (KBr): 2981, 1702, 1437, 1400, 1333, 1175, 908, 823 cm⁻¹.
MS (EI): *m/z* 217 (M⁺), 174, 146, 132, 91, 77.
HRMS (EI): *m/z* calcd. for C₁₃H₁₅NO₂: 217.1103, found 217.1098.

Synthesis of 1-(3,4-dimethyl-benzyl)-pyrrolidin-2-one (147)
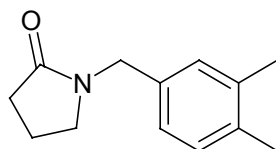
To a stirred solution of 1-prop-2-ynyl-pyrrolidin-2-one (**138**) (155 mg, 1.3 mmol) in dry CH₂Cl₂ (4 ml) were subsequently added CoBr₂(dppe) (77.5 mg, 0.13 mmol, 10 mol%), Zn dust (41 mg, 0.63 mmol, 50 mol%), ZnI₂ (200 mg, 0.63 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.2 ml, 1.88 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: CH₂Cl₂:MeOH = 20:1) over a short pad of silica gel

and concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (343 mg, 1.51 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was washed with an aqueous solution containing 10% NaOH and 10% $Na_2S_2O_3$, the water phase was separated and extracted by CH_2Cl_2 (2x20 ml). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: CH_2Cl_2:MeOH = 40:1) to give 124 mg (48%) of (**147**) as a colourless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.10 (d, 1H, J = 7.7 Hz), 7.06-6.95 (m, 2H), 4.35 (s, 2H), 3.27-3.17 (m, 2H), 2.46-2.34 (m, 2H), 2.21 (s, 6H), 2.02-1.86 (m, 2H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 174.6, 136.7, 135.6, 133.7, 129.6, 129.3, 125.4, 46.3, 46.1, 30.8, 19.5, 19.2, 17.5.
IR (film): 2920, 1686, 1439, 1286, 1262 cm^{-1}.
MS (EI): m/z 203 (M$^+$), 188, 160, 119, 84, 77.
HRMS (EI): m/z calcd. for $C_{13}H_{17}NO$: 203.1310, found 203.1308.

Synthesis of [(3,4-dimethyl-benzyl)-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (148)
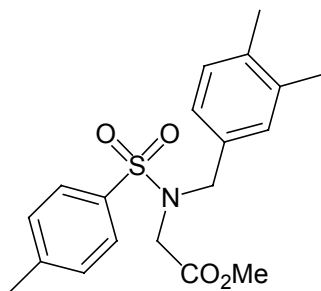
To a solution of (benzenesulfonyl-prop-2-ynyl-amino)-acetic acid methyl ester (**139**) (150 mg, 0.53 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added CoBr$_2$(dppe) (33 mg, 0.053 mmol, 10 mol%), Zn dust (17.4 mg, 0.27 mmol, 50 mol%), ZnI$_2$ (85 mg, 0.27 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.09 ml, 0.80 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (145 mg, 0.64 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered with diethyl ether over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:2) to give 88 mg (46%) of (**148**) as a yellowish oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.81-7.74 (m, 2H), 7.36-7.29 (m, 2H), 7.05 (d, 1H, J = 7.5 Hz), 6.98-6.89 (m, 2H), 4.42 (s, 2H), 3.91 (s, 2H), 3.54 (s, 3H), 2.44 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.2, 143.3, 136.9, 136.4, 132.0, 129.9, 129.8, 129.4, 127.4, 126.1, 51.8, 50.9, 46.3, 21.5, 19.6, 19.4.
IR (KBr): 2950, 1739, 1343, 1169, 1092, 999, 933, 889, 833, 802, 711, 677 cm^{-1}.
MS (ESI): m/z 384 (M+Na$^+$).
HRMS (ESI) for $C_{19}H_{23}NO_4SNa$: calcd. 384.1246 (M+Na$^+$), found 384.1240 (M+Na$^+$).

Synthesis of 1-(3,4-dimethyl-benzyl)-pyrrolidine hydrochloride (150)
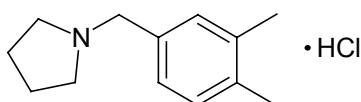
To a solution of 1-prop-2-ynyl-pyrrolidine (**141**) (513 mg, 4.7 mmol) in CH_2Cl_2 (5 ml) were subsequently added $CoBr_2$(dppe) (290 mg, 0.47 mmol, 10 mol%), Zn dust (154 mg, 2.35 mmol, 50 mol%), ZnI_2 (750 mg, 2.35 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.8 ml, 7.05 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered with (eluent: CH_2Cl_2:MeOH = 10:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (1.28 g, 5.64 mmol, 1.2 equiv.) at room temperature. After 2 hours the reaction mixture was washed with an aqueous solution containing 10% NaOH and 10% $Na_2S_2O_3$, the water phase was separated and extracted by diethyl ether (2x20 ml). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure to give a brown solid that was dissolved in dry ether and, under intense stirring, precipitated in the presence of HCl gas. After 1 hour the solid was filtered and dried in high vacuum to give 53 mg (5%) of (**150**) as a white solid.

^{1}H-NMR (300 MHz, D_2O): δ = 7.27-7.13 (m, 3H), 4.22 (s, 2H), 3.49-3.34 (m, 2H), 3.19-3.00 (m, 2H), 2.23 (s, 3H), 2.22 (s, 3H), 2.17-2.02 (m, 2H), 2.00-1.83 (m, 2H).
^{13}C-NMR (75 MHz, D_2O): δ = 139.5, 138.6, 131.7, 130.7, 128.4, 128.1, 58.2, 53.9, 22.9, 19.2, 19.1.
MS (EI): *m/z* 189 (M$^+$), 119, 84, 70, 42, 36.
HRMS (EI) for $C_{13}H_{19}N$: calcd. 189.1517, found 189.1514.

Synthesis of 1-(3,4-dimethyl-benzyl)-1*H*-indole (151)
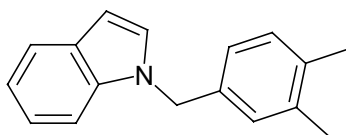
To a solution of 1-prop-2-ynyl-1*H*-indole (**142**) (300 mg, 1.93 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added $CoBr_2$(dppe) (119 mg, 0.193 mmol, 10 mol%), Zn dust (63 mg, 0.96 mmol, 50 mol%), ZnI_2 (308 mg, 0.96 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.33 ml, 2.90 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (525 mg, 2.32 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 50:1) to give a yellowish oil that was subjected to Kugelrohr distillation to give 71 mg of (**151**) (16%) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.95-7.89 (m, 1H), 7.61-7.54 (m, 1H), 7.49-7.27 (m, 4H), 7.23-7.17 (m, 1H), 7.15-7.08 (m, 1H), 6.81 (d, 1H, *J* = 3.0 Hz), 5.50 (s, 2H), 2.48 (s, 3H), 2.46 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 136.9, 136.3, 135.9, 134.8, 129.9, 129.8, 128.6, 128.1, 124.3, 121.5, 120.8, 119.4, 109.7, 101.4, 49.8, 19.7, 19.4.
IR (KBr): 3098, 2933, 1463, 1397, 1335, 1178, 754, 738 cm^{-1}.
MS (EI): *m/z* 235 (M$^+$), 119, 91, 77.
HRMS (EI) for C$_{17}$H$_{17}$N: calcd. 235.1361, found 235.1360.

Synthesis of 9-(3,4-dimethyl-benzyl)-9*H*-carbazole (152)
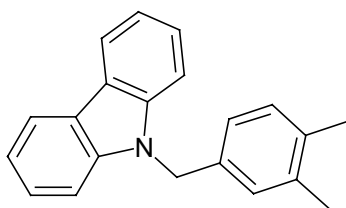
To a solution of 9-prop-2-ynyl-9*H*-carbazole (**143**) (150 mg, 0.73 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (45 mg, 0.073 mmol, 10 mol%), Zn dust (24 mg, 0.36 mmol, 50 mol%), ZnI$_2$ (117 mg, 0.36 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.12 ml, 1.1 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (199 mg, 0.88 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 98 mg of (**152**) (47%) as a brown solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.22 (m, 2H), 7.57-7.41 (m, 4H), 7.38-7.28 (m, 2H), 7.12-7.01 (m, 2H), 6.98-6.90 (m, 1H), 5.49 (s, 2H), 2.27 (s, 3H), 2.23 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 140.7, 136.9, 135.7, 134.5, 129.9, 127.6, 125.7, 123.8, 122.9, 120.3, 119.0, 108.9, 46.3, 19.7, 19.3.
IR (KBr): 3047, 2931, 1594, 1457, 1331, 1208, 751, 720 cm^{-1}.
MS (EI): *m/z* 285 (M$^+$), 268, 167, 119, 91, 41.
HRMS (EI): *m/z* calcd. for C$_{21}$H$_{19}$N: 285.1517, found 285.1518.

Synthesis of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (161)
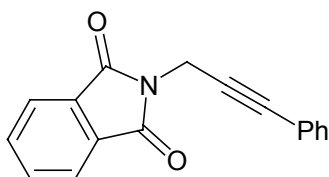
To a stirred solution of 2-prop-2-ynyl-isoindole-1,3-dione (**109**) (500 mg, 2.70 mmol) in dry CH_2Cl_2 (10 ml) were subsequently added triethylamine (1.9 ml, 13.5 mmol, 5.0 equiv.), iodobenzene (**160**) (0.36 ml, 3.24 mmol, 1.2 equiv.), CuI (25.7 mg, 0.13 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (94.6 mg, 0.13 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml), the layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 492 mg (70%) of (**161**) as a white solid. Spectroscopical data were consistent with those reported in the literature[141] and are herein reported.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.85-7.76 (m, 2H), 7.70-7.60 (m, 2H), 7.37-7.28 (m, 2H), 7.23-7.13 (m, 3H), 4.60 (s, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.0, 134.1, 132.0, 131.8, 128.4, 128.1, 123.4, 122.2, 82.9, 82.6, 27.8.
IR (KBr): 1773, 1707, 1425, 1393, 1319, 1113, 942, 755, 730, 709 cm^{-1}.
MS (EI): m/z 261 (M$^+$), 233, 178, 147, 114, 76.
HRMS (EI): m/z calcd. for $C_{17}H_{11}NO_2$: 261.0790, found 261.0790.

Synthesis of 2-(4-phenylbut-3-ynyl)-isoindole-1,3-dione (163)
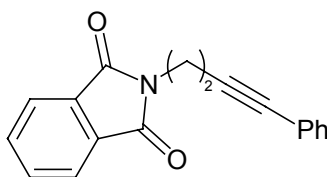
To a stirred solution of 2-but-3-ynyl-isondole-1,3-dione (**117**) (150 mg, 0.75 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added triethylamine (0.53 ml, 3.76 mmol, 5.0 equiv.), iodobenzene (**160**) (0.1 ml, 0.9 mmol, 1.2 equiv.), CuI (7.2 mg, 0.04 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (26.4 mg, 0.04 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (120 ml), the layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 160 mg (77%) of (**163**) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.88-6.76 (m, 2H), 6.73-6.62 (m, 2H), 6.37-6.15 (m, 5H), 3.00-2.89 (m, 2H), 1.87-1.75 (m, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 167.8, 133.8, 131.4, 129.4, 128.0, 127.7, 123.1, 118.7, 85.7, 82.2, 36.6, 19.2.
IR (KBr): 2945, 1771, 1701, 1393, 1116, 998, 760, 715, 691, 527 cm^{-1}.
MS (EI): m/z 275 (M$^+$), 160, 128, 77, 50.
HRMS (EI): m/z calcd. for $C_{18}H_{13}NO_2$: 275.0946, found 275.0939.

Synthesis of 2-(1-methyl-3-phenylprop-2-ynyl)-isoindole-1,3-dione (164)
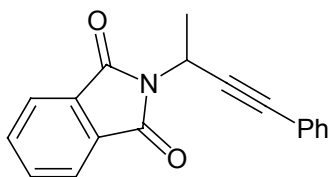
To a stirred solution of 2-(1-methyl-prop-2-ynyl)-isoindole-1,3-dione (**119**) (150 mg, 0.75 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added triethylamine (0.53 ml, 3.77 mmol, 5.0 equiv.), iodobenzene (**160**) (0.10 ml, 0.90 mmol, 1.2 equiv.), CuI (7.2 mg, 0.04 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (26.4 mg, 0.04 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml), the layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 167 mg (81%) of (**164**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.78-7.70 (m, 2H), 7.65-7.56 (m, 2H), 7.33 (dd, 2H, J = 6.7, 3.0 Hz), 7.22-7.11 (m, 3H), 5.34 (q, 1H, J = 7.1 Hz), 1.70 (d, 3H, J = 7.1 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.8, 133.9, 131.8, 131.7, 128.2, 128.0, 123.2, 122.4, 86.5, 82.7, 37.6, 20.2.
IR (KBr): 3063, 1708, 1386, 1148, 1065, 879, 760, 725, 714, 689 cm^{-1}.
MS (EI): *m/z* 275 (M$^+$), 260, 247, 218, 178, 128, 104, 76.
HRMS (EI): *m/z* calcd. for C$_{18}$H$_{13}$NO$_2$: 275.0946, found 275.0952.

Synthesis of 2-(5-phenyl-pent-4-ynyl)-isoindole-1,3-dione (165)
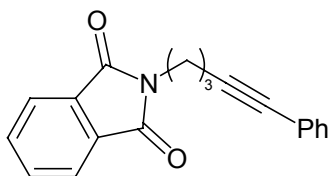
To a stirred solution of 2-pent-4-ynyl-isoindole-1,3-dione (**121**) (200 mg, 0.94 mmol) in dry CH_2Cl_2 (4 ml) were subsequently added triethylamine (0.6 ml, 4.70 mmol, 5.0 equiv.), iodobenzene (**160**) (0.13 ml, 1.13 mmol, 1.2 equiv.), CuI (9 mg, 0.05 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (33 mg, 0.05 mmol, 5 mol%) and the stirring was overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml), the layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether 2:1) to give 234 mg (86%) of (**165**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.87-7.77 (m, 2H), 7.71-7.61 (m, 2H), 7.36-7.17 (m, 5H), 3.87 (t, 2H, J = 7.0 Hz), 2.51 (t, 2H, J = 7.0 Hz), 2.11-1.95 (m, 2H).

¹³C-NMR (75 MHz, CDCl₃): δ = 168.2, 133.7, 131.9, 131.3, 127.9, 127.4, 123.5, 123.0, 88.6, 81.1, 37.2, 27.2, 17.1.
IR (KBr): 2902, 1710, 1400, 1026, 759, 724, 690, 531 cm⁻¹.
MS (EI): *m/z* 289 (M⁺), 160, 142, 115, 77.
HRMS (EI): *m/z* calcd. for $C_{19}H_{15}NO_2$: 289.1103, found 289.1099.

Synthesis of 1,1-dioxo-2-(3-phenyl-prop-2-ynyl)-1,2-dihydro-1-λ⁶-benzo[*d*]isothiazol-3-one (166)
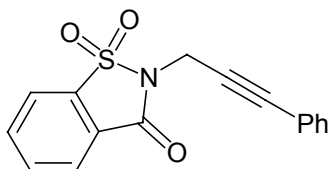
To a stirred solution of 1,1-dioxo-2-prop-2-ynyl-1,2-dihydro-1-λ⁶-benzo[*d*]isothiazol-3-one (**135**) (500 mg, 2.26 mmol) in dry CH₂Cl₂ (10 ml) were subsequently added triethylamine (1.6 ml, 11.3 mmol, 5.0 equiv.), iodobenzene (**160**) (0.3 ml, 2.71 mmol, 1.2 equiv.), CuI (21.5 mg, 0.11 mmol, 5 mol%), PdCl₂(PPh₃)₂ (80 mg, 0.11 mmol, 5 mol%) and stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO₃ solution (20 ml), the layers were separated and the water phase extracted by CH₂Cl₂ (3x20 ml). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluent: pentane:EtOAc 1:1) to give 449 mg (67%) of (**166**) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ = 8.03-7.97 (m, 1H), 7.89-7.83 (m, 1H), 7.78 (dd, 1H, *J* = 7.3, 1.6 Hz), 7.73 (dd, 1H, *J* = 7.3, 1.6 Hz), 7.41-7.34 (m, 2H), 7.25-7.16 (m, 3H), 4.69 (s, 2H).
¹³C-NMR (75 MHz, CDCl₃): δ = 158.1, 137.9, 134.9, 134.3, 131.9, 128.7, 128.2, 127.1, 125.3, 122.0, 120.9, 84.7, 80.9, 28.8.
IR (KBr): 3091, 1729, 1337, 1186, 1057, 751, 589 cm⁻¹.
MS (EI): *m/z* 297 (M⁺), 232, 204, 178, 152, 128, 102, 76.
HRMS (EI): *m/z* calcd. for $C_{16}H_{11}NO_3S$: 297.0460, found 297.0467.

Synthesis of 5,6-dimethyl-2-(3-phenyl-prop-2-ynyl)-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (167)
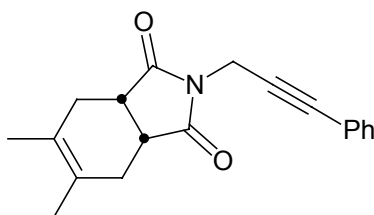
To a stirred solution of 5,6-dimethyl-2-prop-2-ynyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (**136**) (317 mg, 1.46 mmol) in dry CH₂Cl₂ (5 ml) were subsequently added triethylamine (1.0 ml, 7.3 mmol, 5.0 equiv.), iodobenzene (**160**) (0.2 ml, 1.75 mmol, 1.2 equiv.), CuI (13.9 mg,

0.07 mmol, 5 mol%), PdCl$_2$(PPh$_3$)$_2$ (51.2 mg, 0.07 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO$_3$ solution (20 ml), the layers were separated and the water phase extracted by CH$_2$Cl$_2$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:3) to give 279 mg (65%) of (**167**) as a yellowish oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.42-7.35 (m, 2H), 7.32-7.22 (m, 3H), 4.41 (s, 2H), 3.12-3.05 (m, 2H), 2.48 (d, 2H, J = 14.6 Hz), 2.32-2.16 (m, 2H), 1.66 (s, 3H), 1.65 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 178.9, 131.7, 128.4, 128.1, 126.9, 122.3, 82.4, 82.3, 40.0, 30.7, 28.5, 19.1.
IR (KBr): 2913, 2855, 1776, 1707, 1490, 1421, 1394, 1341, 1181, 759, 693 cm^{-1}.
MS (EI): m/z 293 (M$^+$), 250, 212, 171, 130, 115, 107, 91, 77.
HRMS (EI): m/z calcd. for C$_{19}$H$_{19}$NO$_2$: 293.1416, found 293.1418.

Synthesis of 1-(3-phenyl-prop-2-ynyl)-pyrrolidine-2,5-dione (168)
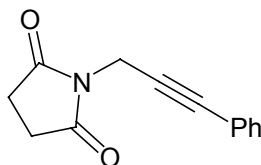
To a stirred solution of 1-prop-2-ynyl-pyrrolidine-2,5-dione (**137**) (200 mg, 1.46 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added triethylamine (1 ml, 7.3 mmol, 5.0 equiv.), iodobenzene (**160**) (0.2 ml, 1.75 mmol, 1.2 equiv.), CuI (14 mg, 0.07 mmol, 5 mol%), PdCl$_2$(PPh$_3$)$_2$ (51 mg, 0.07 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO$_3$ solution (20 ml), the layers were separated and the water phase was extracted by CH$_2$Cl$_2$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluent: pentane:AcOEt = 1:1) to give 207 mg (66%) of (**168**) as a light brown solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.25-7.15 (m, 2H), 7.13-7.00 (m, 3H), 4.25 (s, 2H), 2.49 (s, 4H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 175.7, 131.6, 128.3, 128.0, 121.9, 82.3, 82.0, 28.2, 27.9.
IR (KBr): 2985, 1703, 1422, 1342, 1180, 763, 696, 635, 403 cm^{-1}.
MS (EI): m/z 213 (M$^+$), 185, 156, 115, 105, 63.
HRMS (EI): m/z calcd. for C$_{13}$H$_{11}$NO$_2$: 213.0790, found 213.0793.

Synthesis of 1-(3-phenyl-prop-2-ynyl)-pyrrolidin-2-one (169)
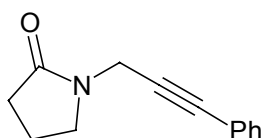
To a stirred solution of 1-prop-2-ynyl-pyrrolidin-2-one (**138**) (189 mg, 1.53 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added triethylamine (1 ml, 7.7 mmol, 5.0 equiv.), iodobenzene (**160**) (0.2 ml, 1.84 mmol, 1.2 equiv.), CuI (14.6 mg, 0.08 mmol, 5 mol%), PdCl$_2$(PPh$_3$)$_2$ (54 mg, 0.08 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO$_3$ solution (20 ml), the layers were separated and the water phase extracted by CH$_2$Cl$_2$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluent: CH$_2$Cl$_2$:MeOH = 40:1) to give 218 mg (71%) of (**169**) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.38-7.29 (m, 2H), 7.26-7.15 (m, 3H), 4.22 (s, 2H), 3.48-3.38 (m, 2H), 2.35-2.25 (m, 2H), 2.02-1.88 (m, 2H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 174.2, 131.4, 128.2, 128.0, 122.2, 83.6, 82.9, 46.1, 32.4, 30.4, 17.3.
IR (film): 2953, 1691, 1491, 1351, 1264, 760, 694 cm^{-1}.
MS (EI): *m/z* 199 (M$^+$), 171, 143, 115, 89, 63.
HRMS (EI): *m/z* calcd. for C$_{13}$H$_{13}$NO: 199.0997, found 199.0998.

Synthesis of [(3-phenyl-prop-2-ynyl)-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (170)
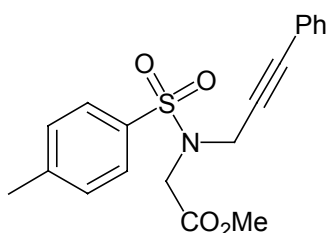
To a stirred solution of (benzenesulfonyl-prop-2-ynyl-amino)-acetic acid methyl ester (**139**) (150 mg, 0.53 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added triethylamine (0.37 ml, 2.67 mmol, 5.0 equiv.), iodobenzene (**160**) (0.07 ml, 0.64 mmol, 1.2 equiv.), CuI (5 mg, 0.026 mmol, 5 mol%), PdCl$_2$(PPh$_3$)$_2$ (19 mg, 0.026 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO$_3$ solution (20 ml), the layers were separated and the water phase extracted by CH$_2$Cl$_2$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a brown oil that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:2) to give 184 mg (96%) of (**170**) as a brown oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.72-7.63 (m, 2H), 7.25-7.11 (m, 5H), 7.09-7.01 (m, 2H), 4.39 (s, 2H), 4.07 (s, 2H), 3.62 (s, 3H), 2.26 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.8, 143.7, 135.8, 131.4, 129.5, 128.5, 128.1, 127.5, 121.8, 86.0, 81.2, 52.2, 46.9, 38.3, 21.3.
IR (film): 2953, 1753, 1439, 1351, 1215, 1163, 1095, 917, 760, 660, 543 cm^{-1}.
MS (ESI): *m/z* 380 (M+Na$^+$).
HRMS (ESI): *m/z* calcd. for C$_{19}$H$_{19}$NO$_4$SNa: 380.0933 (M+Na$^+$), found 380.0930 (M+Na$^+$).

Synthesis of 1-(3-phenyl-prop-2-ynyl)-pyrrolidine (171)
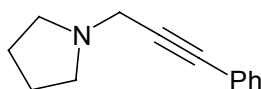
To a stirred solution of 1-prop-2-ynyl-pyrrolidine (**141**) (1 g, 9.25 mmol) in dry CH_2Cl_2 (10 ml) were subsequently added triethylamine (6.5 ml, 46.2 mmol, 5.0 equiv.), iodobenzene (**160**) (1.24 ml, 11.10 mmol, 1.2 equiv.), CuI (88 mg, 0.46 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (324 mg, 0.46 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml), the layers were separated and the water phase extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown oil that was subjected to Kugelrohr distillation to give 1.1 g (62%) of (**171**) as a yellowish oil. Spectroscopical data were consistent with those reported in the literature[142,143] and are herein reported.

¹H-NMR (300 MHz, $CDCl_3$): δ = 7.28-7.19 (m, 2H), 7.12-7.04 (m, 3H), 3.43 (s, 2H), 2.56-2.44 (m, 4H), 1.70-1.59 (m, 4H).
¹³C-NMR (75 MHz, $CDCl_3$): δ = 131.5, 128.0, 127.8, 123.1, 85.1, 84.3, 52.5, 43.7, 23.7.
IR (film): 2975, 2966, 1489, 1323, 1124, 756, 691 cm⁻¹.
MS (EI): *m/z* 185 (M⁺), 156, 115, 89, 70, 55, 42.
HRMS (EI): *m/z* calculated for $C_{13}H_{15}N$: 185.1214, found 185.1196.

Synthesis of 1-(3-phenyl-prop-2-ynyl)-1*H*-indole (172)
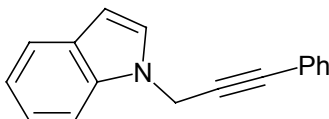
To a stirred solution of 1-prop-2-ynyl-1*H*-indole (**142**) (150 mg, 0.97 mmol) in dry CH_2Cl_2 (4 ml) were subsequently added triethylamine (0.7 ml, 4.83 mmol, 5.0 equiv.), iodobenzene (**160**) (0.13 ml, 1.16 mmol, 1.2 equiv.), CuI (9.2 mg, 0.05 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (34 mg, 0.05 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml). The layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 10:1) to give 150 mg (67%) of (**172**) as a yellowish oil.

**¹H-NMR** (300 MHz, $CDCl_3$): δ = 8.08-8.00 (m, 1H), 7.88-7.74 (m, 3H), 7.71-7.59 (m, 5H), 7.58-7.48 (m, 1H), 6.93 (dd, 1H, *J* = 3.2, 0.8 Hz), 5.39 (s, 2H).
¹³C-NMR (75 MHz, $CDCl_3$): δ = 135.8, 131.7, 128.8, 128.5, 128.2, 127.3, 122.2, 121.7, 120.9, 119.7, 109.4, 101.8, 85.1, 83.1, 36.5.
IR (film): 3345, 3054, 1702, 1489, 1462, 1336, 1314, 1186, 757, 742, 691 cm⁻¹.
MS (EI): *m/z* 231 (M⁺), 154, 115, 89, 63.
HRMS (EI) for $C_{17}H_{13}N$: calcd. 231.1048, found 231.1051.

Synthesis of 1-[3-(3,4,5-trimethoxy-phenyl)-prop-2-ynyl]-1H-indole (173)
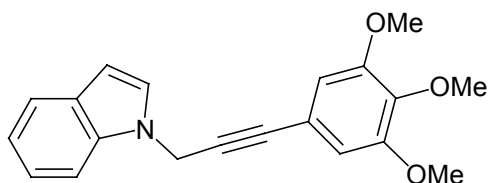
To a stirred solution of 1-prop-2-ynyl-1H-indole (**142**) (150 mg, 0.97 mmol) in dry CH_2Cl_2 (4 ml) were subsequently added triethylamine (0.7 ml, 4.83 mmol), 5-iodo-1,2,3-trimethoxybenzene (341 mg, 1.16 mmol), CuI (9.2 mg, 0.048 mmol), $PdCl_2(PPh_3)_2$ (34 mg, 0.048 mmol) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml). The layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 198 mg (63%) of (**173**) as a brown solid.

**^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.78-7.72 (m, 1H), 7.59-7.52 (m, 1H), 7.40-7.31 (m, 2H), 7.30-7.20 (m, 1H), 6.74 (s, 2H), 6.66-6.62 (m, 1H), 5.13 (s, 2H), 3.93 (s, 3H), 3.88 (s, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 152.9, 138.9, 135.7, 128.7, 127.2, 121.7, 120.9, 119.6, 117.1, 109.3, 108.8, 101.7, 84.9, 82.2, 60.7, 55.9, 36.4.
IR (KBr): 2940, 1576, 1504, 1333, 1238, 1123, 1004, 750 cm^{-1}.
MS (EI): *m/z* 321 (M$^+$), 205, 172, 131, 89, 76.
HRMS (EI) for $C_{20}H_{19}NO_3$: calcd. 321.1365, found 321.1358.

Synthesis of 9-(3-phenyl-prop-2-ynyl)-9H-carbazole (174)
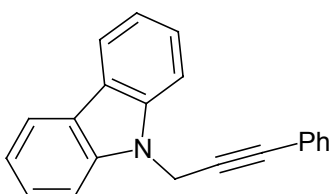
To a solution of 9-prop-2-ynyl-9H-carbazole (**143**) (150 mg, 0.73 mmol) in dry CH_2Cl_2 (4 ml) were subsequently added triethylamine (0.5 ml, 3.65 mmol, 5.0 equiv.), iodobenzene (**160**) (0.1 ml, 1.16 mmol, 1.2 equiv.), CuI (7 mg, 0.036 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (26 mg, 0.036 mmol, 5 mol%) and stirred overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml). The layers were separated and the water phase extracted with CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 95 mg (46%) of (**174**) as a brown solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.03-7.96 (m, 2H), 7.46-7.33 (m, 4H), 7.29-7.05 (m, 7H), 5.09 (s, 2H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 139.9, 131.7, 128.4, 128.2, 125.8, 123.1, 122.3, 120.3, 119.4, 108.8, 83.9, 83.2, 33.1.
IR (KBr): 3047, 1598, 1486, 1460, 1323, 1209, 759, 746, 719, 687 cm^{-1}.

MS (EI): *m/z* 281 (M⁺), 204, 166, 115, 89, 63.
HRMS (EI): *m/z* calcd. for $C_{21}H_{15}N$: 281.1204, found 281.1199.

Synthesis of 2-(3-trimethylsylanyl-prop-2-ynyl)-isoindole-1,3-dione (176)
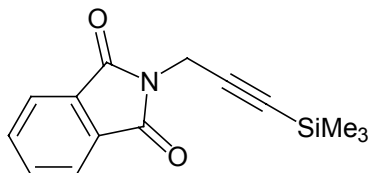
In analogy to the procedure of *Dahlbom*[100], a mixture of phthalimide potassium salt (**113**) (500 mg, 2.7 mmol), (3-bromo-prop-1-ynyl)-trimethyl-silane (**177**) (0.51 ml, 3.24 mmol, 1.2 equiv.) and dry DMF (3 ml) was stirred at 100 °C for 6 hours. The mixture was filtered and the reaction product was precipitated by addition of water. The crude product was filtered and recrystallised in ethanol to give 612 mg (88%) of (**176**) as a white solid.

¹H-NMR (300 MHz, CDCl₃) δ = 7.91-7.83 (m, 2H), 7.77-7.69 (m, 2H), 4.45 (s, 2H), 0.12 (s, 9H).
¹³C-NMR (75 MHz, CDCl₃): δ = 166.9, 134.1, 132.0, 123.5, 98.4, 88.1, 27.9, -0.3.
IR (KBr): 2963, 1713, 1394, 1328, 847 cm⁻¹.
MS (EI): *m/z* 257 (M⁺), 242, 198, 163, 130, 102, 73, 43.
HRMS (EI): *m/z* calcd. for $C_{14}H_{15}NO_2Si$: 257.0872, found 257.0874.

Synthesis of 2-(4,5-dimethylbiphenyl-2-ylmethyl)-isoindole-1,3-dione (162)
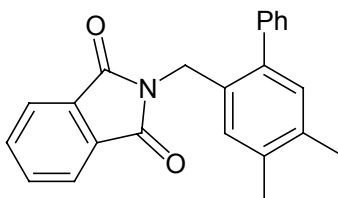
To a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (**161**) (393 mg, 1.50 mmol) in dry CH₂Cl₂ (7 ml) were subsequently added CoBr₂(dppe) (92.6 mg, 0.15 mmol, 10 mol%), Zn dust (49 mg, 0.75 mmol, 50 mol%), ZnI₂ (239 mg, 0.75 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.25 ml, 2.26 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (409 mg, 1.80 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 406 mg (80%) of (**162**) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ = 7.80-7.72 (m, 2H), 7.68-7.59 (m, 2H), 7.37 (d, 4H, *J* = 3.9 Hz), 7.35-7.25 (m, 1H), 6.97 (d, 2H, *J* = 6.6 Hz), 4,75 (s, 2H), 2.19 (s, 3H), 2.17 (s, 3H).
¹³C-NMR (75 MHz, CDCl₃): δ = 167.9, 140.7, 138.9, 135.9, 135.5, 133.8, 132.1, 131.5, 130.7, 129.3, 128.2, 128.1, 126.9, 123.1, 39.1, 19.4, 19.2.

IR (KBr): 1769, 1708, 1396, 1105, 944, 720, 701 cm^{-1}.
MS (EI): *m/z* 341 (M$^+$), 281, 253, 194, 165, 105, 77.
HRMS (EI): *m/z* calcd. for $C_{23}H_{19}NO_2$: 341.1416, found 341.1418.

Synthesis of 2-[1-(4,5-dimethylbiphenyl-2-yl)-ethyl]-isoindole-1,3-dione (178)
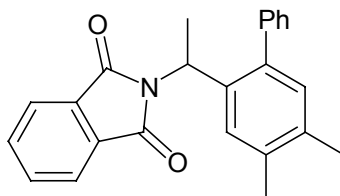
To a solution of 2-(1-methyl-3-phenylprop-2-ynyl)-isoindole-1,3-dione (**164**) (383 mg, 1.39 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added $CoBr_2(dppe)$ (86 mg, 0.14 mmol, 10 mol%), Zn dust (45.5 mg, 0.69 mmol, 50 mol%), ZnI_2 (222 mg, 0.69 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.24 ml, 2.09 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (639 mg, 2.81 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 488 mg (98%) of (**178**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.77-7.70 (m, 2H), 7.69-7.63 (m, 2H), 7.62 (s, 1H), 7.42-7.22 (m, 5H), 6.98 (s, 1H), 5.61 (q, 1H, *J* = 7.2 Hz), 2.37 (s, 3H), 2.28 (s, 3H), 1.81 (d, 3H, *J* = 7.2 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.8, 140.9, 139.0, 135.8, 135.5, 135.4, 133.5, 131.8, 131.4, 128.9, 128.5, 128.0, 126.8, 122.8, 47.2, 19.7, 19.2, 18.9.
IR (KBr): 2972, 2935, 1773, 1708, 1385, 1352, 1328, 1120, 876, 719, 702 cm^{-1}.
MS (EI): *m/z* 355 (M$^+$), 340, 275, 208, 193, 178, 165, 148, 130, 77.
HRMS (EI): *m/z* calcd. for $C_{24}H_{21}NO_2$: 355.1572, found 355.1574.

Synthesis of 2-[2-(4,5-dimethylbiphenyl-2-yl)-ethyl]-isoindole-1,3-dione (179)
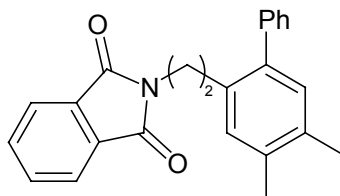
To a solution of 2-(4-phenylbut-3-ynyl)-isoindole-1,3-dione (**163**) (150 mg, 0.54 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added $CoBr_2(dppe)$ (34 mg, 0.054 mmol, 10 mol%), Zn dust (18 mg, 0.27 mmol, 50 mol%), ZnI_2 (187 mg, 0.27 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.1 ml, 0.82 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was

dissolved in benzene and oxidised by DDQ (149 mg, 0.65 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 190 mg (98%) of (**179**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.67-7.59 (m, 2H), 7.57-7.48 (m, 2H), 7.30-7.16 (m, 5H), 6.98 (s, 1H), 6.88 (s, 1H), 3.68-3.57 (m, 2H), 2.86-2.74 (m, 2H), 2.12 (s, 3H) 2.11 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.8, 141.1, 139.7, 135.6, 134.6, 133.6, 132.6, 132.0, 131.4, 131.0, 129.1, 128.0, 126.6, 122.9, 38.9, 31.2, 19.2, 19.1.
IR (KBr): 2921, 1762, 1707, 1397, 1354, 718, 703 cm^{-1}.
MS (EI): *m/z* 355 (M$^+$), 208, 195, 179, 165, 104, 77.
HRMS (EI): *m/z* calcd. for C$_{24}$H$_{21}$NO$_2$: 355.1572, found 355.1578.

Synthesis of 2-[3-(4,5-dimethyl-biphenyl-2-yl)-propyl]-isoindole-1,3-dione (180)
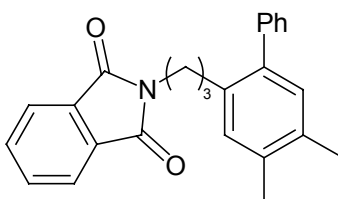
To a stirred solution of 2-(5-phenyl-pent-4-ynyl)-isoindole-1,3-dione (**165**) (177 mg, 0.61 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (38 mg, 0.061 mmol, 10 mol%), Zn dust (97.5 mg, 0.30 mmol, 50 mol%), ZnI$_2$ (97.5 mg, 0.30 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.10 ml, 0.92 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel and concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (166 mg, 0.73 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 203 mg of (**180**) (90%) as a yellowish oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.88-7.78 (m, 2H), 7.77-7.67 (m, 2H), 7.33-7.23 (m, 4H), 7.21-7.07 (m, 2H), 6.99 (s, 1H), 3.62 (t, 2H, *J* = 6.9 Hz), 2.70-2.57 (m, 2H), 2.30 (s, 3H), 2.26 (s, 3H) 1.95-1.78 (m, 2H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.0, 141.4, 139.2, 135.7, 135.5, 133.9, 133.6, 131.9, 131.2, 130.3, 128.9, 127.7, 126.3, 122.9, 37.7, 34.5, 29.9, 19.3, 19.0.
IR (film): 2938, 1706, 1439, 1394, 1029, 719, 704 cm^{-1}.
MS (EI): *m/z* 369 (M$^+$), 195, 161, 133, 77.
HRMS (EI): *m/z* calcd. for C$_{25}$H$_{23}$NO$_2$: 369.1729, found 369.1734.

Synthesis of 2-(4,5-dimethyl-biphenyl-2-ylmethyl)-5,6-dimethyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (181)
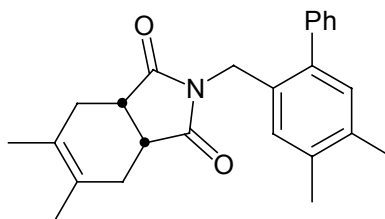
To a stirred solution of 5,6-dimethyl-2-(3-phenyl-prop-2-ynyl)-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (167) (278 mg, 0.95 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added $CoBr_2(dppe)$ (59 mg, 0.095 mmol, 10 mol%), Zn dust (31 mg, 0.475 mmol, 50 mol%), ZnI_2 (152 mg, 0.475 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (42) (0.16 ml, 1.42 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:3) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (259 mg, 1.14 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:3), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:3) to give 349 mg of (181) (98%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.48-7.31 (m, 5H), 7.02 (s, 1H), 6.68 (s, 1H), 4.58 (s, 2H), 3.06-2.99 (m, 2H), 2.55-2.44 (m, 2H), 2.31-2.18 (m, 2H), 2.25 (s, 6H), 1.72 (s, 3H), 1.71 (s, 3H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 179.8, 140.7, 138.7, 135.6, 135.2, 131.4, 129.9, 129.3, 128.1, 126.9, 126.8, 126.7, 40.2, 39.8, 30.5, 19.4, 19.3, 19.2.
IR (film): 2939, 1771, 1698, 1402, 1339, 1179, 769, 703.
MS (EI): *m/z* 373 (M$^+$), 297, 195, 180, 165, 107, 91, 77.
HRMS (EI): *m/z* calcd. for $C_{25}H_{27}NO_2$: 373.2042, found 373.2050.

Synthesis of 1-(4,5-dimethyl-biphenyl-2-ylmethyl)-pyrrolidine-2,5-dione (182)
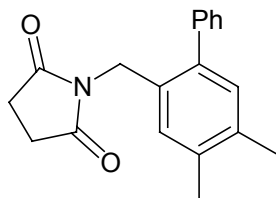
To a stirred solution of 1-(3-phenyl-prop-2-ynyl)-pyrrolidine-2,5-dione (168) (187 mg, 0.88 mmol) in dry CH_2Cl_2 (4 ml) were subsequently added $CoBr_2(dppe)$ (54 mg, 0.09 mmol, 10 mol%), Zn dust (29 mg, 0.44 mmol, 50 mol%), ZnI_2 (140 mg, 0.44 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (42) (0.15 ml, 1.32 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered with diethyl ether over a short pad of silica gel and concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (240 mg, 1.05 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was

washed with an aqueous solution containing 10% NaOH and 10% $Na_2S_2O_3$, the water phase was separated and extracted by CH_2Cl_2 (2x20 ml). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:3) to give 217 mg of (**182**) (84%) as a white solid.

**^{1}H-NMR** (300 MHz, CDCl$_3$): δ = 7.52-7.32 (m, 5H), 7.04 (s, 1H), 6.98 (s, 1H), 4.65 (s, 2H), 2.59 (s, 4H), 2.29 (s, 3H), 2.28 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 176.6, 140.5, 138.7, 135.7, 135.4, 131.4, 129.8, 129.0, 128.1, 127.9, 126.7, 39.8, 27.8, 19.3, 19.1.
IR (KBr): 2938, 1694, 1426, 1345, 1175, 920, 764, 704 cm^{-1};
MS (EI): *m/z* 293 (M$^+$), 208, 194, 179, 165, 55.
HRMS (EI): *m/z* calcd. for $C_{19}H_{19}NO_2$: 293.1416, found 293.1410.

Synthesis of 1-(4,5-dimethyl-biphenyl-2-ylmethyl)-pyrrolidin-2-one (183)
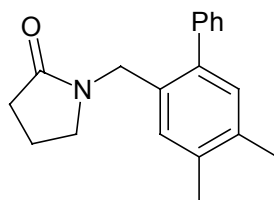
To a stirred solution of 1-(3-phenyl-prop-2-ynyl)-pyrrolidin-2-one (**169**) (196 mg, 0.99 mmol) in dry CH_2Cl_2 (4 ml) were subsequently added CoBr$_2$(dppe) (61 mg, 0.099 mmol, 10 mol%), Zn dust (32 mg, 0.49 mmol, 50 mol%), ZnI$_2$ (157 mg, 0.49 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.17 ml, 1.48 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: CH_2Cl_2:MeOH = 20:1) over a short pad of silica gel and concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (268 mg, 1.18 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was washed with an acqueous solution containing 10% NaOH and 10% $Na_2S_2O_3$, the water phase was separated and extracted by CH_2Cl_2 (2x20 ml). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: CH_2Cl_2:MeOH = 40:1) to give 244 mg of (**183**) (90%) as a colourless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.48-7.28 (m, 5H), 7.13 (s, 1H), 7.08 (s, 1H), 4.49 (s, 2H), 3.11-3.01 (m, 2H), 2.40-2.29 (m, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 1.97-1.82 (m, 2H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 174.4, 140.3, 139.2, 135.9, 135.3, 131.1, 130.6, 129.4, 128.8, 127.8, 126.7, 46.1, 43.3, 30.5, 19.2, 19.0, 17.3.
IR (film): 2969, 1688, 1442, 1285, 761, 704 cm^{-1}.
MS (EI): *m/z* 279 (M$^+$), 194, 181, 165, 116, 86, 41.
HRMS (EI): *m/z* for $C_{19}H_{21}NO$: 279.1623, found 279.1618.

Synthesis of [(4,5-dimethyl-biphenyl-2-ylmethyl)-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (184)
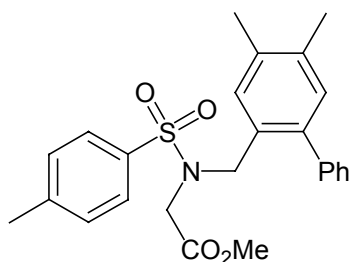
To a solution of [(3-phenyl-prop-2-ynyl)-(toluene-4-sulfonyl)-amino]-acetic acid methyl ester (**170**) (150 mg, 0.42 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added $CoBr_2$(dppe) (26 mg, 0.042 mmol, 10 mol%), Zn dust (13.7 mg, 0.21 mmol, 50 mol%), ZnI_2 (67 mg, 0.21 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.07 ml, 0.63 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (115 mg, 0.50 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered with diethyl ether over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 147 mg (80%) of (**184**) as a yellowish oil.

**^{1}H-NMR** (300 MHz, CDCl$_3$): δ = 7.73-7.65 (m, 2H), 7.42-7.13 (m, 8H), 7.00 (s, 1H), 4.48 (s, 2H), 3.78 (s, 2H), 3.34 (s, 3H), 2.43 (s, 3H), 2.28 (s, 6H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.8, 143.1, 140.2, 140.1, 137.1, 136.3, 136.1, 131.1, 130.6, 129.4, 129.3, 129.2, 128.0, 127.2, 126.8, 51.5, 47.5, 46.5, 21.4, 19.3, 19.2.
IR (film): 3463, 2922, 1754, 1441, 1339, 1157, 1093, 924, 814, 703, 657, 547 cm^{-1}.
MS (ESI): *m/z* 460 (M+Na$^+$).
HRMS (ESI) for C$_{25}$H$_{27}$NO$_4$SNa: calcd. 460.1559 (M+Na$^+$), found 460.1560 (M+Na$^+$).

Synthesis of 2-(4,5-dimethyl-biphenyl-2-ylmethyl)-1,1-dioxo-1,2-dihydro-1λ^6-benzo[*d*]iso -thiazol-3-one (185)
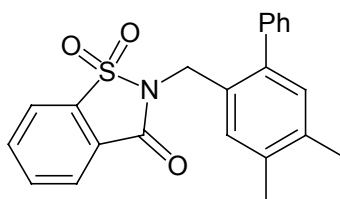
To a stirred solution of 1,1-dioxo-2-(3-phenyl-prop-2-ynyl)-1,2-dihydro-1λ^6- benzo[*d*]isothiazol-3-one (**166**) (410 mg, 1.38 mmol) in dry CH_2Cl_2 (7 ml) were subsequently added $CoBr_2$(dppe) (85 mg, 0.14 mmol, 10 mol%), Zn dust (45 mg, 0.69 mmol, 50 mol%), ZnI_2 (220 mg, 0.69 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.24 ml, 2.07 mmol, 1.5 equiv.) and the stirring continued overnight at room temperature. The mixture was then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (376 mg, 1.66 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered with diethyl ether over a short

pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:EtOAc = 1:1) to give 473 mg of (**185**) (91%) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ = 7.94-7.87 (m, 1H), 7.81-7.64 (m, 3H), 7.38-7.22 (m, 5H), 7.18 (s, 1H), 6.96 (s, 1H), 4.77 (s, 2H), 2.16 (s, 6H).
¹³C-NMR (75 MHz, CDCl₃): δ = 158.8, 140.4, 139.3, 137.9, 136.2, 136.1, 134.6, 134.1, 131.4, 129.4, 129.0, 128.9, 128.2, 127.2, 127.1, 125.1, 120.8, 40.2, 19.4, 19.3.
IR (KBr): 2918, 1732, 1331, 1312, 1288, 1252, 1183, 753.
MS (EI): *m/z* 377 (M⁺), 313, 283, 254, 208, 165, 105, 77.
HRMS (EI): *m/z* calcd. for C₂₂H₁₉NO₃S: 377.1086, found 377.1095.

Synthesis of 1-(4,5-dimethyl-biphenyl-2-ylmethyl)-1*H*-indole (187)
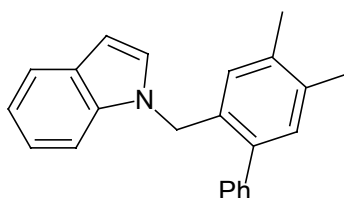
To a solution of 1-(3-phenyl-prop-2-ynyl)-1*H*-indole (**172**) (77 mg, 0.33 mmol) in dry CH₂Cl₂ (3 ml) were subsequently added CoBr₂(dppe) (20.6 mg, 0.033 mmol, 10 mol%), Zn dust (11 mg, 0.17 mmol, 50 mol%), ZnI₂ (53 mg, 0.17 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.57 ml, 0.5 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (90 mg, 0.40 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 10:1) to give 72 mg of (**187**) (70%) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ = 7.71-7.63 (m, 1H), 7.52-7.33 (m, 5H), 7.22-7.09 (m, 4H), 7.00 (d, 1H, *J* = 3.1 Hz), 6.83 (s, 1H), 6.53 (d, 1H, *J* = 3.1 Hz), 5.24 (s, 2H), 2.31 (s, 3H), 2.22 (s, 3H).
¹³C-NMR (75 MHz, CDCl₃): δ = 140.6, 138.9, 136.2, 135.9, 131.7, 131.5, 129.1, 128.5, 128.3, 128.0, 127.1, 121.3, 120.7, 119.2, 109.6, 101.2, 47.5, 19.5, 19.3.
IR (KBr): 3055, 2920, 1612, 1511, 1485, 1462, 1317, 1178, 884, 762, 739, 702 cm⁻¹.
MS (EI): *m/z* 311(M⁺), 195, 180, 165.
HRMS (EI) for C₂₃H₂₁N: calcd. 311.1674, found 311.1688.

Synthesis of 1-(3',4',5'-trimetoxy-4,5-dimethyl-biphenyl-2-ylmethyl)-1*H*-indole (188)
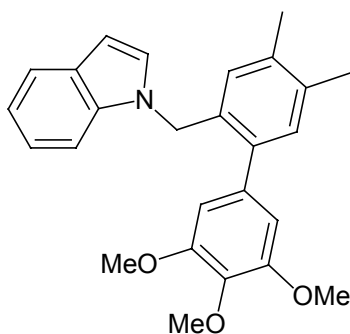
To a solution of 1-[3-(3,4,5-trimethoxy-phenyl)-prop-2-ynyl]-1*H*-indole (**173**) (164 mg, 0.51 mmol) in CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (31.4 mg, 0.051 mmol), Zn dust (17 mg, 0.25 mmol), ZnI$_2$ (81 mg, 0.25 mmol), 2,3-dimethyl-1,3-butadiene (**42**) (0.87 ml, 0.76 mmol). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (139 mg, 0.61 mmol) at room temperature. After 4 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and chromatographed on silica gel (eluent: pentane:diethyl ether = 1:1) to give 97 mg (48%) of (**188**) as a brown oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.65-7.59 (m, 1H), 7.19-7.07 (m, 4H), 7.03 (s, 1H), 6.96 (d, 1H, *J* = 3.2 Hz), 6.49 (d, 1H, *J* = 3.2 Hz), 6.35 (s, 2H), 5.17 (s, 2H), 3.65 (s, 6H), 3.38 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 152.8, 139.6, 136.9, 136.3, 136.2, 135.9, 131.4, 131.2, 130.4, 128.5, 127.3, 121.3, 120.6, 119.3, 109.4, 105.9, 101.2, 60.8, 55.8, 47.8, 19.4, 19.3.
IR (KBr): 2935, 1583, 1494, 1462, 1412, 1235, 1127, 1009, 742 cm^{-1}.
MS (EI): *m/z* 401 (M$^+$), 285, 254, 239.
HRMS (EI) for C$_{26}$H$_{27}$NO$_3$: calcd. 401.1991, found 401.1981.

Synthesis of 9-(4,5-dimethyl-biphenyl-2-ylmethyl)-9*H*-carbazole (189)
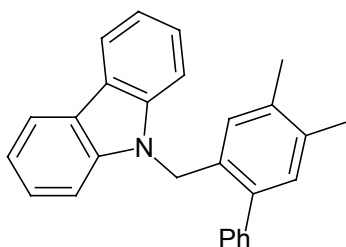
To a solution of 9-(3-phenyl-prop-2-ynyl)-9*H*-carbazole (**174**) (75.5 mg, 0.27 mmol) in dry CH$_2$Cl$_2$ (3 ml) were subsequently added CoBr$_2$(dppe) (17 mg, 0.027 mmol, 10 mol%), Zn dust (28.7 mg, 0.13 mmol, 50 mol%), ZnI$_2$ (43 mg, 0.13 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.05 ml, 0.4 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, than filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (73.5 mg, 0.32 mmol, 1.2 equiv.) at room

temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 97 mg of (**189**) (98%) as a brown solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.20-8.13 (m, 2H), 7.59-7.53 (m, 4H), 7.51-7.40 (m, 3H), 7.32-7.22 (m, 4H), 7.18 (s, 1H), 6.64 (s, 1H), 5.44 (s, 2H), 2.28 (s, 3H), 2.05 (s, 3H).
^{13}C- NMR (75 MHz, CDCl$_3$): δ = 140.7, 138.4, 136.3, 135.5, 131.5, 131.4, 129.2, 128.4, 127.2, 125.7, 122.9, 120.2, 118.9, 108.8, 44.5, 19.5, 19.3.
IR (KBr): 2919, 1597, 1484, 1461, 1451, 1325, 1214, 1151, 747, 717, 701 cm^{-1}.
MS (EI): *m/z* 361 (M$^+$), 195, 180, 165.
HRMS (EI): *m/z* calcd. for C$_{27}$H$_{23}$N: 361.1830, found 361.1832.

Synthesis of 2-(4-methyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (193a) and 2-(5-methyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (193b)
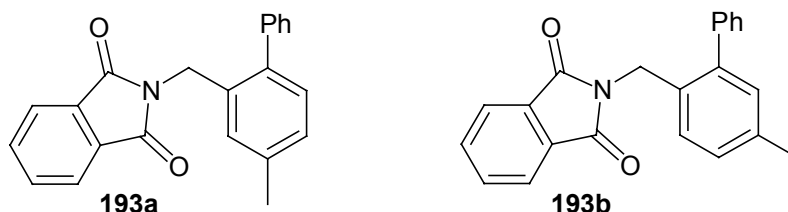
To a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (**161**) (150 mg, 0.574 mmol) in CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (35.5 mg, 0.0574 mmol, 10 mol%), Zn dust (19 mg, 0.287 mmol, 50 mol%), ZnI$_2$ (92 mg, 0.287 mmol, 50 mol%), isoprene (**192**) (0.086 ml, 0.861 mmol, 1.5 equiv.). The resulting mixture stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (156 mg, 0.69 mmol) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 4:1) to give 161 mg (85%) of a non separable mixture of regioisomers (**193a**) and (**193b**) as a white solid (**193a**:**193b** = 3 : 1, estimated by ^{1}H-NMR).

^{1}H-NMR (300 MHz, CDCl$_3$) resolved signals for the major regioisomer (**193a**): δ = 7.88-7.80 (m, 2H), 7.75-7.66 (m, 2H), 4.84 (s, 2H), 2.33 (s, 3H); resolved signals for the minor regioisomer (**193b**): δ = 4.83 (s), 2.36 (s). The remaining signals are unresolved.
^{13}C-NMR (75 MHz, CDCl$_3$): resolved signals for the major regioisomer (**193a**): δ = 167.9, 39.3, 21.1; resolved signals for the minor regioisomer (**193b**): δ = 167.8, 39.1, 20.9. The remaining signals are unresolved.
IR (KBr): 3057, 1768, 1703, 1431, 1097, 1087, 718, 708 cm^{-1}.
MS (EI): *m/z* 327 (M$^+$), 180, 165, 148, 130, 105, 77.
HRMS (EI): *m/z* calcd. for C$_{23}$H$_{17}$NO$_2$: 327.1259, found 327.1257.

Synthesis of 2-(6-methyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (198a) and 2-(3-methyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (198b)
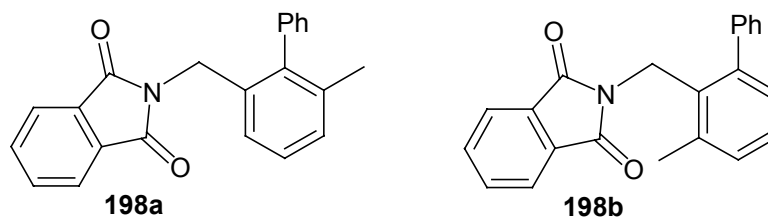
To a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (**161**) (150 mg, 0.574 mmol) in CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (35.5 mg, 0.0574 mmol, 10 mol%), Zn dust (19 mg, 0.287 mmol, 50 mol%), ZnI$_2$ (92 mg, 0.287 mmol, 50 mol%), (*E/Z*)-1,3-pentadiene (**194**) (0.086 ml, 0.861 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (156 mg, 0.69 mmol) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 4:1) to give 77 mg (41%) of a non separable mixture of regioisomers (**198a**) and (**198b**) as a white solid (**198a**:**198b** = 6 : 1, estimated by ^{1}H-NMR). (The 1,3-pentadiene (**195**) was of technical grade, 90%, and GC showed the presence of 4% of a contaminant, successively identified as isoprene (**192**). Therefore the yield and the ratio were corrected by integration of the ^{1}H-NMR spectrum).

^{1}H-NMR (500 MHz, CDCl$_3$) resolved signals for the major regioisomer (**198a**): δ = 7.88-7.81 (m, 2H), 7.76-7.70 (m, 2H), 4.62 (s, 2H), 2.06 (s, 3H); resolved signals for the minor regioisomer (**198b**): δ = 4.89 (s), 2.42 (s). The remaining signals are unresolved.
^{13}C-NMR (125 MHz, CDCl$_3$) resolved signals for the major regioisomer (**198a**): δ = 167.9, 39.9, 20.6; resolved signals for the minor regioisomer (**198b**): δ = 167.8, 37.9, 20.3. The remaining signals are unresolved.
IR (KBr): 3058, 1769, 1717, 1392, 1113, 952, 768, 728, 708 cm^{-1}.
MS (EI): *m/z* 327 (M$^+$), 180, 165, 148, 130, 84;
HRMS (EI): *m/z* calcd. for C$_{23}$H$_{17}$NO$_2$: 327.1259, found 327.1253.

Synthesis of 2-(3,4-dimethyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (199a) and 2-(5,6-dimethyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (199b)
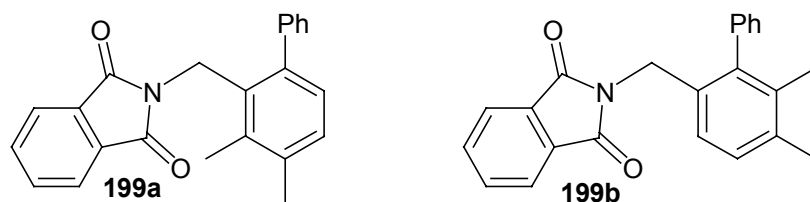
To a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (**161**) (150 mg, 0.574 mmol) in CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (35.5 mg, 0.0574 mmol, 10 mol%), Zn dust (19 mg, 0.287 mmol, 50 mol%), ZnI$_2$ (92 mg, 0.287 mmol, 50 mol%), (*E/Z*)-3-methyl-1,3-pentadiene (**195**) (0.097 ml, 0.861 mmol, 1.5 equiv.). The resulting mixture stirred

overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (156 mg, 0.69 mmol) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 4:1) to give 55 mg (28%) of a non separable mixture of regioisomers (**199a**) and (**199b**) as a white solid (**199a**:**199b** = 4 : 1, estimated by ^{1}H-NMR).

^{1}H-NMR (500 MHz, CDCl$_3$) resolved signals for the major regioisomer (**199a**): δ = 7.77-7.71 (m, 2H), 7.70-7.64 (m, 2H), 7.18 (d, 1H, J = 7.7 Hz) 7.04 (d, 1H, J = 7.7 Hz), 4.92 (s, 2H), 2.34 (s, 3H), 2.28 (s, 3H); resolved signals for the minor regioisomer (**199b**): δ = 7.86-7.82 (m), 7.12 (d, J = 7.9 Hz), 6.99 (d, J = 7.9 Hz), 4.57 (s, 2H), 2.32 (s, 3H), 1.96 (s, 3H). The remaining signals are unresolved.

^{13}C-NMR (125 MHz, CDCl$_3$): resolved signals for the major regioisomer (**199a**): δ = 167.7, 142.2, 141.7, 136.1, 135.6, 133.7, 38.6, 20.7, 15.9; resolved signals for the minor regioisomer (**199b**): δ = 167.9, 140.8, 140.0, 135.8, 135.0, 133.8, 40.1, 20.4, 17.0. The remaining signals are unresolved.

IR (KBr): 2920, 1775, 1711, 1394, 1317, 1066, 949, 771, 719, 700 cm^{-1}.

MS (EI): m/z 341 (M$^+$), 194, 179, 160, 148, 130, 77.

HRMS (EI): m/z calcd. for C$_{23}$H$_{19}$NO$_2$: 341.1416, found 314.1408.

Synthesis of 2-(4,6-dimethyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (200a) and 2-(3,5-dimethyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (200b)
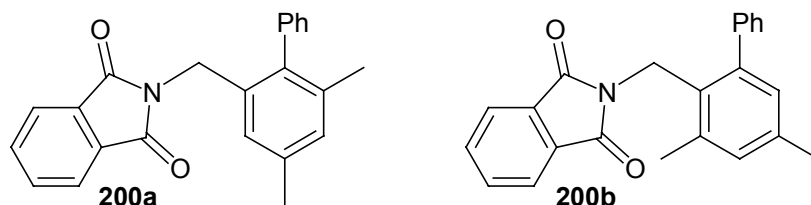
To a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (**161**) (150 mg, 0.574 mmol) in CH$_2$Cl$_2$ (4 ml) were subsequently added CoBr$_2$(dppe) (35.5 mg, 0.0574 mmol, 10 mol%), Zn dust (19 mg, 0.287 mmol, 50 mol%), ZnI$_2$ (92 mg, 0.287 mmol, 50 mol%), (*E/Z*)-2-methyl-1,3-pentadiene (**196**) (0.098 ml, 0.861 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (156 mg, 0.69 mmol) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 4:1) to give 80 mg (41%) of a non separable mixture of regioisomers (**200a**) and (**200b**) as white solids (**200a**:**200b** = 40 : 1, estimated by ^{1}H-NMR).

^{1}H-NMR (500 MHz, CDCl$_3$) signals for the major regioisomer (**200a**): δ = 7.89-7.82 (m, 2H), 7.77-7.70 (m, 2H), 7.50-7.43 (m, 2H), 7.41-7.35 (m, 1H), 7.33-7.26 (m, 2H), 7.04 (s, 1H), 6.88 (s, 1H), 4.60 (s, 2H), 2.31 (s, 3H), 2.03 (s, 3H).

¹³C-NMR (125 MHz, CDCl₃) signals for the major regioisomer (**200b**): δ = 167.9, 139.5, 137.9, 136.9, 136.4, 133.8, 133.7, 132.1, 129.7, 129.5, 128.5, 126.9, 124.5, 123.2, 39.9, 21.1, 20.5.
IR (KBr): 2924, 2854, 1769, 1717, 1389, 1112, 949, 778, 729, 713 cm⁻¹.
MS (EI): *m/z* 341 (M⁺), 194, 179, 148, 130, 77.
HRMS (EI): *m/z* calcd. for C₂₃H₁₉NO₂: 341.1416, found 341.1413.

5 Synthesis of dibenzoazepine derivatives

Synthesis of 2-[3-(3-methoxyphenyl)-prop-2-ynyl]-isoindole-1,3-dione (218)
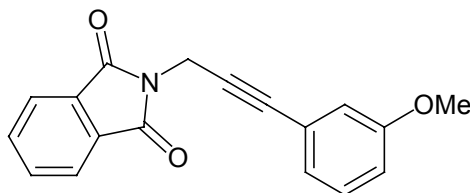
To a stirred solution of 2-prop-2-ynyl-isoindole-1,3-dione (**109**) (150 mg, 0.81 mmol) in dry CH₂Cl₂ (4 ml) were subsequently added triethylamine (0.6 ml, 4.05 mmol, 5.0 equiv.), 3-iodoanisole (0.13 ml, 0.97 mmol, 1.2 equiv.), CuI (7.7 mg, 0.04 mmol, 5 mol%), PdCl₂(PPh₃)₂ (28.4 mg, 0.04 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO₃ solution (20 ml). The layers were separated and the water phase was extracted by CH₂Cl₂ (3x20 ml). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 179 mg (76%) of (**218**) as a white solid.

^{1}**H-NMR** (300 MHz, CDCl₃): δ = 7.92-7.83 (m, 2H), 7.77-7.68 (m, 2H), 7.16 (t, 1H, *J* = 7.9 Hz), 7.04-6.96 (m, 1H), 6.95-6.90 (m, 1H), 6.84 (ddd, 1H, *J* = 8.3, 2.6, 0.9 Hz), 4.67 (s, 2H), 3.75 (s, 3H).
^{13}**C-NMR** (75 MHz, CDCl₃): δ = 167.0, 159.1, 134.0, 132.0, 129.2, 124.4, 123.5, 123.2, 116.5, 115.3, 82.8, 82.4, 55.2, 27.8.
IR (KBr): 1706, 1596, 1417, 1395, 1115, 974, 727 cm^{-1}.
MS (EI): *m/z* 291 (M⁺), 263, 232, 165, 130, 104, 76.
HRMS (EI): *m/z* calcd. for C₁₈H₁₃NO₃: 291.0895, found 291.0886.

Synthesis of 2-[3-(3-methoxyphenyl)-1-methyl-prop-2-ynyl]-isoindole-1,3-dione (219)
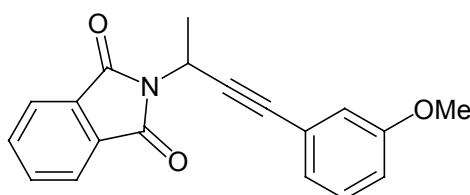
To a stirred solution of 2-(1-methyl-prop-2-ynyl)-isoindole-1,3-dione (**119**) (500 mg, 2.51 mmol) in dry CH₂Cl₂ (10 ml) were subsequently added triethylamine (1.7 ml, 12.5 mmol, 5.0 equiv.), 3-iodoanisole (0.4 ml, 3.01 mmol, 1.2 equiv.), CuI (24 mg, 0.12 mmol, 5 mol%), PdCl₂(PPh₃)₂ (88 mg, 0.12 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO₃ solution (20 ml), the layers were separated and the water phase was extracted with CH₂Cl₂ (3x20 ml). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a brown residue that was purified by column

chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 641 mg (84%) of (**219**) as a white solid.

¹H-NMR (300 MHz, CDCl$_3$): δ = 7.90-7.81 (m, 2H), 7.76-7.67 (m, 2H), 7.18 (t, 1H, J = 7.9 Hz), 7.03 (td, 1H, J = 7.6, 1.0 Hz), 6.98-6.93 (m, 1H), 6.84 (ddd, 1H, J = 8.3, 2.6, 0.9 Hz), 5.43 (q, 1H, J = 7.1 Hz), 3.77 (s, 3H), 1.79 (d, 3H, J = 7.1 Hz).

¹³C-NMR (75 MHz, CDCl$_3$): δ = 166.8, 159.1, 133.9, 131.8, 129.1, 124.4, 123.4, 123.3, 116.4, 115.1, 86.4, 82.7, 55.2, 37.6, 20.2.

IR (KBr): 2938, 1777, 1716, 1383, 1352, 722.

MS (EI): m/z 305 (M$^+$), 290, 277, 246, 218, 158, 130, 115, 104, 76.

HRMS (EI): m/z calcd. for C$_{19}$H$_{15}$NO$_3$: 305.1052, found 305.1050.

Synthesis of 2-[3-(3,4,5-trimethoxyphenyl)-prop-2-ynyl]-isoindole-1,3-dione (220)
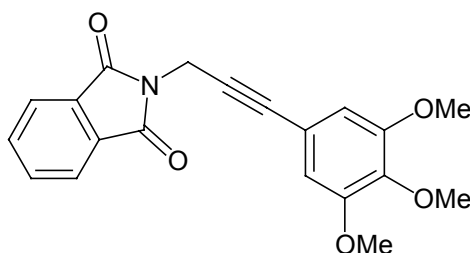
To a stirred solution of 2-prop-2-ynyl-isoindole-1,3-dione (**109**) (150 mg, 0.81 mmol) in dry CH$_2$Cl$_2$ (4 ml) were subsequently added triethylamine (0.57 ml, 4 mmol, 5.0 equiv.), 5-iodo-1,2,3-trimethoxybenzene (286 mg, 0.97 mmol, 1.2 equiv.), CuI (7.7 mg, 0.04 mmol, 5 mol%), PdCl$_2$(PPh$_3$)$_2$ (28.4 mg, 0.04 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated NaHCO$_3$ solution (20 ml), the layers were separated and the water phase was extracted by CH$_2$Cl$_2$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:EtOAc = 1:1) to give 199 mg (70%) of (**220**) as a white solid.

¹H-NMR (300 MHz, CDCl$_3$): δ = 7.89-7.82 (m, 2H), 7.76-7.68 (m, 2H), 6.63 (s, 2H), 4.64 (s, 2H), 3.79 (s, 3H), 3.78 (s, 6H).

¹³C-NMR (75 MHz, CDCl$_3$): δ = 167.0, 152.8, 138.9, 134.1, 131.9, 123.4, 117.1, 109.0, 82.8, 81.6, 60.8, 56.0, 27.7.

IR (KBr): 2934, 1769, 1714, 1580, 1503, 1418, 1392, 1326, 1238, 1123, 721 cm^{-1}.

MS (EI): m/z 351 (M$^+$), 323, 292, 264, 175, 104, 76.

HRMS (EI): m/z calcd. for C$_{20}$H$_{17}$NO$_5$: 351.1107, found 351.1095.

Synthesis of 2-[3-(3,4,5-trimethoxyphenyl)-prop-2-ynyl]-isoindole-1,3-dione (221)
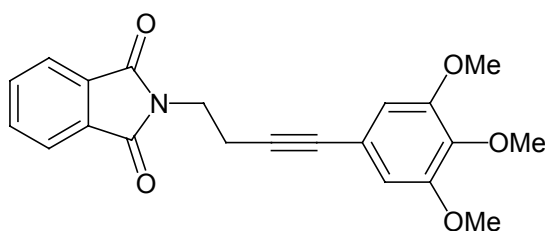
To a stirred solution of 2-but-3-ynyl-isoindole-1,3-dione (**117**) (500 mg, 2.51 mmol) in dry CH_2Cl_2 (10 ml) were subsequently added triethylamine (1.8 ml, 12.5 mmol, 5.0 equiv.), 5-iodo-1,2,3-trimethoxybenzene (886 mg, 3.01 mmol, 1.2 equiv.), CuI (24 mg, 0.12 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (88 mg, 0.12 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml), the layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:EtOAc = 1:1) to give 739 mg (80%) of (**221**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.82-7.73 (m, 2H), 7.69-7.61 (m, 2H), 6.51 (s, 2H), 3.90 (t, 2H, J = 7.0 Hz), 3.75 (s, 3H), 3.74 (s, 6H), 2.75 (t, 2H, J = 7.0 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.7, 152.6, 138.2, 133.7, 131.7, 122.9, 118.1, 108.5, 84.7, 82.1, 60.6, 55.8, 36.5, 19.1.
IR (KBr): 2943, 1768, 1716, 1578, 1505, 1236, 1126, 996, 725 cm^{-1}.
MS (EI): m/z 365 (M$^+$), 334, 218, 205, 160, 105, 77.
HRMS (EI): m/z calcd. for $C_{21}H_{19}NO_5$: 365.1263, found 365.1258.

Synthesis of 2-(3-naphthalen-1-yl-prop-2-ynyl)-isoindole-1,3-dione (222)
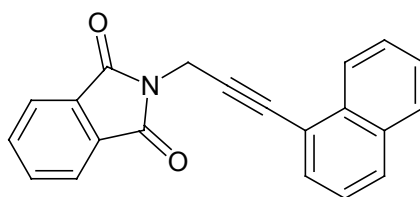
To a stirred solution of 2-prop-2-ynyl-isoindole-1,3-dione (**109**) (500 mg, 2.70 mmol) in dry CH_2Cl_2 (10 ml) were subsequently added triethylamine (1.9 ml, 13.5 mmol, 5.0 equiv.), 1-iodonaphthalene (0.47 ml, 3.24 mmol, 1.2 equiv.), CuI (25.7 mg, 0.13 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (94.6 mg, 0.13 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml), the layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:EtOAc = 3:1) to give 595 mg (70%) of (**222**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.35-8.28 (m, 1H), 7.94-7.86 (m, 2H), 7.84-7.77 (m, 2H), 7.72 (dd, 2H, J = 5.4, 3.1 Hz), 7.65 (dd, 1H, J = 7.2, 1.2 Hz), 7.56 (ddd, 1H, J = 8.4, 6.9, 1.5 Hz), 7.49 (ddd, 1H, J = 8.1, 6.9, 1.5 Hz), 7.37 (dd, 1H, J = 8.3, 7.2 Hz), 4.84 (s, 2H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.1, 134.2, 133.4, 133.0, 132.1, 130.8, 129.0, 128.1, 126.8, 126.3, 126.1, 125.0, 123.5, 87.4, 81.2, 28.1.
IR (KBr): 3044, 1772, 1710, 1424, 1390, 1337, 1316, 1110, 942, 794, 773, 725 cm^{-1}.
MS (EI): m/z 311 (M$^+$), 282, 254, 180, 105, 76.
HRMS (EI): m/z calcd. for $C_{21}H_{13}NO_2$: 311.0946, found 311.0957.

Synthesis of 2-[3-(2-methoxyphenyl)-prop-2-ynyl]-isoindole-1,3-dione (223)
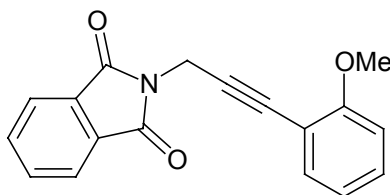
To a stirred solution of 2-prop-2-ynyl-isoindole-1,3-dione (**109**) (150 mg, 0.81 mmol) in dry CH_2Cl_2 (4 ml) were subsequently added triethylamine (0.6 ml, 4.05 mmol, 5.0 equiv.), 2-iodoanisole (0.13 ml, 0.97 mmol, 1.2 equiv.), CuI (7.7 mg, 0.04 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (28.4 mg, 0.04 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml). The layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 187 mg (79%) of (**223**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$) δ = 7.82-7.77 (m, 2H), 7.68-7.62 (m, 2H), 7.29 (dd, 1H, J = 7.5, 1.7 Hz), 7.17 (t, 1H, J = 7.5 Hz), 6.81-6.72 (m, 2H), 4.64 (s, 2H), 3.75 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.1, 159.2, 133.1, 133.0, 131.1, 128.9, 122.4, 119.3, 110.5, 109.6, 85.6, 78.4, 54.7, 27.2.
IR (KBr): 2923, 1711, 1424, 1346, 1262, 1129, 1017, 941, 726 cm^{-1}.
MS (EI): m/z 291 (M$^+$), 144, 130, 115, 105, 76.
HRMS (EI): m/z calcd. for C$_{18}$H$_{13}$NO$_3$: 291.0895, found 291.0892.

Synthesis of 4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-prop-1-ynyl]-benzoic acid ethyl ester (224)
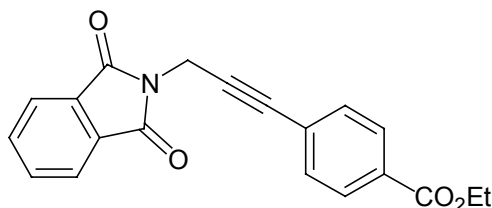
To a stirred solution of 2-prop-2-ynyl-isoindole-1,3-dione (**109**) (500 mg, 2.70 mmol) in dry CH_2Cl_2 (10 ml) were subsequently added triethylamine (1.9 ml, 13.5 mmol, 5.0 equiv.), ethyl 4-iodobenzoate (0.54 ml, 3.24 mmol, 1.2 equiv.), CuI (25.7 mg, 0.13 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (94.6 mg, 0.13 mmol, 5 mol%) and the stirring was continued overnight at room temperature. The reaction mixture was then washed with saturated $NaHCO_3$ solution (20 ml), the layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 792 mg (88%) of (**224**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$) δ = 7.97-7.91 (m, 2H), 7.90-7.84 (m, 2H), 7.77-7.69 (m, 2H), 7.49-7.42 (m, 2H), 4.69 (s, 2H), 4.34 (q, 2H, J = 7.1 Hz), 1.36 (t, 3H, J = 7.1 Hz).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.9, 165.9, 134.2, 132.0, 131.7, 130.1, 129.2, 126.8, 123.5, 85.5, 82.2, 61.1, 27.7, 14.2.
IR (KBr): 2979, 1714, 1417, 1394, 1277, 1108, 938, 718 cm^{-1}.
MS (EI): *m/z* 333 (M$^+$), 305, 276, 232, 204, 104, 84.
HRMS (EI): *m/z* calcd. for C$_{20}$H$_{15}$NO$_4$: 333.1001, found 333.1002.

Synthesis of 2-(2'-methoxy-4,5-dimethyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (231)
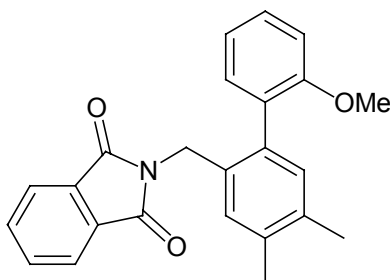
To a solution of 2-[3-(2-methoxyphenyl)-prop-2-ynyl]-isoindole-1,3-dione (**223**) (500 mg, 1.72 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (106 mg, 0.17 mmol, 10 mol%), Zn dust (56 mg, 0.86 mmol, 50 mol%), ZnI$_2$ (274 mg, 0.86 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.30 ml, 2.58 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was immediately dissolved in benzene and oxidised by DDQ (468 mg, 2.06 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:EtOAc = 2:1) to give 531 mg (83%) of (**232**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$) δ = 7.81-7.73 (m, 2H), 7.71-7.63 (m, 2H), 7.37-7.28 (m, 1H), 7.21 (dd, 1H, *J* = 7.4, 1.7 Hz), 7.08 (s, 1H), 7.02-6.94 (m, 2H), 6.91 (d, 1H, *J* = 8.3 Hz), 4.83 (d, 1H, *J* = 15.2 Hz), 4.57 (d, 1H, *J* = 15.2 Hz), 3.73 (s, 3H), 2.24 (s, 6H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.8, 156.6, 135.8, 135.5, 135.2, 133.6, 132.2, 132.0, 131.8, 131.2, 129.5, 128.7, 123.0, 120.5, 110.5, 55.3, 39.7, 19.5, 19.3.
IR (KBr): 2934, 1771, 1714, 1387, 1239, 1106, 1025, 950, 754, 718 cm^{-1}.
MS (EI): *m/z* 371 (M$^+$), 224, 209, 193, 165, 130, 105, 77.
HRMS (EI): *m/z* calcd. for C$_{24}$H$_{21}$NO$_3$: 371.1521, found 371.1504.

Synthesis of 2-(3'-methoxy-4,5-dimethyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (232)
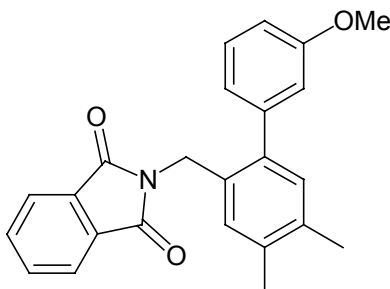
To a solution of 2-[3-(3-methoxyphenyl)-prop-2-ynyl]-isoindole-1,3-dione (**218**) (359 mg, 1.23 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (76 mg, 0.12 mmol, 10 mol%), Zn dust (40 mg, 0.61 mmol, 50 mol%), ZnI$_2$ (196 mg, 0.61 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.21 ml, 1.84 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was immediately dissolved in benzene and oxidised by DDQ (335 mg, 1.48 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 410 mg (90%) of (**232**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.87-7.79 (m, 2H), 7.76-7.67 (m, 2H), 7.33 (t, 1H, J = 8.1 Hz), 7.0 (s, 1H), 7.04-6.98 (m, 3H), 6.94-6.87 (m, 1H), 4.84 (s, 2H), 3.84 (s, 3H), 2.26 (s, 3H), 2,24 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.9, 159.3, 142.1, 138.7, 135.9, 135.5, 133.8, 132.1, 131.3, 130.7, 129.1, 128.3, 123.1, 121.7, 114.7, 112.8, 55.2, 39.1, 19.4, 19.2.

IR (KBr): 2923, 1769, 1714, 1598, 1399, 1240, 1113, 1038, 952, 806, 730, 714 cm^{-1}.

MS (EI): *m/z* 371 (M$^+$), 311, 283, 224, 209, 166, 105, 77.

HRMS (EI): *m/z* calcd. for C$_{24}$H$_{21}$NO$_3$: 371.1521, found 371.1522.

Synthesis of 2-(3',4',5'-trimethoxy-4,5-dimethylbiphenyl-2-ylmethyl)-isoindole-1,3-dione (233)
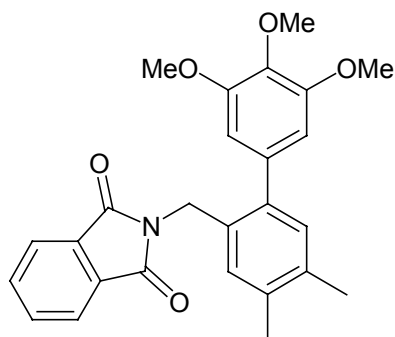
To a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (**220**) (502 mg, 1.43 mmol) in dry CH$_2$Cl$_2$ (8 ml) were subsequently added CoBr$_2$(dppe) (88 mg, 0.14 mmol, 10 mol%), Zn dust (46.5 mg, 0.71 mmol, 50 mol%), ZnI$_2$ (227 mg, 0.71 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.24 ml, 2.13 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (389 mg, 1.71 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was washed with an aqueous solution containing 10% NaOH and 10% Na$_2$S$_2$O$_3$ (3x20 ml), the organic phase separated, dried over Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:EtOAc = 1:1) to give 475 mg (77%) of (**233**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.85-7.77 (m, 2H), 7.75-7.67 (m, 2H), 7.02 (s, 1H), 6.99 (s, 1H), 6.62 (s, 2H), 4.83 (s, 2H), 3.87 (s, 3H), 3.84 (s, 6H), 2.25 (s, 3H), 2.23 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.9, 152.9, 138.8, 136.9, 136.3, 136.0, 135.5, 133.8, 132.1, 131.3, 130.8, 128.6, 123.1, 106.6, 60.8, 56.1, 39.4, 19.4, 19.2.
IR (KBr): 2939, 1766, 1707, 1585, 1466, 1430, 1415, 1390, 1339, 1127, 1104, 1001, 946, 873, 854, 824, 796, 748, 722, 706, 671, 634 cm^{-1}.
MS (EI): *m/z* 431 (M$^+$), 353, 283, 269, 211, 160, 105.
HRMS (EI): *m/z* calcd. for C$_{26}$H$_{25}$NO$_5$: 431.1733, found 431.1726.

Synthesis of 2-(4,5-dimethyl-2-naphthalen-1-yl-benzyl)-isoindole-1,3-dione (234)
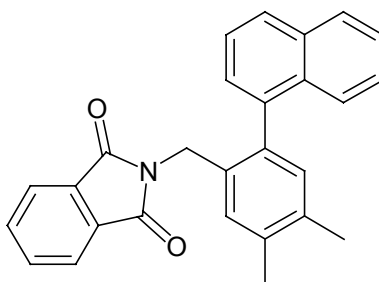
To a solution of 2-(3-naphthalen-1-yl-prop-2-ynyl)-isoindole-1,3-dione (**222**) (300 mg, 0.96 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (59.5 mg, 0.096 mmol, 10 mol%), Zn dust (31.5 mg, 0.48 mmol, 50 mol%), ZnI$_2$ (154 mg, 0.48 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.16 ml, 1.44 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (263 mg, 1.16 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:EtOAc = 3:1) to give 340 mg (90%) of (**234**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.88-7.77 (m, 2H), 7.68-7,57 (m, 4H), 7.56-7.49 (m, 1H), 7.48-7.41 (m, 2H), 7.33 (ddd, 1H, *J* = 8.2, 6.9, 1.3 Hz), 7.24 (ddd, 1H, *J* = 8.2, 6.9, 1.3 Hz), 7.17 (s, 1H), 7.05 (s, 1H), 4.70 (d, 1H, *J* = 15.3 Hz), 4.41 (d, 1H, *J* = 15.3 Hz), 2.31 (s, 3H), 2.27 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.5, 138.1, 136.9, 136.1, 135.6, 133.5, 133.4, 132.4, 132.1, 131.9, 129.1, 128.0, 127.6, 127.1, 125.9, 125.8, 125.6, 125.4, 122.9, 39.7, 19.5, 19.2.
IR (KBr): 1771, 1717, 1424, 1395, 1112, 950, 781, 721 cm^{-1}.
MS (EI): *m/z* 391 (M$^+$), 303, 258, 244, 229, 195, 105, 77.
HRMS (EI): *m/z* calcd. for C$_{27}$H$_{21}$NO$_2$: 391.1572, found 391.1558.

Synthesis of 2-(4-methoxybiphenyl-2-ylmethyl)-isoindole-1,3-dione (235a) and 2-(5-methoxybiphenyl-2-ylmethyl)-isoindole-1,3-dione (235b)
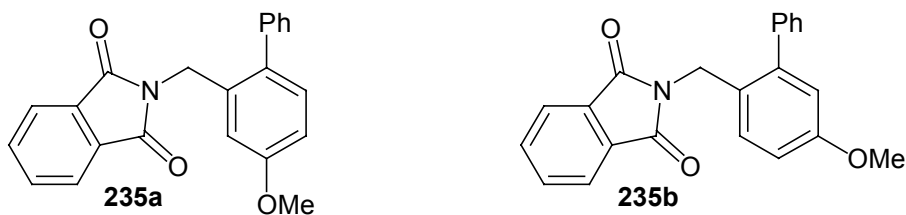
To a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (161) (150 mg, 0.57 mmol) in dry CH_2Cl_2 (4 ml) were subsequently added $CoBr_2$(dppe) (35.5 mg, 0.057 mmol, 10 mol%), Zn dust (19 mg, 0.29 mmol, 50 mol%), ZnI_2 (92 mg, 0.29 mmol, 50 mol%), 2-metoxy-1,3-butadiene (255) (72 mg, 0.86 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (156 mg, 0.69 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 113 mg (57%) of a non separable mixture of regioisomers (235a) and (235b) as white solids (235a:235b = 6 : 1, estimated by ^{1}H-NMR).

^{1}**H-NMR** (300 MHz, $CDCl_3$) resolved signals for the major regioisomer (235a): δ = 7.76-7.65 (m, 2H), 7.63-7.53 (m, 2H), 7.37-7.20 (m, 5H), 7.08 (d, 1H, J = 8.4 Hz), 6.77-6.64 (m, 2H), 4.71 (s, 2H), 3.65 (s, 3H); resolved signals for the minor regioisomer (235b): δ = 4.67 (s), 3.67 (s). The remaining signals are unresolved.
^{13}**C-NMR** (75 MHz, $CDCl_3$) resolved signals for the major regioisomer (235a): δ =167.8, 159.0, 140.3, 133.8, 131.2, 129.5, 128.1, 126.9, 112.9, 111.9, 55.1, 39.4; resolved signals for the minor regioisomer (235b): δ = 167.9, 158.4, 140.6, 115.2, 113.4, 55.2, 38.8. The remaining signals are unresolved.
IR (KBr): 3006, 1706, 1609, 1426, 1392, 1285, 1109, 948, 719, 705 cm^{-1}.
MS (EI): m/z 343 (M$^+$), 196, 181, 148, 130, 77.
HRMS (EI): m/z calcd. for $C_{22}H_{17}NO_3$: 343.1208, found 343.1215.

Synthesis of 2-[1-(3'-methoxy-4,5-dimethylbiphenyl-2-yl)-ethyl]-isoindole-1,3-dione (236)
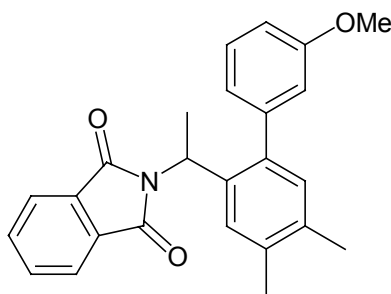
To a solution of 2-[3-(3-methoxyphenyl)-1-methyl-prop-2-ynyl]-isoindole-1,3-dione (219) (379 mg, 1.24 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added $CoBr_2$(dppe) (77 mg, 0.12 mmol, 10 mol%), Zn dust (40.5 mg, 0.62 mmol, 50 mol%), ZnI_2 (198 mg, 0.62 mmol, 50

mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.21 ml, 1.86 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel and concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (338 mg, 1.49 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 387 mg of (81%) (**236**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.73-7.66 (m, 2H), 7.65-7.59 (m, 2H), 7.55 (s, 1H), 7.21 (t, 1H, J = 7.8 Hz), 6.96 (s, 1H), 6.82 (dd, 2H, J = 8.3, 2.2 Hz), 6.75 (s, 1H), 5.62 (q, 1H, J = 7.2 Hz), 3.66 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H), 1.77 (d, 3H, J = 7.2 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 167.7, 159.1, 142.2, 138.8, 135.7, 135.4, 135.3, 133.5, 131.8, 131.2, 129.1, 128.3, 122.7, 121.2, 113.9, 112.8, 54.8, 47.1, 19.6, 19.1, 18.8.
IR (KBr): 2943, 1777, 1711, 1586, 1385, 1239, 1125, 717 cm^{-1}.
MS (EI): *m/z* 385 (M$^+$), 238, 223, 193, 165, 130, 105, 77.
HRMS (EI): *m/z* calcd. for C$_{25}$H$_{23}$NO$_3$: 385.1678, found 385.1680.

Synthesis of 2-[2-(3',4',5'-trimethoxy-4,5-dimethylbiphenyl-2-yl)-ethyl]-isoindole-1,3-dione (237)
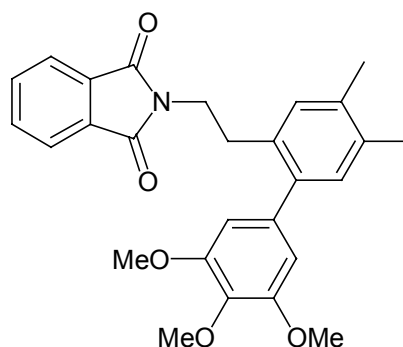
To a solution of 2-[4-(3,4,5-trimethoxyphenyl)-but-3-ynyl]-isoindole-1,3-dione (**221**) (150 mg, 0.41 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (25.4 mg, 0.04 mmol, 10 mol%), Zn dust (13.4 mg, 0.2 mmol, 50 mol%), ZnI$_2$ (65.5 mg, 0.2 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.07 ml, 0.62 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (112 mg, 0.49 mmol, 1.2 equiv.) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was washed with an aqueous solution containing 10% of NaOH and 10% of Na$_2$S$_2$O$_3$, the water phase separated and extracted by CH$_2$Cl$_2$ (2x20 ml). The combined organic phases were dried over Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:EtOAc = 1:1) to give 156 mg (85%) of (**237**) as a white solid.

^{1}H-NMR (300 MHz,CDCl$_3$): δ = 7.81-7.73 (m, 2H), 7.72-7.62 (m, 2H), 7.07 (s, 1H), 7.02 (s, 1H), 6.53 (s, 2H), 3.91 (s, 3H), 3.87 (s, 6H), 3.84-3.75 (m, 2H), 2.99-2.88 (m, 2H), 2.24 (s, 3H), 2.21 (s, 3H).

^{13}**C-NMR** (75 MHz, CDCl$_3$): 167.9, 152.7, 139.8, 136.9, 136.7, 135.8, 134.6, 133.7, 132.7, 132.0, 131.2, 131.0, 122.9, 106.3, 60.8, 56.0, 39.7, 31.2, 19.2, 19.1.
IR (KBr): 2937, 1717, 1585, 1395, 1127, 718 cm^{-1}.
MS (EI): *m/z* 445 (M$^+$), 430, 285, 267, 254, 239, 160, 77.
HRMS (EI): *m/z* calcd. for C$_{27}$H$_{27}$NO$_5$: 445.1889, found 445.1887.

Synthesis of 2-(9-phenyltetracyclo-[4.3.0.0^{2,4}.0^{3,7}]-non-8-en-8-ylmethyl)-2,3-dihydro-1*H*-1-isoindolone (238)
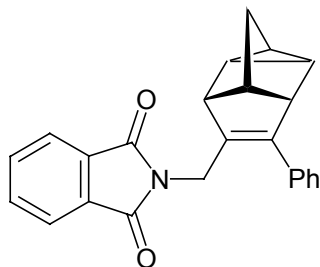
To a solution of 2-(3-phenyl-prop-2-ynyl)-isoindole-1,3-dione (**161**) (315 mg, 1.20 mmol) in CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (74.4 mg, 0.12 mmol, 10 mol%), zinc (39.5 mg, 0.60 mmol, 50 mol%), ZnI$_2$ (192 mg, 0.60 mmol, 50 mol%), 2,5-norbornadiene (**7**) (0.18 ml, 1.81 mmol, 1.5 equiv.). The resulting mixture was stirred overnight at room temperature, then filtered (pentane:diethyl ether = 1:1) over a short pad of silica gel and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 416 mg (98%) of (**238**) as a white solid.

^{1}**H-NMR** (300 MHz, CDCl$_3$): δ = 8.06-7.95 (m, 2H), 7.91-7.81 (m, 2H), 7.65 (d, 2H, *J* = 7.2 Hz), 7.52 (t, 2H, *J* = 7.6 Hz), 7.41-7.35 (m, 1H), 4.82 (d, 1H, *J* = 15.4 Hz), 4.71 (d, 1H, *J* = 15.4 Hz), 3.00 (s, 1H), 2.79 (s, 1H), 2.21 (s, 1H), 1.98-1.50 (m, 5H).
^{13}**C-NMR** (75 MHz, CDCl$_3$): δ = 168.1, 144.5, 137.4, 136.7, 133.8, 132.0, 128.2, 127.2, 126.3, 123.1, 54.8, 54.0, 51.3, 36.5, 32.2, 24.8, 23.3, 23.1.
IR (KBr): 2924, 1704, 1392, 1326, 1263, 1099, 1078, 930, 767, 720, 701 cm^{-1}.
MS (EI): *m/z* 353 (M$^+$), 206, 193, 178, 161, 115, 91, 51.
HRMS (EI): *m/z* calcd. for C$_{24}$H$_{19}$NO$_2$: 353.1416, found 353.1410.

Synthesis of 2'-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4',5'-dimethyl-biphenyl-4-carboxylic acid ethyl ester (239)
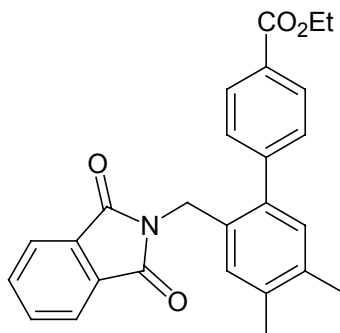
To a solution of 4-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-prop-1-ynyl]-benzoic acid ethyl ester (**224**) (500 mg, 1.50 mmol) in CH_2Cl_2 (7 ml) were subsequently added $CoBr_2$(dppe) (92.5 mg, 0.15 mmol, 10 mol%), Zn dust (49 mg, 0.75 mmol, 50 mol%), ZnI_2 (239 mg, 0.75 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.25 ml, 2.25 mmol, 1.5 equiv.). The resulting mixture stirred overnight at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (409 mg, 1.79 mmol) at room temperature. An orange precipitate appeared almost immediately. After 2 hours the reaction mixture was filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:EtOAc = 2:1) to give 471 mg (76%) of (**239**) as a white solid.

¹H-NMR (300 MHz, CDCl₃) δ = 8.13-8.07 (m, 2H), 7.83-7.77 (m, 2H), 7.73-7.66 (m, 2H), 7.53-7.47 (m, 2H), 7.03 (s, 1H), 7.01 (s, 1H), 4.78 (s, 2H), 4.40 (q, 2H, *J* = 7.1 Hz), 2.24 (s, 3H), 2.22 (s, 3H), 1.42 (t, 3H, *J* = 7.1 Hz).
¹³C-NMR (75 MHz, CDCl₃): δ = 167.9, 166.4, 145.5, 138.0, 136.6, 135.8, 133.9, 132.0, 131.1, 130.7, 129.5, 129.4, 129.1, 128.6, 123.2, 60.8, 38.9, 19.5, 19.2, 14.3.
IR (KBr): 2980, 2941, 1765, 1721, 1393, 1280, 1100, 945, 720 cm⁻¹.
MS (EI): *m/z* 413 (M⁺), 368, 266, 237, 193, 130, 105, 77.
HRMS (EI): *m/z* calcd. for $C_{26}H_{23}NO_4$: 413.1627, found 413.1626.

Synthesis of (±)-6,7-dimethyl-11,15b-dihydro-9*H*-dibenzo-[3,4:5,6]-azepino-[2,1-*a*]-isoindol-11-one (242)
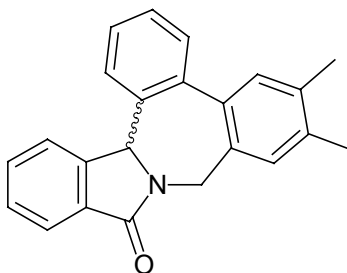
A solution of 2-(4,5-dimethylbiphenyl-2-ylmethyl)-isoindole-1,3-dione (**162**) (191 mg, 0.56 mmol) in 4 ml of a 1:1 mixture of CH_2Cl_2 and MeOH was cooled at 0 °C, then NaBH₄ (106 mg, 2.8 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of NaBH₄ was carefully quenched by 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residual white solid was dissolved in 3 ml of chloroform, 1 ml of TFA was added and the mixture was stirred overnight at room temperature. The excess of TFA was carefully quenched by 10% NaOH. The layers were separated and the water phase extracted by CHCl₃ (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:2) to give 168 mg (92%) of (**242**) as a white solid.

¹H-NMR (300 MHz, CDCl₃): δ = 7.97 (d, 1H, *J* = 6.9 Hz), 7.64-7.46 (m, 5H), 7.36 (s, 1H), 7.29 (dt, 1H, *J* = 7.6, 1.3 Hz), 7.25 (s, 1H), 7.06 (d, 1H, *J* = 7.6 Hz), 5.35 (s, 1H), 5.03 (d, 1H, *J* = 13.7 Hz), 3.91 (d, 1H, *J* = 13.7 Hz), 2.39 (s, 3H), 2.35 (s, 3H).

^{13}C-NMR (75 MHz, CDCl$_3$): δ = 165.5, 141.8, 140.5, 137.7, 136.9, 136.8, 134.2, 133.6, 131.2, 130.8, 130.6, 130.3, 128.9, 128.7, 128.4, 127.9, 125.2, 124.1, 123.8, 60.7, 44.2, 19.4, 19.3.
IR (KBr): 2921, 2851, 1687, 1403, 1245, 749, 721, 703 cm^{-1}.
MS (EI): *m/z* 325 (M$^+$), 296, 252, 178, 165, 130, 77.
HRMS (EI): *m/z* calcd. for C$_{23}$H$_{19}$NO: 325.1467, found 325.1473.

Synthesis of (±)-3-methoxy-6,7-dimethyl-11,15b-dihydro-9*H*-dibenzo[3,4:5,6]-azepino [2,1-*a*]isoindol-11-one (244)
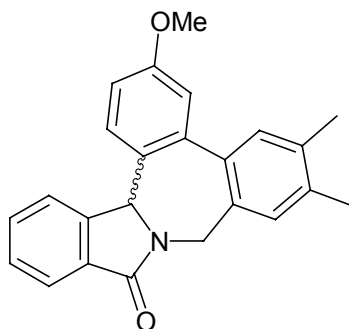
A solution of 2-(3'-methoxy-4,5-dimethylbiphenyl-2-ylmethyl)-isoindole-1,3-dione (**232**) (126 mg, 0.34 mmol) in 6 ml of a 2:1 mixture of CH$_2$Cl$_2$ and MeOH was cooled at 0 °C, then NaBH$_4$ (64 mg, 1.7 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After 30 minutes the excess of NaBH$_4$ was carefully quenched using 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase extracted with CH$_2$Cl$_2$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residual white solid was dissolved in 3 ml of chloroform, 1 ml of TFA was added and stirring continued overnight at room temperature. The excess of TFA was carefully quenched with 10% NaOH. The layers were separated and the water phase extracted with CHCl$_3$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:6) to give 111 mg (92%) of (**244**) as a white solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.93 (d, 1H, *J* = 7.1 Hz), 7.63-7.48 (m, 2H), 7.44 (d, 1H, *J* = 6.9 Hz), 7.34 (s, 1H), 7.22 (s, 1H), 7.10 (d, 1H, *J* = 2.6 Hz), 6.94 (d, 1H, *J* = 8.5 Hz), 6.78 (dd, 1H, *J* = 8.5, 2.6 Hz), 5.28 (s, 1H), 4.98 (d, 1H, *J* = 13.7 Hz), 3.89 (d, 1H, *J* = 13.7 Hz), 3.85 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 165.5, 159.7, 142.2, 141.9, 137.8, 137.1, 137.0, 134.2, 131.3, 130.8, 130.7, 130.2, 128.3, 126.5, 126.1, 124.1, 123.8, 114.5, 112.9, 60.4, 55.3, 44.3, 19.5, 19.3.
IR (KBr): 2918, 1685, 1392, 1227, 748, 729, 712 cm^{-1}.
MS (EI): *m/z* 355 (M$^+$), 340, 325, 311, 223, 209, 130, 84.
HRMS (EI): *m/z* calcd. for C$_{24}$H$_{21}$NO$_2$: 355.1572, found 355.1578.

Synthesis of (±)-1,2,3-trimethoxy-6,7-dimethyl-11,15b-dihydro-9*H*-dibenzo[3,4:5,6]-azepino[2,1-*a*]isoindol-11-one (245)
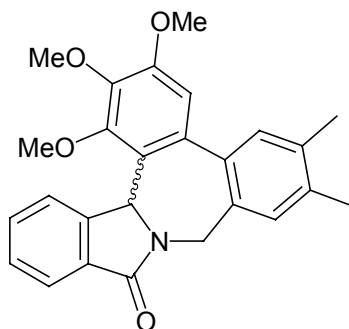
A solution of 2-(3',4',5'-trimethoxy-4,5-dimethylbiphenyl-2-ylmethyl)-isoindole-1,3-dione (**233**) (365 mg, 0.85 mmol) in 10 ml of a 1:1 mixture of CH_2Cl_2 and MeOH was cooled at 0 °C, $NaBH_4$ (160 mg, 4.23 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of $NaBH_4$ was carefully quenched using 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residual white solid was dissolved in 3 ml of chloroform, 1 ml of TFA was added and the stirring was continued overnight at room temperature. The excess of TFA was carefully quenched by 10% NaOH, then the layers were separated and the water phase was extracted by $CHCl_3$ (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:EtOAc = 1:2) to give 339 mg (96%) of (**245**) as a white solid.

¹H-NMR (300 MHz, CDCl₃) signals for the major diasteroisomer: δ = 7.95 (d, 1H, *J* = 7.2 Hz), 7.61-7.50 (m, 3H), 7.45 (s, 1H), 7.30 (s, 1H), 6.98 (s, 1H), 5.28 (s, 1H), 5.14 (d, 1H, *J* = 13.6 Hz), 4.06 (s, 3H), 3.96 (s, 3H), 3.94 (d, 1H, *J* = 13.6 Hz), 3,17 (s, 3H), 2.47 (s, 3H), 2.41 (s, 3H).
¹³C-NMR (75 MHz, CDCl₃) signals for the major diastereoisomer: δ = 165.4, 153.2, 151.5, 143.9, 142.0, 138.0, 137.4, 137.0, 136.9, 132.2, 131.8, 130.4, 129.9, 129.6, 127.2, 124.6, 122.5, 119.1, 108.6, 61.0, 60.8, 58.8, 55.9, 43.8, 19.5, 19.3.
IR (KBr): 2935, 1687, 1485, 1455, 1412, 1120, 734 cm⁻¹.
MS (EI): *m/z* 415 (M⁺), 400, 383, 283, 253, 200, 130, 77.
HRMS (EI): *m/z* calcd. for $C_{26}H_{25}NO_4$: 415.1784, found 415.1780.

Synthesis of (±)-6,7-dimethyl-11,15b-dihydro-9*H*-benzo[5,6]naphtha-[2',1':3,4]azepino [2,1-*a*]isoindol-11-one (246)
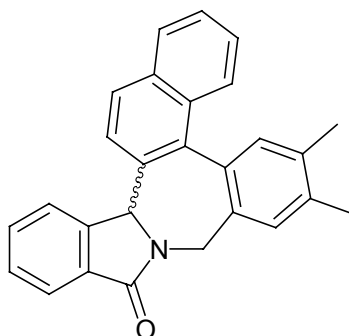
A solution of 2-(4,5-dimethyl-2-naphthalen-1-yl-benzyl)-isoindole-1,3-dione (**234**) (307 mg, 0.78 mmol) in 10 ml of a 1:1 mixture of CH_2Cl_2 and MeOH was cooled at 0 °C, then $NaBH_4$ (148 mg, 3.92 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of $NaBH_4$ was carefully quenched using 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residual white solid was dissolved in 10 ml of chloroform, 1 ml of TFA was added and the stirring was continued overnight at room temperature. The excess of TFA was carefully quenched by 10% NaOH. The layers were separated and the water phase was extracted by $CHCl_3$ (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane: EtOAc = 1:1) to give 269 mg (92%) of (**246**) as a white solid. Suitable crystals for x-ray diffraction were obtained from CH_2Cl_2/petroleum ether.

¹H-NMR (300 MHz, CDCl₃): δ = 8.21-8.11 (m, 1H), 7.95 (d, 1H, *J* = 7.3 Hz), 7.92-7.85 (m, 1H), 7.77 (d, 1H, *J* = 8.5 Hz), 7.66-7.48 (m, 5H), 7.46 (s, 1H), 7.35 (s, 1H), 7.14 (d, 1H, *J* = 8.5 Hz), 5.39 (s, 1H), 5.01 (d, 1H, *J* = 13.4 Hz), 3.86 (d, 1H, *J* = 13.4 Hz), 2.39 (s, 3H), 2.38 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ = 165.4, 142.1, 137.1, 136.9, 135.9, 134.8, 134.3, 133.8, 133.1, 132.6, 131.2, 131.0, 130.9, 130.8, 128.5, 128.4, 128.3, 126.5, 126.3, 126.0, 124.2, 123.9, 122.6, 61.2, 44.1, 19.6, 19.5.

IR (KBr): 3050, 2912, 2847, 1688, 1466, 1403, 1240, 750, 729, 721 cm⁻¹.

MS (EI): *m/z* 375 (M⁺), 360, 346, 243, 187, 173, 157, 130.

HRMS (EI): *m/z* calcd. for $C_{27}H_{21}NO$: 375.1623, found 375.1621.

Synthesis of (±)-7-methoxy-11,15b-dihydro-9*H*-dibenzo[3,4:5,6]azepino[2,1-*a*]isoindol-11-one (247)
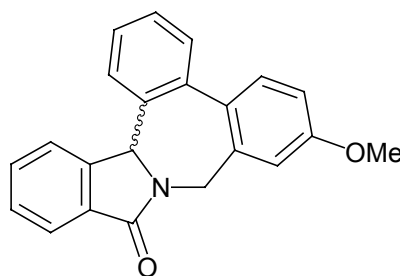
A solution of 2-(4-methoxybiphenyl-2-ylmethyl)-isoindole-1,3-dione (**235**) (334 mg, 0.97 mmol) in 8 ml of a 1:1 mixture of CH_2Cl_2 and MeOH was cooled at 0 °C, then $NaBH_4$ (184 mg, 4.9 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of $NaBH_4$ was carefully quenched using 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residual white solid was dissolved in 3 ml of chloroform, then 1 ml of TFA was added and stirring was continued overnight at room temperature. The excess of TFA was carefully quenched by 10% NaOH. The layers were separated and the water phase extracted with $CHCl_3$ (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:6) to give 263 mg (83%) of (**247**) as a white solid. Suitable crystals for x-ray diffraction were obtained from CH_2Cl_2/petroleum ether.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.86 (d, 1H, J = 7.1 Hz), 7.56-7.32 (m, 6H), 7.18 (td, 1H, J = 7.6, 1.4 Hz), 7.00-6.90 (m, 3H), 5.28 (s, 1H), 4.94 (d, 1H, J = 13.7 Hz), 3.83 (d, 1H, J = 13.7 Hz), 3.77 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 165.7, 159.7, 141.9, 140.3, 135.2, 134.1, 133.5, 132.7, 131.0, 130.3, 128.9, 128.8, 128.5, 127.9, 125.3, 124.2, 123.9, 114.7, 114.2, 60.9, 55.4, 44.9.
IR (KBr): 1682, 1614, 1400, 1251, 755, 707 cm^{-1}.
MS (EI): *m/z* 327 (M$^+$), 298, 254, 195, 164, 130, 105.
HRMS (EI): *m/z* calcd. for $C_{22}H_{17}NO_2$: 327.1259, found 327.1251.

Synthesis of (±)-6,7,9-trimethyl-11,15b-dihydro-9H-dibenzo[3,4:5,6]azepino[2,1-a]-isoindol-11-one (248a) and (248b)

(±)-248a   (±)-248b
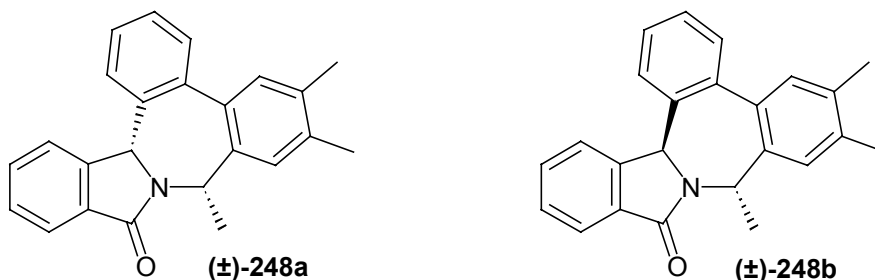
A solution of 2-[1-(4,5-dimethylbiphenyl-2-yl)-ethyl]-isoindole-1,3-dione (**178**) (424 mg, 1.19 mmol) in 8 ml of a 1:1 mixture of CH_2Cl_2 and MeOH was cooled at 0 °C, then $NaBH_4$ (226 mg, 5.96 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of $NaBH_4$ was carefully quenched by 1.0M HCl and adjusted to pH = 6.0. The phases were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure. The residue was dissolved in toluene, 1 ml of TFA and the mixture was refluxed overnight at 120 °C. After cooling at room temperature the excess TFA was carefully quenched by 10% NaOH. The organic phase was separated and the aqueous phase was extracted by CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:2) to give 43 mg (11%) of (±)-(**248a**) and 308 mg (76%) of (±)-

(**248b**) as white solids. Suitable crystals for x-ray diffraction were obtained from CH₂Cl₂/petroleum ether.

Data for (±)-(**248a**)
¹H-NMR (300 MHz, CDCl₃): δ = 7.79 (d, 1H, J = 6.8 Hz), 7.54-7.34 (m, 4H), 7.33-7.26 (m, 2H), 7.25-7.15 (m, 2H), 6.84 (d, 1H, J = 6.9 Hz), 5.29 (s, 1H), 4.56-4.35 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.10 (d, 3H, J = 6.9 Hz).
¹³C-NMR (75 MHz, CDCl₃): δ = 167.0, 142.1, 140.0, 137.5, 136.9, 136.6, 136.4, 135.1, 134.9, 131.1, 130.3, 128.7, 128.6, 128.4, 128.0, 127.5, 125.7, 123.9, 123.5, 63.1, 51.7, 19.8, 19.4, 15.9.
IR (KBr): 2938, 1676, 1388, 1303, 1214, 756, 718 cm⁻¹.
MS (EI): m/z 324 (M⁺- CH₃), 309, 252, 193, 155, 43.
HRMS (EI): m/z calcd. for C₂₄H₂₁NO: 339.1623, found 339.1622.

Data for (±)-(**248b**)
¹H-NMR (300 MHz, CDCl₃):   = 7.86 (d, 1H, J = 6.9 Hz), 7.55-7.32 (m, 5H), 7.26 (s, 1H), 7.22-7.13 (m, 1H), 7.09 (s, 1H), 6.96 (d, 1H, J = 7.6 Hz), 5.38 (s, 1H), 5.26 (q, 1H, J = 6.9 Hz), 2.28 (s, 3H), 2.24 (s, 3H), 0.92 (d, 3H, J = 6.9 Hz).
¹³C-NMR (75 MHz, CDCl₃): δ = 165.4, 141.8, 141.3, 137.0, 136.8, 136.7, 135.9, 134.2, 133.9, 131.7, 130.8, 130.7, 128.9, 128.7, 128.4, 127.8, 124.9, 124.0, 123.8, 60.8, 54.1, 21.1, 19.4, 19.3.
IR (KBr): 2972, 2925, 1686, 1448, 1385, 751, 732, 709 cm⁻¹.
MS (EI): m/z 324 (M⁺- CH₃), 309, 252, 193, 155, 43.
HRMS (EI): m/z calcd. for C₂₄H₂₁NO: 339.1623, found 339.1622.

Synthesis of (±)-3-methoxy-6,7,9-trimethyl-11,15b-dihydro-9*H*-dibenzo[3,4:5,6]azepino [2,1-*a*]isoindol-11-one (249a) and (249b)

(±)-**249a**   (±)-**249b**
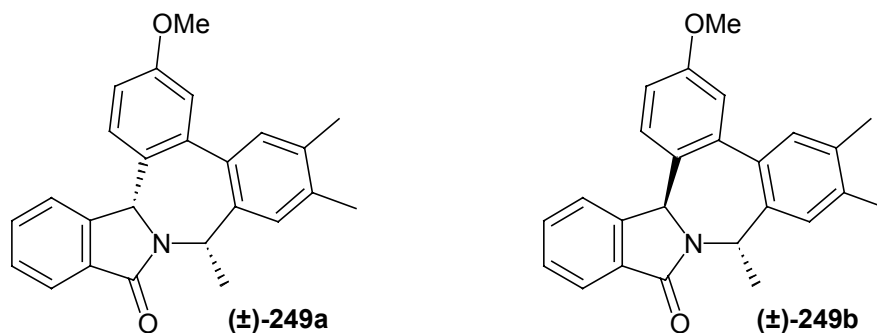
A solution of 2-[1-(3'-methoxy-4,5-dimethylbiphenyl-2-yl)-ethyl]-isoindole-1,3-dione (**236**) (351 mg, 0.91 mmol) in 9 ml of a 2:1 mixture of CH₂Cl₂ and MeOH was cooled at 0 °C, then NaBH₄ (172 mg, 4.55 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of NaBH₄ was carefully quenched by 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase was extracted by CH₂Cl₂ (3x20 ml). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residual white solid was dissolved in 3 ml of chloroform, 1 ml of TFA was added and the mixture was stirred overnight at room temperature. The excess of TFA was carefully quenched by 10% NaOH. The layers were separated and the water phase was extracted by CHCl₃ (3x20 ml). The combined organic phases were washed with brine, dried over Na₂SO₄, concentrated under reduced pressure and purified by column

chromatography on silica gel (eluent: pentane:diethyl ether = 1:6) to give 268 mg (80%) of (±)-(**249a**) and 34 mg (10%) of (±)-(**249b**) as white solids. Suitable crystals for x-ray diffraction were obtained from CH_2Cl_2/petroleum ether.

Data for (±)-(**249a**)
^{1}H-NMR (300 MHz, CDCl$_3$): δ = 8.06 (d, 1H, J = 6.6 Hz), 7.75-7.65 (m, 2H), 7.56-7.48 (m, 3H), 7.30 (s, 1H), 7.00 (s, 2H), 5.45 (br.s, 1H), 4.70 (br.s, 1H), 4.05 (s, 3H), 2.56 (s, 3H), 2.55 (s, 3H), 2.40 (d, 3H, J = 6.8 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 166.7, 159.6, 142.2, 141.3, 137.4, 136.7, 136.6, 136.3, 134.9, 133.8 130.8, 129.9, 128.1, 127.3, 126.8, 123.6, 123.3, 113.8, 113.0, 62.5, 55.2, 51.5, 19.6, 19.3, 15.8.
IR (KBr): 2936, 1765, 1684, 1606, 1303, 1217, 1041, 736 cm^{-1}.
MS (EI): m/z 369 (M$^+$), 354, 237, 223, 184, 169, 105, 77.
HRMS (EI): m/z calcd. for C$_{25}$H$_{23}$NO$_2$: 369.1729, found 369.1735.

Data for (±)-(**249b**)
^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.92 (d, 1H, J = 6.9 Hz), 7.63-7.48 (m, 2H), 7.44 (d, 1H, J = 6.8 Hz), 7.35 (s, 1H), 7.18 (s, 1H), 7.11 (d, 1H, J = 2.6 Hz), 6.97 (d, 1H, J = 8.5 Hz), 6.78 (dd, 1H, J = 8.5, 2.6 Hz), 5.41 (s, 1H), 5.33 (q, 1H, J = 6.9 Hz), 3.87 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H), 1.04 (d, 3H, J = 6.9 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 165.3, 159.9, 142.7, 142.1, 137.2, 136.8, 136.7, 135.9, 134.3, 131.6, 130.9, 130.8, 128.3, 126.4, 126.2, 123.9, 123.7, 114.4, 112.7, 60.3, 55.4, 54.1, 21.2, 19.4, 19.3.
IR (KBr): 2926, 1673, 1388, 1126, 1211, 1038, 749, 717 cm^{-1}.
MS (EI): m/z 369 (M$^+$), 354, 237, 223, 184, 169, 105, 77.
HRMS (EI): m/z calcd. for C$_{25}$H$_{23}$NO$_2$: 369.1729, found 369.1735.

Synthesis of (±)-1,2-dimethyl-4-phenyl-5,6,8,12b-tetrahydroisoindolo [1,2-*a*]isoquinolin-8-one (250)
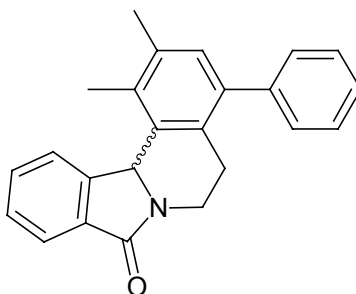
A solution of 2-[2-(4,5-dimethylbiphenyl-2-yl)-ethyl]-isoindole-1,3-dione (**179**) (150 mg, 0.42 mmol) in 6 ml of a 1:1 mixture of CH_2Cl_2 and MeOH was cooled at 0 °C, then NaBH$_4$ (80 mg, 2.11 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of NaBH$_4$ was carefully quenched using 1.0 M HCl and adjusted to pH = 6.0. The phases were separated and the water phase extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, concentrated under reduced pressure. The residue was dissolved in toluene, then 1 ml of TFA was added and the mixture was refluxed overnight at 120 °C. After cooling to room temperature the excess of TFA carefully quenched by 10% NaOH. The organic phase was separated and the aqueous

phase extracted by CH$_2$Cl$_2$. The combined organic phases were dried over Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:3) to give 111 mg (60%) of (**250**) as a white solid. Suitable crystals for x-ray diffraction were obtained from CH$_2$Cl$_2$/petroleum ether.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.96-7.86 (m, 1H), 7.79-7.69 (m, 1H), 7.58-7.43 (m, 2H), 7.40-7.17 (m, 5H), 7.06 (s, 1H), 6.26 (s, 1H), 4.64-4.51 (m, 1H), 2.97 (dt, 1H, *J* = 12.3, 2.3 Hz), 2.89-2.74 (m, 1H), 2.71 (s, 3H), 2.46-2.35 (m, 1H), 2.38 (s, 3H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 169.8, 146.5, 140.8, 140.4, 136.1, 133.1, 133.0, 132.7, 131.8, 131.3, 130.0, 129.3, 128.3, 128.1, 127.1, 123.8, 123.5, 60.1, 39.4, 30.7, 20.3, 18.4.
IR (KBr): 2926, 1684, 1464, 1389, 742, 710, 698 cm^{-1}.
MS (EI): *m/z* 339 (M$^+$), 324, 310, 262, 178, 146, 126, 77.
HRMS (EI): *m/z* calcd. for C$_{24}$H$_{21}$NO: 339.1623, found 339.1618.

Synthesis of (±)-1,2,3-trimethoxy-6,7-dimethyl-9,10,12,16b-tetrahydrodibenzo[3,4:5,6]-azocino[2,1-*a*]isoindol-12-one (251a) and (251b).

(±)-(**251a**)   (±)-(**251b**)
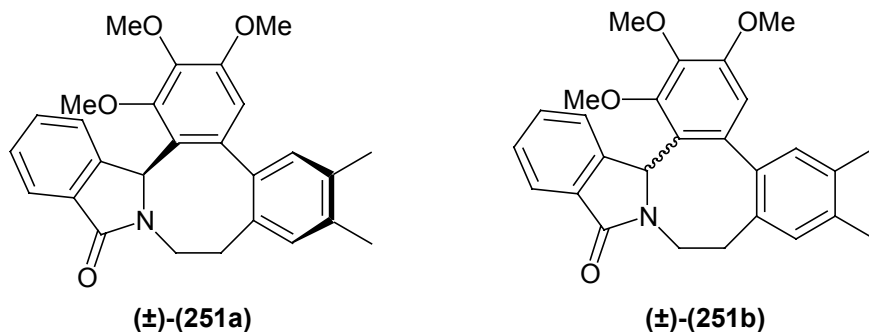
A solution of 2-[2-(3',4',5'-trimethoxy-4,5-dimethylbiphenyl-2-yl)-ethyl]-isoindole-1,3-dione (**237**) (100 mg, 0.22 mmol) in 4 ml of a 3:2 mixture of CH$_2$Cl$_2$ and MeOH was cooled at 0 °C, then NaBH$_4$ (41.6 mg, 1.10 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of NaBH$_4$ was carefully quenched by 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase was extracted by CH$_2$Cl$_2$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residual white solid was dissolved in 3 ml of chloroform, 1 ml of TFA was added and the mixture was stirred overnight at room temperature. The excess of TFA was carefully quenched by 10% NaOH. The layers were separated and the water phase was extracted by CHCl$_3$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:EtOAc = 1:1) to give 82 mg (85%) of the diastereoisomers mixture as white solids. The diastereoisomers were separated by preparative HPLC (eluent: *n*-hexan:*i*-PrOH = 100 : 7, flow 0.7 ml/min, 25 °C, UV detector 254 nm) to give 25 mg of (±)-(**251a**) and 8 mg of (±)-(**251b**) as white solids. Suitable crystals for x-ray diffraction were obtained only from (±)-(**251a**) from CH$_2$Cl$_2$/petroleum ether. Attempted crystallisation of (±)-(**251b**) was unsuccessful and furnished only amorphous material. For (±)-(**251b**) only spectroscopical data are given.

Data for (±)-(**251a**)
R$_f$ = 13.2 min.
^{1}H-NMR (400 MHz, CDCl$_3$): δ = 7.51 (d, 1H, *J* = 7.4 Hz), 7.40-7.33 (m, 1H), 7.31-7.20 (m, 2H), 7.06 (s, 1H), 6.42 (s, 1H), 6.23 (s, 1H), 6.14 (s, 1H), 4.55-4.40 (m, 1H), 4.13 (s, 3H), 4.01 (s, 3H), 3.78 (s, 3H), 3.31 (dd, 1H, *J* = 7.4 Hz, *J* = 13.4 Hz), 2.91-2.71 (m, 2H), 2.24 (s, 3H), 2.03 (s, 3H).
^{13}C-NMR (100.6 MHz, CDCl$_3$): δ = 168.2, 152.3, 151.4, 145.8, 141.2, 137.7, 135.8, 135.7, 134.5, 132.7, 131.2, 130.6, 130.0, 128.9, 127.5, 123.0, 122.4, 121.5, 111.6, 61.5, 60.9, 60.1, 55.9, 40.2, 31.4, 19.4, 19.1.
IR (KBr): 2937, 1736, 1696, 1488, 1407, 1114, 732 cm^{-1}.
MS (EI): *m/z* 429 (M$^+$), 398, 296, 283, 146.
HRMS (EI) for C$_{27}$H$_{27}$NO$_4$: calcd. 429.1940, found 429.1936.

Data for (±)-(**251b**)
R$_f$ = 16.6 min.
^{1}H-NMR (400 MHz, CDCl$_3$): δ = 7.91-7.86 (m, 1H), 7.45-7.33 (m, 3H), 7.31 (s, 1H), 7.13 (s, 1H), 7.09 (d, 1H, *J* = 7.5 Hz), 6.68 (s, 1H), 5.10 (s, 1H), 4.52-4.40 (m, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 3.44-3.33 (m, 1H), 3.11 (s, 3H), 2.90-2.78 (m, 1H), 2.60-2.47 (m, 1H), 2.35 (s, 3H), 2.31 (s, 3H).
^{13}C-NMR (100.6 MHz, CDCl$_3$): δ = 170.6, 153.6, 152.7, 148.1, 141.7, 138.8, 138.1, 137.8, 137.2, 135.3, 131.6, 131.1, 130.8, 129.2, 127.1, 123.2, 122.4, 121.5, 107.4, 60.7, 60.3, 59.6, 55.9, 44.6, 30.3, 19.5, 19.4.

Synthesis of (±)-18-Azaoctacyclo[16.7.0.0^{2,7}.0^{8,16}.0^{9,14}.0^{10,12}.0^{11,15}.0^{20,25}]pentacosa-2,4,6, 8(16),20(25),21,23-heptaen-19-one (252)
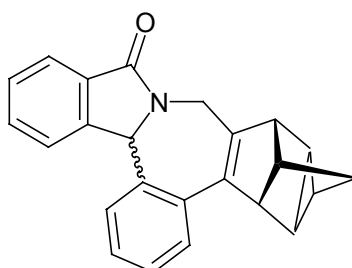
A solution of 2-(9-phenyltetracyclo-[4.3.0.0^{2,4}.0^{3,7}]-non-8-en-8-ylmethyl)-2,3-dihydro-1*H*-1-isoindolone (**238**) (160 mg, 0.45 mmol) in 9 ml of a 2:1 mixture of CH$_2$Cl$_2$ and MeOH was cooled at 0 °C, then NaBH$_4$ (86 mg, 2.26 mmol, 5 equiv.) and 6 drops of a 0.2M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After 30 minutes the excess of NaBH$_4$ was carefully quenched by 1.0M HCl and adjusted to pH = 6.0. The layers were separated and the water phase was extracted by CH$_2$Cl$_2$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residual white solid was dissolved in 3 ml of chloroform, then 1 ml of TFA was added and the mixture was stirred overnight at room temperature. The excess of TFA was carefully quenched by 10% NaOH. The layers were separated and the water phase was extracted by CHCl$_3$ (3x20 ml). The combined organic phases were washed with brine, dried over Na$_2$SO$_4$, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:4) to give 147 mg (97%) of (**252**) as a white solid. Suitable crystals for x-ray diffraction were obtained from CH$_2$Cl$_2$/petroleum ether or CH$_2$Cl$_2$/toluene.

¹H-NMR (300 MHz, CDCl₃) signals for the major diastereoisomer: δ = 7.96-7.88 (m, 1H), 7.68-7.44 (m, 3H), 7.41-7.30 (m, 2H), 7.17-7.00 (m, 2H), 5.67 (s, 1H), 4.53 (d, 1H, *J* = 17.7 Hz), 4.30 (d, 1H, *J* = 17.6 Hz), 3.07 (s, 1H), 2.74 (s, 1H), 2.28 (s, 1H), 1.88-1.79 (m, 1H), 1.71-1.46 (m, 4H).

¹³C-NMR (75 MHz, CDCl₃) signals for the major diastereoisomer: δ = 167.9, 142.7, 142.5, 141.8, 138.0, 133.9, 133.7, 130.7, 128.4, 128.3, 126.8, 126.0, 125.6, 124.9, 123.8, 61.6, 56.2, 54.2, 53.4, 44.0, 32.2, 25.3, 24.2, 23.1.

IR (KBr): 2953, 1680, 1399, 771, 758, 720 cm⁻¹.

MS (EI): *m/z* 337 (M⁺), 271, 83.

HRMS (EI): *m/z* calcd. for $C_{24}H_{19}NO$: 337.1467, found 337.1470.

Synthesis of 2-(4,6-dimethyl-biphenyl-2-ylmethyl)-3-*p*-tolyl-2,3-dihydro-isoindol-1-one (257)
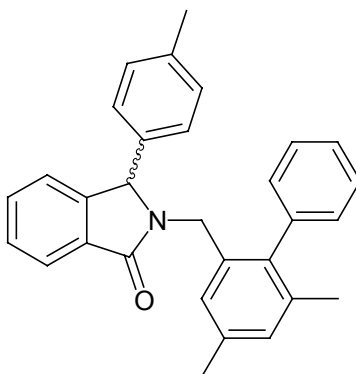
A solution of 2-(4,6-dimethyl-biphenyl-2-ylmethyl)-isoindole-1,3-dione (**200**) (171 mg, 0.50 mmol) in 4 ml of a 1:1 mixture of CH₂Cl₂ and MeOH was cooled at 0 °C, then NaBH₄ (95 mg, 2.50 mmol, 5 equiv.) and 6 drops of a 0.2 M solution of concentrated HCl in ethanol were added. The reaction was monitored by TLC. After all the starting material had been consumed the excess of NaBH₄ was carefully quenched by 1.0 M HCl and adjusted to pH = 6.0. The layers were separated and the water phase was extracted by CH₂Cl₂ (3x20 ml). The combined organic phases were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residual white solid was dissolved in 10 ml of dry toluene, 1 ml of TFA was added and the mixture refluxed overnight at 120 °C. The excess of TFA was carefully quenched by 10% NaOH. The layers were separated and the water phase extracted by CHCl₃ (3x20 ml). The combined organic phases were washed with brine, dried over Na₂SO₄, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 178 mg (85%) of (**257**) as a yellowish oil.

¹H-NMR (300 MHz, CDCl₃) signal for the major regioisomer: δ = 7.92-7.83 (m, 1H), 7.49-7.38 (m, 2H), 7.28-7.08 (m, 4H), 7.05 (d, 2H, *J* = 7.9 Hz), 6.99 (s, 1H), 6.97-6.90 (m, 1H), 6.85 (s, 1H), 6.80-6.70 (m, 3H), 5.18 (s, 1H), 5.03 (d, 1H, *J* = 15.6 Hz), 3.56 (d, 1H, *J* = 15.6 Hz), 2.34 (s, 3H), 2.29 (s, 3H), 1.96 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃) signals for the major regioisomer: δ = 168.5, 146.5, 139.2, 138.5, 138.1, 136.9, 136.3, 134.5, 133.7, 131.6, 131.4, 129.6, 129.5, 129.3, 128.8, 128.2, 128.0, 127.4, 126.6, 126.2, 123.6, 122.9, 63.5, 41.9, 21.2, 21.1, 20.6.

IR (film): 3022, 2917, 2850, 1696, 1468, 1397, 735. 704 cm⁻¹.

MS (EI): *m/z* 417 (M⁺), 222, 194, 179, 165, 105.

HRMS (EI): *m/z* calcd. for $C_{30}H_{27}NO$: 417.2093, found 417.2098.

6 Catalytic C-H activation by means of metal-carbenoid induced C-H insertion and cyclopropanation

Synthesis of (4,5-dimethyl-cyclohexa-1,4-dienyl)-benzene (43)
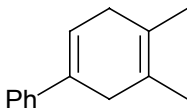
Following the procedure of *Hilt*[31a], to a solution of phenylacetylene (**24**) (0.77 ml, 715 mg, 7 mmol) in dry CH_2Cl_2 (7 ml) were subsequently added $CoBr_2(dppe)$ (216 mg, 0.35 mmol, 5 mol%), anhydrous ZnI_2 (335 mg, 1.05 mmol), 2,3-dimethyl-1,3-butadiene (**42**) (0.95 ml, 690 mg, 8.4 mmol, 1.2 equiv.) and NBu_4BH_4 (99 mg, 0.38 mmol). The resulting mixture was stirred 4 hours at room temperature **(caution: exotermic reaction!)**, then filtered with pentane over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 1.08 g (84%) of (**43**) as a colorless oil. Because of the air-sensitivity of the product only ^{1}H-NMR and ^{13}C-NMR were measured.

^{1}**H-NMR** (300 MHz, CDCl$_3$): δ = 7.56-7.24 (m, 5H), 6.20 (tt, 1H, J = 3.5, 1.6 Hz), 3.13-3.02 (m, 2H), 2.96-2.84 (m, 2H), 1.82 (s, 3H), 1.79 (s, 3H).
^{13}**C-NMR** (75 MHz, CDCl$_3$): δ = 141.3, 134.1, 128.2, 126.7, 124.9, 123.1, 122.5, 121.8, 34.9, 34.4, 18.6, 18.1.

Synthesis of (±)-2-(4,5-dimethyl-biphenyl-3-yl)-propionic acid ethyl ester (266)
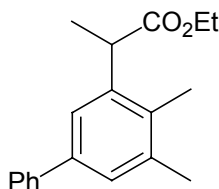
A solution of ethyl 2-diazopropionate (**259**) (222 mg, 1.73 mmol, 2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour via syringe pump to a 0 °C solution of freshly made (4,5-dimethyl-cyclohexa-1,4-dienyl)-benzene (**43**) (159,5 mg, 0.86 mmol) and $Rh_2(OAc)_4$ (1.9 mg, 4.3 μmol, 0.5 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (236 mg, 1.04 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 126 mg (52%) of (**266**) as a colorless oil.

^{1}**H-NMR** (600 MHz, CDCl$_3$): δ = 7.67-7.61 (m, 2H), 7.47 (t, 2H, J = 7.7 Hz), 7.43 (br s, 1H), 7.40-7.35 (m, 2H), 4.28-4.16 (m, 2H), 4.12 (q, 1H, J = 7.2 Hz), 2.43 (s, 3H), 2.36 (s, 3H), 1.59 (d, 3H, J = 7.2 Hz), 1.28 (t, 3H, J = 7.2 Hz).
^{13}**C-NMR** (150 MHz, CDCl$_3$): δ = 174.9, 141.0, 139.6, 138.6, 137.4, 133.3, 128.7, 127.4, 126.9, 123.1, 60.6, 41.9, 21.1, 18.1, 14.9, 14.1.

IR (film): 2979, 1732, 1474, 1191, 1097, 762, 698 cm^{-1}.
MS (EI): m/z 282 (M$^+$), 209, 179, 152, 115.
HRMS (EI): m/z calcd. for $C_{19}H_{22}O_2$: 282.1620, found 218.1623.

Synthesis of (±)-(4,5-dimethyl-biphenyl-3-yl)-phenyl-acetic acid methyl ester (267)
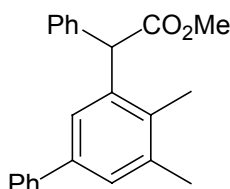
A solution of methyl 2-diazophenylacetate (**92**) (333 mg, 1.89 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made (4,5-dimethyl-cyclohexa-1,4-dienyl)-benzene (**43**) (174 mg, 0.94 mmol) and Rh$_2$(OAc)$_4$ (2 mg, 4.7 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (257 mg, 1.13 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 276 mg (89%) of (**267**) as a colorless oil.

A solution of methyl 2-diazophenylacetate (**92**) (333 mg, 1.89 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made (4,5-dimethyl-cyclohexa-1,4-dienyl)-benzene (**92**) (174 mg, 0.94 mmol) and Cu(hfacac)$_2$ (4.5 mg, 9.4 μmol, 1 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (257 mg, 1.13 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 257 mg (83%) of (**267**) as a colorless oil.

^{1}H-NMR (600 MHz, CDCl$_3$): δ = 7.60 (d, 2H, J = 7.9 Hz), 7.49-7.30 (m, 10H), 5.41 (s, 1H), 3.82 (s, 3H), 2.42 (s, 3H), 2.28 (m, 3H).
^{13}C-NMR (150 MHz, CDCl$_3$): δ = 173.3, 140.9, 138.4, 137.9, 137.6, 137.2, 134.0, 128.9, 128.6, 128.5, 127.9, 127.2, 127.0, 126.9, 124.7, 54.2, 52.3, 21.0, 15.1.
IR (film): 3029, 2949, 1740, 1599, 1473, 1196, 1009, 762, 699 cm^{-1}.
MS (EI): m/z 330 (M$^+$), 271, 241, 181, 91.
HRMS (EI): m/z calcd. for $C_{23}H_{22}O_2$: 330.1620, found 330.1609.

Synthesis of (±)-2-(4,5-dimethyl-biphenyl-3-yl)-4-phenyl-but-3-enoic acid ethyl ester (277)
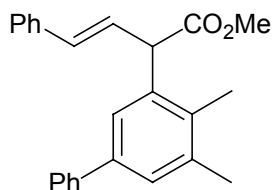
A solution of 2-diazo-4-phenyl-but-3-enoic acid ethyl ester (**274**) (359 mg, 1.66 mmol, 2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour via syringe pump to a solution of freshly made (4,5-dimethyl-cyclohexa-1,4-dienyl)-benzene (**43**) (153 mg, 0.83 mmol) and $Rh_2(OAc)_4$ (1.8 mg, 4.1 μmol, 0.5 mol%) in 3 ml of dry CH_2Cl_2 at room temperature. After the addition was completed the reaction mixture was stirred one additional hour and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (226 mg, 0.99 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 15:1) to give 185 mg (60%) of (**277**) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.51-7.44 (m, 2H), 7.38-7.05 (m, 10H), 6.54 (dd, 1H, J = 16.0, 7.6 Hz), 6.32 (d, 1H, J = 16.0 Hz), 4.68 (dd, 1H, J = 7.6, 1.0 Hz), 4,17-4.04 (m, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 1.15 (t, 3H, J = 7.1 Hz).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 172.8, 140.9, 138.6, 137.6, 137.2, 133.7, 132.2, 128.6, 128.4, 127.8, 127.5, 127.2, 126.9, 126.8, 126.4, 124.6, 61.1, 51.8, 21.1, 15.2, 14.1.
IR (film): 3435, 2980, 1730, 1473, 1235, 1178, 1027, 759, 698 cm^{-1}.
MS (EI): m/z 370 (M$^+$), 297, 219, 165, 115, 91, 47.
HRMS (EI): m/z calcd. for $C_{26}H_{26}O_2$: 370.1933, found 370.1924.

Synthesis of (4,5-dimethyl-cyclohexa-1,4-dienyl)-trimethyl-silane (44)
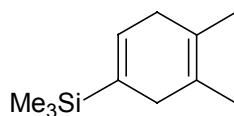
Following the procedure of *Hilt*[31a], to a solution of trimethylsilylacetylene (**25**) (0.97 ml, 687.5 mg, 7 mmol) in dry CH_2Cl_2 (7 ml) were subsequently added $CoBr_2(dppe)$ (216 mg, 0.35 mmol, 5 mol%), anhydrous ZnI_2 (335 mg, 1.05 mmol), 2,3-dimethyl-1,3-butadiene (**42**) (0.95 ml, 690 mg, 8.4 mmol, 1.2 equiv.) and NBu_4BH_4 (99 mg, 0.38 mmol). The resulting mixture was stirred 4 hours at room temperature **(caution: exotermic reaction!)**, then filtered with pentane over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 1.03 g (82%) of (**44**) as a colorless oil. Because of the air-sensitivity of the product only ^{1}H-NMR and ^{13}C-NMR were measured.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.04-5.98 (m, 1H), 2.63 (s, 4H), 1.67 (s, 3H), 1.65 (s, 3H), 0.07 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 136.2, 133.2, 123.4, 122.7, 34.2, 34.0, 18.4, -2.3.

Synthesis of (±)-2-(2,3-dimethyl-5-trimethylsilanyl-phenyl)-propionic acid ethyl ester (269)
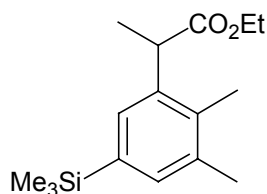
A solution of ethyl 2-diazopropionate (**259**) (223 mg, 1.74 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made (4,5-dimethyl-cyclohexa-1,4-dienyl)-trimethyl-silane (**44**) (157 mg, 0.87 mmol) and Rh$_2$(OAc)$_4$ (1.9 mg, 4.3 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (237 mg, 1.04 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 30:1) to give 133 mg (55%) of (**269**) as a colorless oil.

^{1}H-NMR (600 MHz, CDCl$_3$): δ = 7.29 (s, 1H), 7.27 (s, 1H), 4.20 (q, 2H, J = 7.1 Hz), 4.06 (q, 1H, J = 7.1 Hz), 2.37 (s, 3H), 2.32 (s, 3H), 1.53 (d, 3H, J = 7.2 Hz), 1.27 (t, 3H, J = 7.1 Hz), 0.31 (s, 9H).
^{13}C-NMR (150 MHz, CDCl$_3$): δ = 175.0, 138.6, 137.3, 136.2, 135.0, 133.6, 129.4, 60.6, 42.0, 20.9, 18.1, 15.1, 14.1, -1.1.
IR (film): 2956, 1734, 1248, 1184, 906, 834, 755 cm^{-1}.
MS (EI): m/z 278 (M+), 263, 205, 191, 73, 43.
HRMS (EI): m/z calcd. for C$_{16}$H$_{26}$O$_2$Si: 278.1702, found 278.1707.

Synthesis of (±)-(2,3-dimethyl-5-trimethylsilanyl-phenyl)-phenyl-acetic acid methyl ester (270)
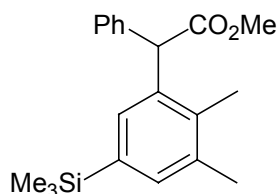
A solution of methyl 2-diazophenylacetate (**92**) (290,5 mg, 1.65 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made (4,5-dimethyl-cyclohexa-1,4-dienyl)-trimethyl-silane (**44**) (149 mg, 0.82 mmol) and Rh$_2$(OAc)$_4$ (1.8 mg, 4.1 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (224.5 mg, 0.99 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether =

1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 206 mg (77%) of (**270**) as a colorless oil.

^{1}H-NMR (600 MHz, CDCl$_3$): δ = 7.40-7.35 (m, 2H), 7.34-7.27 (m, 5H), 5.36-5.34 (m, 1H), 3.80 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H), 0.29 (s, 9H).
^{13}C-NMR (150 MHz, CDCl$_3$): δ = 173.5, 138.0, 137.1, 136.5, 136.0, 135.8, 134.1, 130.9, 128.9, 128.4, 127.1, 54.3, 52.2, 20.8, 15.3, -1.2.
IR (film): 2952, 1732, 1150, 906, 834 cm^{-1}.
MS (EI): *m/z* 326 (M$^+$), 311, 267, 251, 193, 178, 89, 73.
HRMS (EI): *m/z* calcd. for C$_{20}$H$_{26}$O$_2$Si: 326.1702, found 326.1707.

Synthesis of 1,2-diethyl-4,5-dimethyl-cyclohexa-1,4-diene (45)
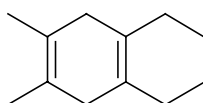
Following the procedure of *Hilt*[34], to a solution of 3-hexyne (**33**) (0.79 ml, 575 mg, 7 mmol) in dry CH$_2$Cl$_2$ (7 ml) were subsequently added CoBr$_2$(dppe) (216 mg, 0.35 mmol, 5 mol%), anhydrous ZnI$_2$ (335 mg, 1.05 mmol), 2,3-dimethyl-1,3-butadiene (**42**) (0.95 ml, 690 mg, 8.4 mmol, 1.2 equiv.) and NBu$_4$BH$_4$ (99 mg, 0.38 mmol). The resulting mixture was stirred 4 hours at room temperature **(caution: exotermic reaction!)**, then filtered with pentane over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 1.13 g (98%) of (**45**) as a colorless oil. Because of the air-sensitivity of the product only ^{1}H-NMR and ^{13}C-NMR were measured.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 2.49 (s, 4H), 1.97 (q, 4H, *J* = 7.6 Hz), 1.56 (s, 6H), 0.91 (t, 6H, *J* = 7.6 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 129.0, 123.3, 37.2, 24.9, 18.0, 13.1.

Synthesis of (±)-2-(2,3-diethyl-5,6-dimethyl-phenyl)-propionic acid ethylester (278)
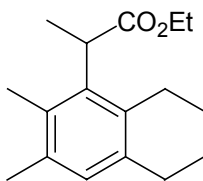
A solution of ethyl 2-diazopropionate (**259**) (254 mg, 1.98 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made 1,2-diethyl-4,5-dimethyl-cyclohexa-1,4-diene (**45**) (163 mg, 0.99 mmol) and Rh$_2$(OAc)$_4$ (2,2 mg, 4.95 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (297 mg, 1.19 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced

pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 24 mg (9%) of (**278**) as a colorless oil.

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 6.94 (s, 1H), 4.28-4.18 (m, 1H), 4.16-4.07 (m, 2H), 2.80-2.53 (m, 4H), 2.22 (s, 3H), 2.07 (s, 3H), 1.50 (d, 3H, *J* = 7.2 Hz), 1.29-1.14 (m, 9H).
^{13}C-NMR (125 MHz, CDCl$_3$): δ = 175.9, 139.2, 138.1, 137.3, 135.0, 132.3, 129.2, 60.6, 40.6, 26.2, 22.4, 20.6, 16.8, 16.2, 15.7, 15.4, 14.2.
IR (film): 2966, 1726, 1445, 1377, 1216, 1097, 1066 cm^{-1}.
MS (EI): *m/z* 262 (M$^+$), 189, 161, 129, 91.
HRMS (EI): *m/z* calcd. for C$_{17}$H$_{26}$O$_2$: 262.1933, found 262.1929.

Synthesis of (±)-(2,3-diethyl-5,6-dimethyl-phenyl)-phenyl-acetic acid methyl ester (281)
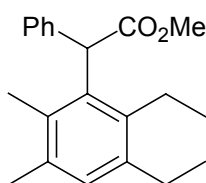
A solution of methyl 2-diazophenylacetate (**92**) (328 mg, 1.86 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made 1,2-diethyl-4,5-dimethyl-cyclohexa-1,4-diene (**45**) (153 mg, 0.93 mmol) and Rh$_2$(OAc)$_4$ (2 mg, 4.65 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (254 mg, 1.12 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 127 mg (44%) of (**281**) as a colorless oil.

A solution of methyl 2-diazophenylacetate (**92**) (328 mg, 1.86 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made 1,2-diethyl-4,5-dimethyl-cyclohexa-1,4-diene (**45**) (153 mg, 0.93 mmol) and Cu(hfacac)$_2$ (4.4 mg, 9.3 μmol, 1 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (257 mg, 1.13 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 159 mg (55%) of (**281**) as a colorless oil.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.27-7.00 (m, 5H), 6.94 (s, 1H), 5.38 (s, 1H), 3.62 (s, 3H), 2.68-2.51 (m, 3H), 2.50-2.33 (m, 1H), 2.16 (s, 3H), 1.88 (s, 3H), 1.15 (t, 3H, *J* = 7.5 Hz), 0.98 (t, 3H, *J* = 7.6 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 174.1, 139.5, 138.6, 137.3, 135.1, 134.6, 134.0, 129.9, 128.9, 127.9, 126.5, 52.2, 50.9, 26.0, 22.6, 20.6, 17.1, 15.6, 15.0.
IR (film): 2965, 1738, 1448, 1196, 1174, 1014, 757 cm^{-1}.
MS (EI): *m/z* 310 (M$^+$), 251, 223, 161, 117, 91, 77.

HRMS (EI): *m/z* calcd. for $C_{21}H_{26}O_2$: 310.1933, found 310.1924.

Synthesis of 1,2-diethyl-4-methyl-cyclohexa-1,4-diene (282)
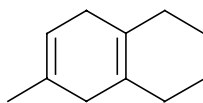
Following the procedure of *Hilt*[34], to a solution of 3-hexyne (**33**) (0.79 ml, 575 mg, 7 mmol) in dry CH_2Cl_2 (7 ml) were subsequently added $CoBr_2$(dppe) (216 mg, 0.35 mmol, 5 mol%), anhydrous ZnI_2 (335 mg, 1.05 mmol), isoprene (**192**) (0.81 ml, 572 mg, 8.4 mmol, 1.2 equiv.) and NBu_4BH_4 (99 mg, 0.38 mmol). The resulting mixture was stirred 4 hours at room temperature (**caution: exotermic reaction!**), then filtered with pentane over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 1.04 g (99%) of (**282**) as a colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.46-5.39 (m, 1H), 2.72-2.61 (m, 2H), 2.60-2.50 (m, 2H), 2.14-2.01 (m, 4H), 1.72-1.66 (m, 3H), 1.00 (dt, 6H, *J* = 7.6, 5.1 Hz).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 131.5, 128.6, 118.9, 118.8, 34.9, 31.2, 25.3, 25.1, 22.9, 13.1, 12.9.

Synthesis of (±)-(2,3-diethyl-5methyl-phenyl)-phenyl-acetic acid methyl ester (283)
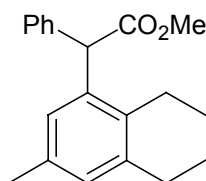
A solution of methyl 2-diazophenylacetate (**92**) (381,5 mg, 2.16 mmol, 2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour via syringe pump to a 0 °C solution of freshly made 1,2-diethyl-4-methyl-cyclohexa-1,4-diene (**282**) (163 mg, 1.08 mmol) and $Rh_2(OAc)_4$ (2.4 mg, 5.41 μmol, 0.5 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (295 mg, 1.30 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 192 mg (60%) of (**283**) as a colorless oil.

A solution of methyl 2-diazophenylacetate (**92**) (381,5 mg, 2.16 mmol, 2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour via syringe pump to a 0 °C solution of freshly made 1,2-diethyl-4-methyl-cyclohexa-1,4-diene (**282**) (163 mg, 1.08 mmol) and $Cu(hfacac)_2$ (5.1 mg, 10.8 μmol, 1 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (295 mg,

1.30 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 186 mg (58%) of (**283**) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃): δ = 7.41-7.36 (m, 2H), 7.35-7.29 (m, 3H), 7.09 (s, 1H), 7.06 (s, 1H), 5.42 (s, 1H), 3.81 (s, 3H), 2.80-2.65 (m, 4H), 2.37 (s, 3H), 1.32 (t, 3H, J = 7.5 Hz), 1.21 (t, 3H, J = 7.6 Hz).
¹³C-NMR (150 MHz, CDCl₃): δ = 173.7, 142.3, 138.9, 136.9, 135.9, 135.2, 128.8, 128.7, 128.3, 127.0, 126.9, 52.9, 52.1, 25.8, 21.3, 21.1, 15.5, 15.1.
IR (film): 2965, 1742, 1609, 1452, 1160, 698 cm⁻¹.
MS (EI): m/z 296 (M⁺), 237, 209, 192, 117, 91.
HRMS (EI): m/z calcd. for $C_{20}H_{24}O_2$: 296.1776, found 296.1772.

Synthesis of 1,2-bis-methoxymethyl-4,5-dimethyl-cyclohexa-1,4-diene (52)
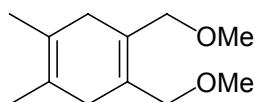
Following the procedure of *Hilt*[34], to a solution of 1,4-dimethoxy-2-but-yne (**50**) (847 mg, 800 mg, 7 mmol) in dry CH₂Cl₂ (7 ml) were subsequently added CoBr₂(dppe) (216 mg, 0.35 mmol, 5 mol%), anhydrous ZnI₂ (335 mg, 1.05 mmol), 2,3-dimethyl-1,3-butadiene (**42**) (0.95 ml, 690 mg, 8.4 mmol, 1.2 equiv.) and NBu₄BH₄ (99 mg, 0.38 mmol). The resulting mixture was stirred 4 hours at room temperature **(caution: exotermic reaction!)**, then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 1.29 g (94%) of (**52**) as a colorless oil. Because of the air-sensitivity of the product only ¹H-NMR and ¹³C-NMR were measured.

¹H-NMR (300 MHz, CDCl₃): δ = 3.94 (s, 4H), 3.26 (s, 6H), 2.67 (s, 4H), 1.60 (s, 6H).
¹³C-NMR (75 MHz, CDCl₃): δ = 130.1, 122.5, 70.9, 57.6, 36.0, 17.8.

Synthesis of (±)-(2,3-bis-methoxymethyl-5,6-dimethyl-phenyl)-phenyl-acetic acid methyl ester (284)
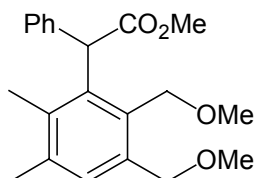
A solution of methyl 2-diazophenylacetate (**92**) (279 mg, 1.58 mmol, 2 equiv.) in 2 ml of dry CH₂Cl₂ was added over one hour via syringe pump to a 0 °C solution of freshly made 1,2-bis-methoxymethyl-4,5-dimethyl-cyclohexa-1,4-diene (**52**) (155 mg, 0.79 mmol) and Rh₂(OAc)₄ (1.7 mg, 3.95 μmol, 0.5 mol%) in 3 ml of dry CH₂Cl₂. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (215 mg,

0.95 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered with diethyl ether over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 168 mg (62%) of (**284**) as a colorless oil.

A solution of methyl 2-diazophenylacetate (**92**) (279 mg, 1.58 mmol, 2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour via syringe pump to a 0 °C solution of freshly made 1,2-bis-methoxymethyl-4,5-dimethyl-cyclohexa-1,4-diene (**52**) (155 mg, 0.79 mmol) and Cu(hfacac)$_2$ (3.8 mg, 7.9 μmol, 1 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (215 mg, 0.95 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered with diethyl ether over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 138 mg (51%) of (**284**) as a colorless oil.

1H-NMR (300 MHz, CDCl$_3$): δ = 7.23-7.09 (m, 4H), 7.07-6.99 (m, 2H), 5.59 (s, 1H), 4.44-4.39 (m, 2H), 4.35 (d, 1H, J = 11.4 Hz), 4.22 (d, 1H, J = 11.4 Hz), 3.61 (s, 3H), 3.32 (s, 3H), 3.16 (s, 3H), 2.19 (s, 3H), 1.94 (s, 3H).
13C-NMR (75 MHz, CDCl$_3$): δ = 173.7, 137.6, 137.3, 137.0, 136.5, 135.1, 133.3, 130.5, 128.6, 127.9, 126.4, 72.9, 68.2, 58.1, 57.9, 52.1, 50.8, 20.8, 16.9.
IR (film): 2925, 1736, 1448, 1384, 1197, 1094 cm^{-1}.
MS (ESI): *m/z* 365 (M+Na$^+$).
HRMS (ESI): *m/z* calcd. for $C_{21}H_{26}O_2Na$: 365.1729 (M+Na$^+$), found 365.1723 (M+Na$^+$).

Synthesis of 1,2-bis-methoxymethyl-4-methyl-cyclohexa-1,4-diene (279)
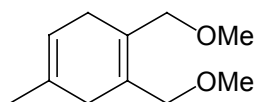
Following the procedure of *Hilt*[34], to a solution of 1,4-dimethoxy-2-but-yne (**50**) (847 mg, 800 mg, 7 mmol) in dry CH_2Cl_2 (7 ml) were subsequently added CoBr$_2$(dppe) (216 mg, 0.35 mmol, 5 mol%), anhydrous ZnI$_2$ (335 mg, 1.05 mmol), isoprene (**192**) (0.84 ml, 572 mg, 8.4 mmol, 1.2 equiv.) and NBu$_4$BH$_4$ (99 mg, 0.38 mmol). The resulting mixture was stirred 4 hours at room temperature **(caution: exotermic reaction!)**, then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 1.25 g (98%) of (**279**) as a colorless oil. Because of the air-sensitivity of the product only ^{1}H-NMR and ^{13}C-NMR were measured.

1H-NMR (300 MHz, CDCl$_3$): δ = 5.39-5.31 (m, 1H), 3.94 (s, 2H), 3.93 (s, 2H), 3.26 (s, 3H), 3.24 (s, 3H), 2.80-2.68 (m, 2H), 2.67-2.57 (m, 2H), 1.66-1.61 (m, 3H).
13C-NMR (75 MHz, CDCl$_3$): δ = 130.6, 129.9, 129.8, 71.1, 71.0, 57.6, 57.5, 33.8, 30.1, 22.6.

Synthesis of (±)-(2,3-bis-methoxymethyl-5-methyl-phenyl)-phenyl-acetic acid methyl ester (285)
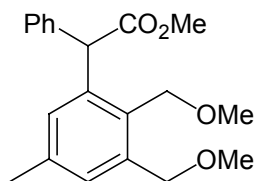
A solution of methyl 2-diazophenylacetate (**92**) (309 mg, 1.75 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made 1,2-bis-methoxymethyl-4-methyl-cyclohexa-1,4-diene (**279**) (160 mg, 0.88 mmol) and Rh$_2$(OAc)$_4$ (1.9 mg, 4.4 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (239 mg, 1.05 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered with diethyl ether over a short pad of silica, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 214 mg (74%) of (**285**) as a colorless oil.

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.38-7.25 (m, 5H), 7.16 (s, 1H), 7.13 (1H), 5.58 (s, 1H), 4.58 (dd, 2H, J = 11.5, 4.3 Hz), 4.52 (dd, 2H, J = 11.5, 7.2 Hz), 3.77 (s, 3H), 3.44 (s, 3H), 3.40 (s, 3H), 2.33 (s, 3H).
^{13}C-NMR (125 MHz, CDCl$_3$): δ = 173.2, 138.7, 138.6, 137.8, 137.2, 131.5, 129.7, 129.2, 128.6, 128.3, 126.9, 72.9, 67.2, 58.0, 57.9, 52.5, 52.0, 21.1.
IR (film): 2924, 1737, 1611, 1452, 1194, 1158, 1090 cm^{-1}.
MS (ESI): m/z 351 (M+Na$^+$).
HRMS (ESI): m/z calcd. for C$_{20}$H$_{24}$O$_4$Na: 351.1573 (M+Na$^+$), found 351.1567 (M+Na$^+$).

Synthesis of 2-(4,5-dimethyl-2-phenyl-cyclohexa-1,4-dienylmethyl)-isoindole-1,3-dione (286)
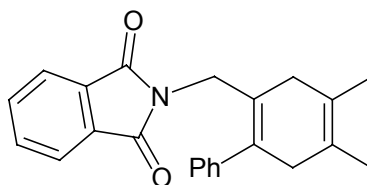
Following the procedure of *Hilt*[97], to a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (**161**) (500 mg, 1.91 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (118 mg, 0.19 mmol, 10 mol%), Zn dust (62 mg, 0.95 mmol, 50 mol%), ZnI$_2$ (305 mg, 0.95 mmol, 50 mol%), 2,3-dimethyl-1,3-butadiene (**42**) (0.32 ml, 2.86 mmol, 1.5 equiv.). The resulting mixture was stirred 4 hours at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 524 mg (80%) of (**286**) as a white solid. Because of the air-sensitivity of the product only ^{1}H-NMR and ^{13}C-NMR were measured.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 7.80-7.54 (m, 5H), 7.34-7.08 (m, 4H), 4.17 (s, 1H), 4.11 (s, 1H), 2.85-2.72 (m, 1H), 2.59-2.41 (m, 3H), 1.53 (s, 6H).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 168.1, 141.8, 134.7, 133.7, 131.9, 129.8, 128.1, 126.6, 124.4, 123.0, 122.4, 122.3, 34.6, 34.2, 33.4, 18.0, 17.8.

Synthesis of (±)-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5,6-dimethyl-3-phenyl-cyclohexa-2,5-dienyl]-phenyl-acetic acid methyl ester (287)
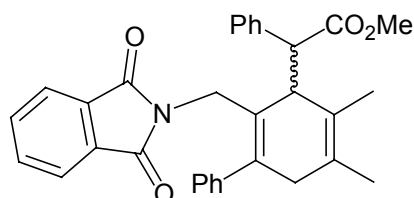
A solution of methyl 2-diazophenylacetate (**92**) (110 mg, 0.62 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made 2-(4,5-dimethyl-2-phenyl-cyclohexa-1,4-dienylmethyl)-isoindole-1,3-dione (**286**) (107 mg, 0.31 mmol) and Rh$_2$(OAc)$_4$ (0.7 mg, 1.6 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 68 mg (45%) of (**287**) as a white solid. Suitable crystals for x-ray diffraction were obtained from CH$_2$Cl$_2$/petroleum ether.

^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.81-7.76 (m, 2H), 7.70-7.64 (m, 2H), 7.29-7.18 (m, 7H), 7.13-7.07 (m, 1H), 7.04-6.97 (m, 2H), 4.49 (dd, 1H, J = 15.7, 2.0 Hz), 4.37 (d, 1H, J = 15.7 Hz), 4.08 (d, 1H, J = 3.3 Hz), 3.63 (s, 3H), 3.58 (s, 1H), 2.16 (d, 1H, J = 21.6 Hz), 1.67 (s, 3H), 1.61-1.51 (m, 1H), 1.53 (s, 3H).
^{13}C-NMR (125 MHz, CDCl$_3$): δ = 173.6, 168.2, 141.5, 139.4, 134.8, 133.8, 132.1, 130.9, 130.5, 128.2, 127.7, 127.1, 126.9, 126.6, 126.2, 123.8, 123.1, 53.3, 51.8, 48.0, 40.9, 38.7, 18.4, 18.2.
IR (KBr): 3026, 2900, 1715, 1388, 1336, 1168, 725, 704 cm^{-1}.
MS (ESI): *m/z* 514 (M+Na$^+$).
HRMS (ESI): *m/z* calcd. for C$_{32}$H$_{29}$NO$_4$Na: 514.1995 (M+Na$^+$), found 514.2000 (M+Na$^+$).

Synthesis of 2-(5-methyl-2-phenyl-cyclohexa-1,4-dienylmethyl)-isoindole-1,3-dione (288a) and 2-(4-methyl-2-phenyl-cyclohexa-1,4-dienylmethyl)-isoindole-1,3-dione (288b)
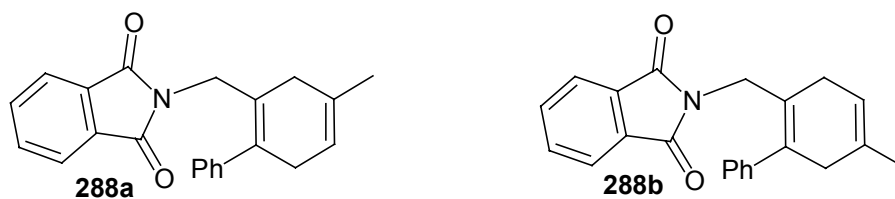
Following the procedure of *Hilt*[97], to a solution of 2-(3-phenylprop-2-ynyl)-isoindole-1,3-dione (**161**) (500 mg, 1.91 mmol) in dry CH$_2$Cl$_2$ (5 ml) were subsequently added CoBr$_2$(dppe) (118 mg, 0.19 mmol, 10 mol%), Zn dust (62 mg, 0.95 mmol, 50 mol%), ZnI$_2$ (305 mg, 0.95 mmol, 50 mol%), isoprene (**192**) (0.29 ml, 2.86 mmol, 1.5 equiv.). The resulting mixture was

stirred 4 hours at room temperature, then filtered (eluent: pentane:diethyl ether = 1:1) over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 1:1) to give 535 mg (85%) of a non separable mixture of regioisomers (**288a**) and (**288b**) as white solids. Because of the air-sensitivity of the product only ^{1}H-NMR and ^{13}C-NMR were measured.

^{1}**H-NMR** (300 MHz, CDCl$_3$) signals for the major regioisomer (**288a**): δ = 7.86-7.76 (m, 2H), 7.74-7.64 (m, 2H), 7.45-7.20 (m, 5H), 5.48-5.37 (m, 1H), 4.28 (s, 2H), 3.01-2.79 (m, 2H), 2.75-2.52 (m, 2H), 1.67 (s, 3H). The signals for the minor regioisomer (**288b**) are not resolved.

^{13}**C-NMR** (75 MHz, CDCl$_3$) resolved signals for the major regioisomer (**288a**): δ = 168.3, 128.3, 128.2, 126.7, 124.2, 123.1, 118.5, 40.4, 35.1, 32.5, 22.9; resolved signals for the minor regioisomer (**288b**): δ = 168.2, 128.1, 126.8, 124.3, 123.0, 118.4, 117.7, 40.3, 38.9, 28.9, 22.6. The remaining signals are unresolved.

Synthesis of (±)-[6-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-4-methyl-biphenyl-2-yl]-phenyl-acetic acid methyl ester (289a)
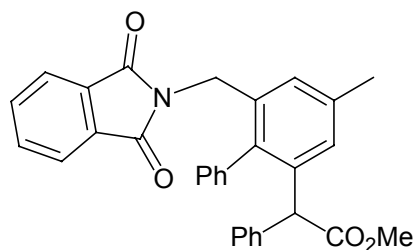
A solution of methyl 2-diazophenylacetate (**92**) (148 mg, 0.84 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made (**288**) (139 mg, 0.42 mmol) and Rh$_2$(OAc)$_4$ (1 mg, 2.1 µmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered with diethyl ether over a short pad of silica gel. The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (115 mg, 0.50 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered with diethyl ether over a short pad of silica gel, concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 2:1) to give 137 mg (68%) of an inseparable mixture of regioisomers in a ratio 85:11:4. By means of two dimensional NMR techniques (**289a**) was determined to be the main product. The structure of the two other regioisomers could not be assigned.

^{1}**H-NMR** (500 MHz, CDCl$_3$) signals for the major regioisomer (**289a**): δ = 7.77-7.68 (m, 2H), 7.65-7.56 (m, 2H), 7.51-7.45 (m, 1H), 7.40-7.31 (m, 3H), 7.25-7.18 (m, 3H), 7.16 (s, 1H), 7.05-6.99 (m, 3H), 6.92 (s, 1H), 4.86 (s, 1H), 4.51 (s, 2H), 3.63 (s, 3H), 2.28 (s, 3H).

^{13}**C-NMR** (125 MHz, CDCl$_3$) resolved signals for the major regioisomer (**289a**): δ = 173.2, 167.9, 138.0, 137.5, 134.3, 133.9, 132.0, 128.1, 126.1, 123.2, 53.4, 52.0, 39.9, 21.4. The remaining signals are unresolved.

IR (KBr): 3029, 1718, 1389, 1161, 953, 715 cm^{-1}.

MS (ESI): m/z 498 (M+Na$^+$).

HRMS (ESI): m/z calcd. for C$_{31}$H$_{25}$NO$_4$Na: 498.1682 (M+Na$^+$), found 498.1661 (M+Na$^+$).

Synthesis of (4,5-diethyl-cyclohexa-1,4-dienyloxy)-trimethyl-silane (296)
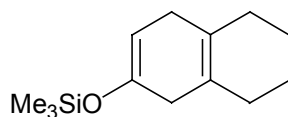


Following the procedure of *Hilt*[35], to a solution of 3-hexyne (**33**) (0.79 ml, 575 mg, 7 mmol) in dry CH_2Cl_2 (7 ml) were subsequently added $CoBr_2$(dppe) (216 mg, 0.35 mmol, 5 mol%), anhydrous ZnI_2 (335 mg, 1.05 mmol), 2-(trimethylsiloxy)-1,3-butadiene (**51**) (1.23 ml, 8.4 mmol, 1.2 equiv.) and NBu_4BH_4 (99 mg, 0.38 mmol). The resulting mixture was stirred 4 hours at room temperature (**caution: exotermic reaction!**), then filtered (eluent: pentane:diethyl ether = 100:1 containing 2% of triethylamine) over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 1.37 g (87%) of (**296**) as a colorless oil. Because of the air-sensitivity of the product only ^{1}H-NMR and ^{13}C-NMR were measured.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.64-4.58 (m, 1H), 2.57-2.47 (m, 2H), 2.45-2.35 (m, 2H), 1.83 (q, 4H, J = 7.6 Hz), 0.78 (t, 3H, J = 7.6 Hz), 0.77 (t, 3H, J = 7.6 Hz), 0.00 (s, 9H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 147.9, 128.6, 128.2, 100.7, 34.2, 30.9, 25.2, 24.8, 13.2, 12.8, 0.3.

Synthesis of (±)-(2,3-diethyl-5-oxo-cyclohex-2-enyl)-phenyl-acetic acid methyl ester (297)
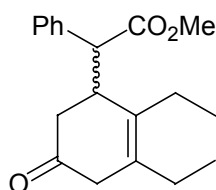
A solution of methyl 2-diazophenylacetate (**92**) (297 mg, 1.68 mmol, 2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour via syringe pump to a 0 °C solution of freshly made (4,5-diethyl-cyclohexa-1,4-dienyloxy)-trimethyl-silane (**296**) (189 mg, 0.84 mmol) and Rh_2(OAc)$_4$ (1.9 mg, 4.2 μmol, 0.5 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then cooled to 0 °C. TBAF (0.84 ml, 1 M solution in THF) was added dropwise and the stirring continued 1 hour at room temperature. The reaction mixture was washed with saturated NH_4Cl (20 ml), the layers were separated and the water phase was extracted by CH_2Cl_2 (3x20 ml). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue that was purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 3:1) to give 87 mg (35%) of (**297**) as a yellow oil.

^{1}H-NMR (600 MHz, C_6D_6): δ = 7.29-7.26 (m, 2H), 7.09-7.05 (m, 2H), 7.03-6.99 (m, 1H), 3.54 (d, 1H, J = 8.2 Hz), 3.20 (s, 3H), 3.14-3.10 (m, 1H), 2.56 (dd, 1H, J = 16.2, 1.7 Hz), 2.36-2.21 (m, 3H), 1.99-1.82 (m, 3H), 1.64-1.62 (m, 1H), 0.90 (t, 3H, J = 7.5 Hz), 0.71 (t, 3H, J = 7.5 Hz).
^{13}C-NMR (100 MHz, C_6D_6): δ = 207.8, 173.3, 136.4, 134.4, 132.9, 129.8, 128.7, 127.9, 54.5, 51.4, 42.4, 42.3, 25.8, 24.7, 13.8, 12.8.
IR (film): 2965, 1734, 1455, 1434, 1197, 1157, 699 cm^{-1}.
MS (ESI): *m/z* 323 (M+Na$^+$).
HRMS (ESI): *m/z* calcd. for $C_{19}H_{24}O_3Na$: 300.1725 (M+Na$^+$), found 300.1728 (M+Na$^+$).

Synthesis of 2-butyl-4,5-dimethyl-1,4-hexadiene (64)
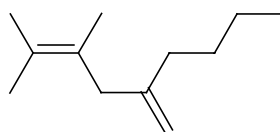
Following the procedure of *Hilt*[36,77], to a solution of 1-hexene (**63**) (0.88 ml, 7 mmol) in dry CH_2Cl_2 (5 ml) were subsequently added $CoBr_2$(dppe) (43.2 mg, 0.07 mmol, 1.0 mol%), anhydrous ZnI_2 (112 mg, 0.35 mmol, 5 equiv.), 2,3-dimethyl-1,3-butadiene (**42**) (1 ml, 9.1 mmol, 1.3 equiv.) and NBu_4BH_4 (27 mg, 0.10 mmol, 1.5 equiv.). The resulting mixture was stirred at 40 °C in a sealed tube overnight, then filtered with pentane over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 1.05 g (90%) of (**64**) as a colorless oil. Spectroscopical data were consistent with those reported in the literature[36a] and are herein reported.

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 4.72 (br s, 1H), 4.65 (br s, 1H), 2.73 (br s, 2H), 1,96 (t, 2H, *J* = 7.4 Hz), 1.69 (br s, 3H), 1.66 (br s, 3H), 1.60 (br s, 3H), 1.52-1.26 (m, 4H), 0.91 (t, 3H, *J* = 7.1 Hz).
^{13}C-NMR (75 MHz, CDCl$_3$): δ = 148.2, 125.9, 125.6, 109.2, 41.3, 36.0, 30.3, 22.7, 20.7, 20.5, 18.5, 14.2.

Synthesis of (±)-2-butyl-2-(2,3-dimethyl-but-2-enyl)-1-methyl-cyclopropanecarboxylic acid ethyl ester (306a) and (306b)
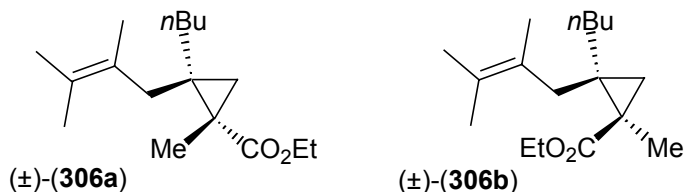
A solution of ethyl 2-diazopropionate (**259**) (240 mg, 1.87 mmol, 2 equiv.) in 2 ml of dry CH_2Cl_2 was added over one hour via syringe pump to a 0 °C solution of freshly made 2-butyl-4,5-dimethyl-hexa-1,4-diene (**64**) (156 mg, 0.94 mmol) and Rh_2(OAc)$_4$ (2 mg, 4.7 μmol, 0.5 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 40:1) to give 146 mg (58%) of an inseparable mixture of diasteroisomers (±)-(**306a**) and (±)-(**306b**) as colorless oils (**306a**:**306b** = 1 : 1, estimated by ^{1}H-NMR).

^{1}H-NMR (300 MHz, CDCl$_3$): δ = 4.10 (q, 4H, *J* = 7.1 Hz), 2.62 (d, 1H, *J* = 14.4 Hz), 2.44 (d, 1H, *J* = 14.4 Hz), 1.90 (d, 1H, *J* = 14.4 Hz), 1.77 (d, 1H, *J* = 14.4 Hz), 1.68 (s, 3H), 1.67 (s, 6H), 1.64 (s, 6H), 1.57 (s, 3H), 1.46-0.93 (m, 28H), 0.85 (t, 3H, *J* = 7.1 Hz), 0.79 (t, 3H, *J* = 7.2 Hz), 0.54 (d, 1H, *J* = 4.7 Hz), 0.47 (d, 1H, *J* = 4.7 Hz).
**^{13}C-NMR** (75 MHz, CDCl$_3$): δ = 174.9, 174.6, 126.2, 125.9, 125.8, 125.3, 60.4, 60.3, 35.3, 34.2, 31.8, 31.7, 31.5, 31.3, 28.9, 28.4, 27.8, 27.3, 26.4, 23.1, 23.0, 20.7, 20.6, 20.5, 17.4, 17.3, 17.0, 16.9, 14.3, 14.2, 13.9, 13.8.
IR (film): 2958, 2063, 1720, 1458, 1311, 1136 cm^{-1};

MS (ESI): *m/z* 267 (M+H$^+$).
HRMS (ESI): *m/z* calcd. for C$_{17}$H$_{31}$O$_2$: 267.2325 (M+H$^+$), found 267.2319 (M+H$^+$).

Synthesis of (±)-2-butyl-2-(2,3-dimethyl-but-2-enyl)-1-phenyl-cyclopropanecarboxylic acid methyl ester (307a) and (307b).

(±)-(**307a**)   (±)-(**307b**)
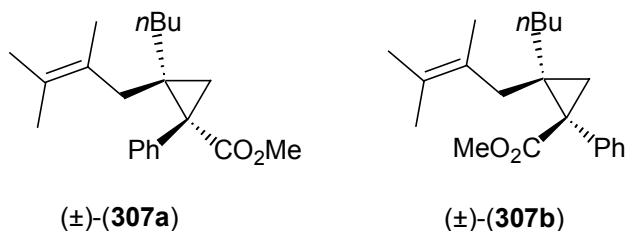
A solution of methyl 2-diazophenylacetate (**92**) (348 mg, 1.97 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made 2-butyl-4,5-dimethyl-hexa-1,4-diene (**64**) (164 mg, 0.99 mmol) and Rh$_2$(OAc)$_4$ (2 mg, 4.9 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether 1:1). The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 20:1) to give 218 mg (70%) of an inseparable mixture of diasteroisomers (±)-(**307a**) and (±)-(**307b**) as colorless oils (**307a**:**307b** = 1 : 1, estimated by ^{1}H-NMR).

^{1}**H-NMR** (300 MHz, CDCl$_3$): δ = 7.45-7.17 (m, 10H), 3.61-3.57 (m, 6H), 2.42 (s, 3H), 1.76-1.70 (m, 10H), 1.68 (s, 4H), 1.63-1.53 (m, 6H), 1.45-0.92 (m, 13H), 0.87 (t, 2H, *J* = 7.1 Hz), 0.68 (t, 4H, *J* = 7.2 Hz), 0.65-0.55 (m, 2H).
^{13}**C-NMR** (75 MHz, CDCl$_3$): δ = 172.9, 172.6, 137.9, 137.7, 131.4, 131.3, 127.6, 126.8, 126.7, 126.1, 125.8, 125.7, 125.6, 51.9, 40.2, 38.6, 37.6, 34.6, 34.3, 34.2, 32.9, 30.6, 29.0, 28.5, 27.7, 23.9, 23.0, 22.8, 20.7, 20.6, 20.5, 20.4, 17.6, 17.2, 13.9, 13.8.
IR (film): 2954, 1721, 1447, 1434, 1239, 1196, 700 cm^{-1}.
MS (ESI): *m/z* 337 (M+Na$^+$).
HRMS (ESI): *m/z* calcd. for C$_{21}$H$_{30}$O$_2$Na: 337.2144 (M+Na$^+$), found 337.2138 (M+Na$^+$).

Synthesis of 4-isopropenyl-1,2-dimethyl-cyclohexa-1,4-diene (299)
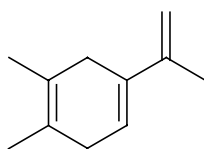
Following the procedure of *Hilt*[140], to a solution of 2-methyl-but-1-en-3-yne (463 mg, 7 mmol) in dry CH$_2$Cl$_2$ (7 ml) were subsequently added CoBr$_2$(dppe) (216 mg, 0.35 mmol, 5 mol%), anhydrous ZnI$_2$ (335 mg, 1.05 mmol), 2,3-dimethyl-1,3-butadiene (**42**) (0.81 ml, 572 mg, 8.4 mmol, 1.2 equiv.) and NBu$_4$BH$_4$ (99 mg, 0.38 mmol). The resulting mixture was stirred 4 hours at room temperature **(caution: exotermic reaction!)**, then filtered with pentane over a short pad of silica gel. The filtrate was concentrated under reduced pressure and purified by Kugelrohr distillation to give 986 mg (95%) of (**299**) as a colorless oil.

Spectroscopical data were consistent with those reported in the literature[140] and are herein reported.

^{1}H-NMR (300 MHz, C$_6$D$_6$): δ = 5.78 (t, 1H, J = 3.7 Hz), 5.03 (d, 1H, J = 0.6 Hz), 4.94 (s, 1H), 2.79 (t, 2H, J = 7.2 Hz), 2.67-2.57 (m, 2H), 1.90 (d, 3H, J = 0.6 Hz), 1.58 (s, 3H), 1.55 (s, 3H).
^{13}C-NMR (75 MHz, C$_6$D$_6$): δ = 142.9, 134.5, 123.5, 122.6, 122.0, 110.5, 34.6, 33.7, 20.6, 18.7, 18.2.

Synthesis of (±)-2-(3,4-dimethyl-phenyl)-1,2-dimethyl-cyclopropanecarboxylic acid ethyl ester (300a) and (300b) and of (±)-2-[3-(1-ethoxycarbonyl-ethyl)-4,5-dimethyl-phenyl]-1,2-dimethyl-cyclopropanecarboxylic acid ethyl ester (301).
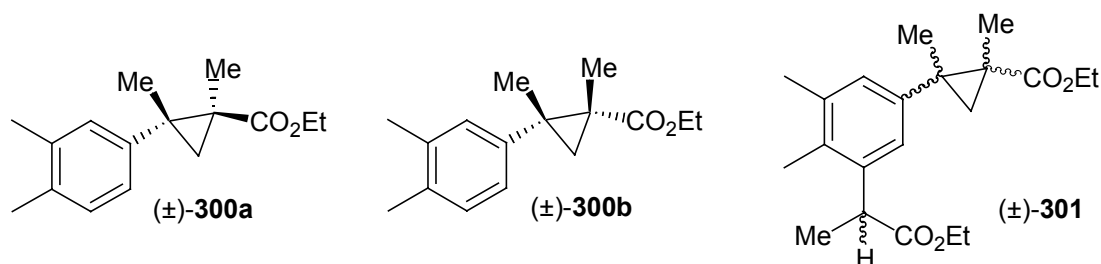
A solution of ethyl 2-diazopropionate (**259**) (278 mg, 2.17 mmol, 2 equiv.) in 2 ml of dry CH$_2$Cl$_2$ was added over one hour via syringe pump to a 0 °C solution of freshly made 4-isopropenyl-1,2-dimethyl-cyclohexa-1,4-diene (**299**) (153 mg, 1.03 mmol) and Rh$_2$(OAc)$_4$ (2,2 mg, 4.95 μmol, 0.5 mol%) in 3 ml of dry CH$_2$Cl$_2$. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (281 mg, 1.24 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel. The diastereomeric cyclopropanes were separated (eluent: pentane:diethyl ether = 30:1), giving 102 mg (40%) of (±)-(**300a**) and (±)-(**300b**) as colorless oils (**300a**:**300b** = 1:1). Attempted separation of the ciclopropanation plus insertion diastereoisomers (eluent: pentane:diethyl ether = 10:1) gave only two main fractions (±)-(**301a**) of 60 mg (17%) and (±)-(**301b**) of 19 mg (5%) as colorless oils, each contaning complex mixtures of diastereoisomers. An exact structure determination by means of two dimensional NMR techniques was not possible.

Data for (±)-(**300a**)
^{1}H-NMR (500 MHz, CDCl$_3$): δ = 7.10-7.06 (m, 1H), 7.03-7.00 (m, 1H), 6.99-6.95 (m, 1H), 4.22 (q, 2H, J = 7.1 Hz), 2.27 (s, 3H), 2.25 (s, 3H), 1.58 (d, 1H, J = 4.8 Hz), 1.42 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz), 1.11 (d, 1H, J = 4.8 Hz), 0.95 (s, 3H).
^{13}C-NMR (125 MHz, CDCl$_3$): δ = 174.4, 140.6, 136.4, 134.6, 130.0, 129.5, 126.1, 60.5, 33.8, 29.9, 24.4, 22.7, 19.8, 19.3, 18.9, 14.4.
IR (film): 2979, 1720, 1454, 1289, 1266, 1143, 823, 758 cm^{-1}.
MS (ESI): m/z 247 (M+H$^+$).
HRMS (ESI): m/z calcd. for C$_{16}$H$_{23}$O$_2$ (M+H$^+$): 247.1699 (M+H$^+$), found 247.1693 (M+H$^+$).

Data for (±)-(**300b**)
¹H-NMR (500 MHz, CDCl₃): δ = 7.01-6.97 (m, 2H), 6.96-6.92 (m, 1H), 3.79-3.71 (m, 1H), 3.69-3.60 (m, 1H), 2.21 (s, 3H), 2.19 (s, 3H), 2.03 (d, 1H, J = 4.7 Hz), 1.50 (s, 3H), 1.43 (s, 3H), 0.82 (t, 3H, J = 7.1 Hz), 0.73 (d, 1H, J = 4.7 Hz).
¹³C-NMR (125 MHz, CDCl₃): δ = 173.6, 141.7, 135.9, 134.3, 129.7, 129.3, 125.7, 60.0, 33.8, 29.9, 25.0, 23.8, 19.7, 19.3, 16.4, 13.7.
IR (film): 2976, 1715, 1451, 1318, 1188, 1135, 822 cm⁻¹.
MS (ESI): m/z 247 (M+H⁺).
HRMS (ESI): m/z calcd. for $C_{16}H_{23}O_2$ (M+H⁺): 247.1699 (M+H⁺), found 247.1693 (M+H⁺).

Data for (±)-(**301a**)
¹H-NMR (500 MHz, CDCl₃): δ = 6.95-6.90 (m, 4H), 4.25-4.05 (m, 8H), 3.98 (q, 2H, J = 7.1 Hz), 2.29 (s, 6H), 2.22 (s, 6H), 1.55 (d, 2H, J = 4.8 Hz), 1.45 (d, 3H, J = 5.3 Hz), 1.44 (d, 3H, J = 5.3 Hz), 1.39 (s, 6H), 1.31 (t, 3H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz), 1.21 (t, 3H, J = 7.1 Hz), 1.17 (t, 3H, J = 7.1 Hz), 1.08 (t, 2H, J = 5.4 Hz), 0.91 (s, 6H).
¹³C-NMR (125 MHz, CDCl₃): δ = 174.9, 174.8, 174.2, 140.4, 140.3, 139.3, 139.2, 136.9, 132.2, 129.0, 128.9, 124.7, 124.6, 60.6, 60.5, 41.9, 41.8, 33.9, 33.8, 29.9, 29.8, 24.5, 24.4, 22.5, 22.4, 21.0, 18.9, 18.8, 18.1, 14.8, 14.4, 14.1.
IR (film): 2980, 1732, 1457, 1368, 1286, 1140, 1079, 1028, 861 cm⁻¹.
MS (ESI): m/z 369 (M+Na⁺).
HRMS (ESI): m/z calcd. for $C_{21}H_{30}O_4Na$: 369.2042 (M+Na⁺), found 369.2036 (M+Na⁺).

Data for (±)-(**301b**)
¹H-NMR (500 MHz, CDCl₃): δ = 6.95-6.88 (m, 4H), 4.20-4.05 (m, 4H), 3.93 (q, 2H, J = 7.1 Hz), 3.73-3.52 (m, 4H), 2.24 (s, 6H), 2.18 (s, 6H), 1.48 (s, 6H), 1.45-1.38 (m, 13H), 1.21 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz), 0.92 (d, 1H, J = 15.6 Hz), 0.79 (t, 3H, J = 7.1 Hz), 0.75 (t, 3H, J = 7.1 Hz), 0.71 (d, 1H, J = 1.9 Hz), 0.71 (d, 1H, J = 1.9 Hz).
¹³C-NMR (125 MHz, CDCl₃): δ = 175.0, 174.9, 173.6, 173.5, 141.7, 141.6, 138.9, 138.8, 136.5, 136.4, 131.9, 131.8, 128.7, 124.5, 124.4, 60.6, 60.5, 59.9, 59.8, 41.9, 41.8, 33.9, 33.8, 29.7, 25.1, 23.8, 23.7, 20.9, 20.8, 18.2, 18.1, 16.5, 16.4, 14.8, 14.1, 13.5, 13.4.
IR (film): 2979, 1731, 1448, 1367, 1319, 1191, 1095, 1029, 862 cm⁻¹.
MS (ESI): m/z 369 (M+Na⁺).
HRMS (ESI): m/z calcd. for $C_{21}H_{30}O_4Na$: 369.2042 (M+Na⁺), found 369.2036 (M+Na⁺).

Synthesis of (±)-2-[3-(1-ethoxycarbonyl-ethyl)-4,5-dimethyl-phenyl]-1,2-dimethyl-cyclopropanecarboxylic acid ethyl ester (303)
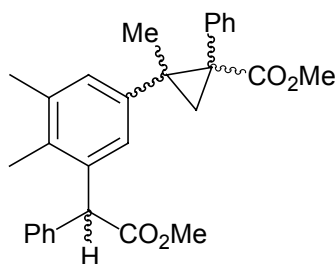
(±)-(**303**)

A solution of methyl 2-diazophenylacetate (**92**) (350 mg, 1.99 mmol, 2 equiv.) in 2 ml of dry CH₂Cl₂ was added over one hour via syringe pump to a 0 °C solution of freshly made 4-isopropenyl-1,2-dimethyl-cyclohexa-1,4-diene (**299**) (147.5 mg, 0.99 mmol) and Rh₂(OAc)₄

(2.2 mg, 5 µmol, 0.5 mol%) in 3 ml of dry CH_2Cl_2. After the addition was completed the reaction mixture was stirred one additional hour at room temperature and then filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1). The filtrate was concentrated under reduced pressure to give an oily residue that was dissolved in benzene and oxidised by DDQ (271 mg, 1.19 mmol, 1.2 equiv) at room temperature. After 2 hours the reaction mixture was filtered over a short pad of silica gel (eluent: pentane:diethyl ether = 1:1), concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: pentane:diethyl ether = 3:1) to give 334 mg (76%) of an inseparable mixture of diastereoisomers (±)-(**303**) as a colorless oil. Because of the difficulty of a correct ^{1}H-NMR and ^{13}C-NMR assignment for (±)-(**303**), only IR, MS and HRMS data are reported.

IR (film): 3025, 2951, 1725, 1495, 1448, 1343, 1268, 1210, 1162, 757, 800 cm^{-1}.
MS (ESI): *m/z* 465 (M+Na^{+}).
HRMS (ESI): *m/z* calcd. for $C_{29}H_{30}O_4Na$: 465.2042 (M+Na^{+}), found 465.2036 (M+Na^{+}).

D Appendix

1   Abbreviations

Ac	Acetate
acac	acetylacetonate
BINOL	1,1´-binaphthyl-2,2´-diol
Bn	benzyl
br	broad
calc.	calculated
COD	1,5-cyclooctadiene
Cy	cyclohexyl
d	duplet
DBU	1,8-diazabicyclo[5.4.0]undec-7-en
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethyl formamide
DMSO	dimethyl sulfoxide
DOSP	dodecylbenzenesulfonylprolinate
dppe	bis(diphenylphosphanyl)ethane
EDA	ethyldiazoacetate
EI	electron ionization
Eq.	equivalents
ESI	electrospray
Et	ethyl
GABA	gamma-aminobutyric acid
GC	gaschromatography
HDA	*homo Diels-Alder*
hfacac	hexafluoroacetylacetonate
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
i-Pr	isopropyl
KHMDS	potassium-hexamethyldisilazide
M	multiplet
Me	methyl
MPPIM	methyl 1-(3-phenylpropanoyl)-2-oxoimidazoline-4-carboxylate
MS	mass spectra
NBD	norbornadiene
t-Bu	*tert*-butyl
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
p-ABSA	4-acetamidobenzenesulfonyl azide
PDE4	phosphodiesterase 4
PNB	paranitrobenzyl
Ph	phenyl
PROPHOS	1,2-bis(diphenylphosphanyl)propane
PTLL	phthaloyl-*tert*-leucinate
Py	pyridyne
q	quartet
r.t.	room temperature
s	singulet

TBAF	tetra-*n*-butylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
t	triplet
Ts	4-toluenesulfonyl

1   Crystallographic data

2.1   Crystallographic data for 1,2-dimethyl-4-phenyl-5,6,8,12b-tetrahydroisoindolo [1,2-*a*]-isoquinolin-8-one (250)

Table 22   Crystal data

Habitus, colour	prism, colorless
Crystal size	0.54 x 0.33 x 0.33 mm^3
Crystal system	Monoclinic
Space group	P 2$_1$/c Z = 4
Unit cell dimensions	a = 14.5603(15) Å α = 90°.
	b = 13.1890(16) Å β= 106.413(11)°.
	c = 9.5293(10) Å γ = 90°.
Volume	1755.4(3) Å^3
Cell determination	4156 peaks with Theta 2 to 25°.
Empirical formula	C$_{24}$H$_{21}$NO
Formula weight	339.42
Density (calculated)	1.284 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	720
Wavelength	0.71073 Å
Temperature	193(2) K
Theta range for data collection	2.12 to 25.00°.
Index ranges	-17<=h<=17, -15<=k<=15, -9<=l<=11
Reflections collected	10815
Independent reflections	3081 [R(int) = 0.0707]
Completeness to theta = 25.00°	99.6 %
Observed reflections	1596[I>2sigma(I)]
Reflections used for refinement	3081
Absorption correction	None
Largest diff. peak and hole	0.138 and -0.128 e.Å^{-3}
Refinement	Full-matrix least-squares on F^2
Treatment of hydrogen atoms	Located, isotropic refinement
Data / restraints / parameters	3081 / 0 / 319
Goodness-of-fit on F^2	0.751
R index (all data)	wR2 = 0.0549
R index conventional [I>2sigma(I)]	R1 = 0.0314

Table 23   Bond lengths [Å] and angles [°]

C1-O1	1.228(2)	C10-C5-C4	119.68(16)
C1-N2	1.367(2)	C5-C6-C7	119.64(16)
C1-C17	1.475(2)	C5-C6-C18	121.94(16)
C3-N2	1.450(2)	C7-C6-C18	118.41(16)
C3-C4	1.515(3)	C8-C7-C6	121.72(18)
C4-C5	1.514(2)	C7-C8-C9	119.37(17)
C5-C6	1.391(2)	C7-C8-C25	119.40(18)
C5-C10	1.413(2)	C9-C8-C25	121.22(17)
C6-C7	1.391(2)	C8-C9-C10	119.67(15)
C6-C18	1.500(2)	C8-C9-C26	117.95(16)
C7-C8	1.388(2)	C10-C9-C26	122.29(17)
C8-C9	1.397(2)	C9-C10-C5	119.93(16)
C8-C25	1.507(3)	C9-C10-C11	119.66(15)
C9-C10	1.412(2)	C5-C10-C11	120.22(15)
C9-C26	1.511(2)	N2-C11-C12	101.45(13)
C10-C11	1.520(2)	N2-C11-C10	113.08(13)
C11-N2	1.472(2)	C12-C11-C10	119.39(14)
C11-C12	1.516(2)	C13-C12-C17	118.89(16)
C12-C13	1.386(2)	C13-C12-C11	131.79(16)
C12-C17	1.391(2)	C17-C12-C11	109.26(14)
C13-C14	1.389(3)	C12-C13-C14	118.60(19)
C14-C15	1.381(3)	C15-C14-C13	121.48(19)
C15-C16	1.384(3)	C14-C15-C16	120.39(19)
C16-C17	1.375(2)	C17-C16-C15	117.78(19)
C18-C19	1.367(3)	C16-C17-C12	122.78(16)
C18-C23	1.382(2)	C16-C17-C1	128.19(17)
C19-C20	1.394(3)	C12-C17-C1	109.02(14)
C20-C21	1.362(4)	C19-C18-C23	117.91(18)
C21-C22	1.358(4)	C19-C18-C6	121.76(17)
C22-C23	1.388(3)	C23-C18-C6	120.26(16)
		C18-C19-C20	120.8(2)
O1-C1-N2	125.41(15)	C21-C20-C19	120.5(2)
O1-C1-C17	128.32(16)	C22-C21-C20	119.4(2)
N2-C1-C17	106.27(15)	C21-C22-C23	120.4(3)
N2-C3-C4	107.12(14)	C18-C23-C22	121.0(2)
C5-C4-C3	110.24(15)	C1-N2-C3	121.28(15)
C6-C5-C10	119.52(15)	C1-N2-C11	113.65(13)
C6-C5-C4	120.41(15)	C3-N2-C11	119.30(14)

Table 24   Torsion angles [°]

N2-C3-C4-C5	58.8(2)	C7-C6-C18-C23	-103.3(2)
C3-C4-C5-C6	143.15(16)	C23-C18-C19-C20	-1.3(3)
C3-C4-C5-C10	-29.6(2)	C6-C18-C19-C20	-178.2(2)
C10-C5-C6-C7	3.1(2)	C18-C19-C20-C21	1.4(4)
C4-C5-C6-C7	-169.72(16)	C19-C20-C21-C22	-0.5(4)
C10-C5-C6-C18	-177.96(15)	C20-C21-C22-C23	-0.4(4)
C4-C5-C6-C18	9.2(2)	C19-C18-C23-C22	0.4(3)
C5-C6-C7-C8	0.2(3)	C6-C18-C23-C22	177.3(2)
C18-C6-C7-C8	-178.77(16)	C21-C22-C23-C18	0.5(4)
C6-C7-C8-C9	-2.2(2)	O1-C1-N2-C3	25.5(3)
C6-C7-C8-C25	176.92(18)	C17-C1-N2-C3	-153.87(14)
C7-C8-C9-C10	0.8(2)	O1-C1-N2-C11	178.55(16)
C25-C8-C9-C10	-178.31(16)	C17-C1-N2-C11	-0.85(18)
C7-C8-C9-C26	177.49(16)	C4-C3-N2-C1	94.00(19)
C25-C8-C9-C26	-1.6(2)	C4-C3-N2-C11	-57.5(2)
C8-C9-C10-C5	2.5(2)	C12-C11-N2-C1	-2.61(17)
C26-C9-C10-C5	-174.07(16)	C10-C11-N2-C1	-131.71(15)
C8-C9-C10-C11	177.55(14)	C12-C11-N2-C3	150.99(14)
C26-C9-C10-C11	1.0(2)	C10-C11-N2-C3	21.9(2)
C6-C5-C10-C9	-4.4(2)		
C4-C5-C10-C9	168.41(15)		
C6-C5-C10-C11	-179.45(15)		
C4-C5-C10-C11	-6.6(2)		
C9-C10-C11-N2	-163.08(14)		
C5-C10-C11-N2	11.9(2)		
C9-C10-C11-C12	77.7(2)		
C5-C10-C11-C12	-107.24(17)		
N2-C11-C12-C13	-177.45(17)		
C10-C11-C12-C13	-52.5(3)		
N2-C11-C12-C17	5.29(17)		
C10-C11-C12-C17	130.26(16)		
C17-C12-C13-C14	2.7(3)		
C11-C12-C13-C14	-174.38(17)		
C12-C13-C14-C15	-0.6(3)		
C13-C14-C15-C16	-1.8(3)		
C14-C15-C16-C17	2.0(3)		
C15-C16-C17-C12	0.2(3)		
C15-C16-C17-C1	-178.31(17)		
C13-C12-C17-C16	-2.5(3)		
C11-C12-C17-C16	175.14(15)		
C13-C12-C17-C1	176.21(15)		
C11-C12-C17-C1	-6.12(18)		
O1-C1-C17-C16	3.7(3)		
N2-C1-C17-C16	-176.97(16)		
O1-C1-C17-C12	-174.99(17)		
N2-C1-C17-C12	4.38(18)		
C5-C6-C18-C19	-105.5(2)		
C7-C6-C18-C19	73.5(2)		
C5-C6-C18-C23	77.7(2)		

2.2   Crystallographic data for (±)-1,2,3-trimethoxy-6,7-dimethyl-9,10,12,16b-tetrahydrodibenzo [3,4:5,6]-azocino[2,1-*a*]isoindol-12-one (251)

Table 25   Crystal data

Habitus, colour	prism, colourless	
Crystal size	0.26 x 0.18 x 0.05 mm^3	
Crystal system	Triclinic	
Space group	P -1	Z = 2
Unit cell dimensions	a = 9.4410(12) Å	α= 92.453(11)°.
	b = 10.4901(14) Å	β= 105.156(10)°.
	c = 12.0200(15) Å	γ= 108.020(10)°.
Volume	1082.7(2) Å^3	
Cell determination	17321 peaks with Theta 1.7 to 26°.	
Empirical formula	$C_{27}H_{27}N O_4$	
Formula weight	429.50	
Density (calculated)	1.317 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	456	
Wavelength	0.71073 Å	
Temperature	193(2) K	
Theta range for data collection	1.77 to 25.00°.	
Index ranges	-11<=h<=11, -12<=k<=12, -14<=l<=14	
Reflections collected	15328	
Independent reflections	3797 [R(int) = 0.0421]	
Completeness to theta = 25.00°	99.5 %	
Observed reflections	2698[I>2sigma(I)]	
Reflections used for refinement	3797	
Extinction coefficient	X = 0.0082(18)	
Absorption correction	None	
Largest diff. peak and hole	0.182 and -0.151 e.Å^{-3}	
Refinement	Full-matrix least-squares on F^2	
Treatment of hydrogen atoms	Located, isotropic refinemnet	
Data / restraints / parameters	3797 / 0 / 398	
Goodness-of-fit on F^2	0.990	
R index (all data)	wR2 = 0.0824	
R index conventional [I>2sigma(I)]	R1 = 0.0369	

Table 26   **Bond lengths [Å] and angles [°]**

C1-O1	1.2296(19)	C6-C7-C8	119.05(15)
C1-N2	1.362(2)	C6-C7-C24	120.47(17)
C1-C23	1.481(2)	C8-C7-C24	120.48(18)
C3-N2	1.456(2)	C9-C8-C7	118.05(17)
C3-C4	1.534(3)	C9-C8-C25	120.63(16)
C4-C5	1.496(2)	C7-C8-C25	121.32(15)
C5-C6	1.398(2)	C10-C9-C8	122.87(15)
C5-C10	1.407(2)	C9-C10-C5	118.69(14)
C6-C7	1.375(3)	C9-C10-C11	118.62(14)
C7-C8	1.412(2)	C5-C10-C11	121.85(16)
C7-C24	1.514(2)	C16-C11-C12	119.00(14)
C8-C9	1.394(2)	C16-C11-C10	127.35(14)
C8-C25	1.496(3)	C12-C11-C10	113.63(14)
C9-C10	1.392(2)	C13-C12-C11	121.77(15)
C10-C11	1.509(2)	O26-C13-C12	125.02(15)
C11-C16	1.402(2)	O26-C13-C14	114.75(13)
C11-C12	1.407(2)	C12-C13-C14	120.23(14)
C12-C13	1.372(2)	O27-C14-C15	121.33(14)
C13-O26	1.3710(19)	O27-C14-C13	119.63(14)
C13-C14	1.402(2)	C15-C14-C13	118.81(14)
C14-O27	1.3780(18)	O28-C15-C14	124.19(14)
C14-C15	1.387(2)	O28-C15-C16	114.00(14)
C15-O28	1.3749(19)	C14-C15-C16	121.73(15)
C15-C16	1.422(2)	C11-C16-C15	118.44(14)
C16-C17	1.534(2)	C11-C16-C17	126.79(14)
C17-N2	1.4649(19)	C15-C16-C17	114.55(14)
C17-C18	1.521(2)	N2-C17-C18	101.16(13)
C18-C23	1.383(2)	N2-C17-C16	117.40(13)
C18-C19	1.395(2)	C18-C17-C16	110.72(13)
C19-C20	1.384(3)	C23-C18-C19	120.35(15)
C20-C21	1.389(3)	C23-C18-C17	109.61(13)
C21-C22	1.391(2)	C19-C18-C17	129.99(15)
C22-C23	1.384(3)	C20-C19-C18	117.94(16)
C26-O26	1.425(2)	C19-C20-C21	121.79(15)
C27-O27	1.439(3)	C20-C21-C22	119.94(18)
C28-O28	1.426(2)	C23-C22-C21	118.39(17)
		C18-C23-C22	121.53(15)
O1-C1-N2	125.91(15)	C18-C23-C1	108.64(15)
O1-C1-C23	127.78(17)	C22-C23-C1	129.81(15)
N2-C1-C23	106.28(13)	C1-N2-C3	122.56(13)
N2-C3-C4	111.15(14)	C1-N2-C17	114.01(13)
C5-C4-C3	110.97(15)	C3-N2-C17	123.01(14)
C6-C5-C10	118.15(16)	C13-O26-C26	117.60(13)
C6-C5-C4	120.43(15)	C14-O27-C27	114.31(15)
C10-C5-C4	121.42(14)	C15-O28-C28	123.30(14)
C7-C6-C5	123.10(16)		

Table 27   Torsion angles [°]

N2-C3-C4-C5	45.34(19)	N2-C17-C18-C19	-178.13(16)
C3-C4-C5-C6	94.01(18)	C16-C17-C18-C19	56.7(2)
C3-C4-C5-C10	-85.30(19)	C23-C18-C19-C20	1.4(2)
C10-C5-C6-C7	-3.3(3)	C17-C18-C19-C20	-176.17(17)
C4-C5-C6-C7	177.34(17)	C18-C19-C20-C21	0.6(3)
C5-C6-C7-C8	1.5(3)	C19-C20-C21-C22	-2.0(3)
C5-C6-C7-C24	-178.58(19)	C20-C21-C22-C23	1.3(3)
C6-C7-C8-C9	1.4(3)	C19-C18-C23-C22	-2.1(2)
C24-C7-C8-C9	-178.56(19)	C17-C18-C23-C22	175.91(15)
C6-C7-C8-C25	-178.0(2)	C19-C18-C23-C1	176.27(14)
C24-C7-C8-C25	2.0(3)	C17-C18-C23-C1	-5.69(18)
C7-C8-C9-C10	-2.4(3)	C21-C22-C23-C18	0.7(3)
C25-C8-C9-C10	177.01(19)	C21-C22-C23-C1	-177.29(17)
C8-C9-C10-C5	0.5(3)	O1-C1-C23-C18	-172.83(17)
C8-C9-C10-C11	-169.15(16)	N2-C1-C23-C18	5.03(18)
C6-C5-C10-C9	2.3(2)	O1-C1-C23-C22	5.4(3)
C4-C5-C10-C9	-178.40(16)	N2-C1-C23-C22	-176.75(17)
C6-C5-C10-C11	171.60(15)	O1-C1-N2-C3	2.8(3)
C4-C5-C10-C11	-9.1(2)	C23-C1-N2-C3	-175.06(14)
C9-C10-C11-C16	-132.29(18)	O1-C1-N2-C17	175.52(16)
C5-C10-C11-C16	58.4(2)	C23-C1-N2-C17	-2.38(18)
C9-C10-C11-C12	49.2(2)	C4-C3-N2-C1	-117.10(17)
C5-C10-C11-C12	-120.10(17)	C4-C3-N2-C17	70.9(2)
C16-C11-C12-C13	-0.2(2)	C18-C17-N2-C1	-0.87(17)
C10-C11-C12-C13	178.39(16)	C16-C17-N2-C1	119.69(16)
C11-C12-C13-O26	178.73(15)	C18-C17-N2-C3	171.77(14)
C11-C12-C13-C14	-1.4(2)	C16-C17-N2-C3	-67.7(2)
O26-C13-C14-O27	-3.8(2)	C12-C13-O26-C26	-7.0(2)
C12-C13-C14-O27	176.33(15)	C14-C13-O26-C26	173.13(15)
O26-C13-C14-C15	-178.27(14)	C15-C14-O27-C27	-114.5(2)
C12-C13-C14-C15	1.9(2)	C13-C14-O27-C27	71.2(2)
O27-C14-C15-O28	1.5(3)	C14-C15-O28-C28	18.4(3)
C13-C14-C15-O28	175.83(15)	C16-C15-O28-C28	-164.77(16)
O27-C14-C15-C16	-175.06(15)		
C13-C14-C15-C16	-0.7(2)		
C12-C11-C16-C15	1.4(2)		
C10-C11-C16-C15	-177.03(16)		
C12-C11-C16-C17	-172.93(15)		
C10-C11-C16-C17	8.7(3)		
O28-C15-C16-C11	-177.78(14)		
C14-C15-C16-C11	-0.9(2)		
O28-C15-C16-C17	-2.8(2)		
C14-C15-C16-C17	174.07(15)		
C11-C16-C17-N2	-24.6(2)		
C15-C16-C17-N2	160.90(14)		
C11-C16-C17-C18	90.81(18)		
C15-C16-C17-C18	-83.68(18)		
N2-C17-C18-C23	4.08(17)		
C16-C17-C18-C23	-121.10(14)		

2.3 Crystallographic data for 3-methoxy-6,7,9-trimethyl-11,15b-dihydro-9*H*-dibenzo [3,4:5,6]azepino[2,1-*a*]isoindol-11-one (249)

Table 28   Crystal data

Habitus, colour	prism, colourless	
Crystal size	$0.36 \times 0.18 \times 0.15$ mm^3	
Crystal system	Monoclinic	
Space group	P 2_1/c	Z = 4
Unit cell dimensions	a = 8.7653(8) Å	$\alpha = 90°$.
	b = 11.9990(8) Å	$\beta = 103.098(11)°$.
	c = 18.4357(17) Å	$\gamma = 90°$.
Volume	1888.5(3) Å^3	
Cell determination	8000 peaks with Theta 2 to 26°.	
Empirical formula	$C_{25}H_{23}NO_2$	
Formula weight	369.44	
Density (calculated)	1.299 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	784	
Wavelength	0.71073 Å	
Temperature	193(2) K	
Theta range for data collection	2.04 to 26.00°.	
Index ranges	-10<=h<=10, -14<=k<=14, -22<=l<=22	
Reflections collected	14558	
Independent reflections	3689 [R(int) = 0.0436]	
Completeness to theta = 25.00°	99.8 %	
Observed reflections	2510[I>2sigma(I)]	
Reflections used for refinement	3689	
Absorption correction	None	
Largest diff. peak and hole	0.212 and -0.148 e.Å^{-3}	
Solution	Direct methods	
Refinement	Full-matrix least-squares on F^2	
Treatment of hydrogen atoms	Located, isotropic refinement	
Data / restraints / parameters	3689 / 0 / 345	
Goodness-of-fit on F^2	0.919	
R index (all data)	wR2 = 0.0804	
R index conventional [I>2sigma(I)]	R1 = 0.0339	

Table 29   Bond lengths [Å] and angles [°]

C1-O1	1.2243(16)	C9-C4-C3	123.28(12)
C1-N2	1.3523(17)	C4-C5-C6	122.54(13)
C1-C22	1.489(2)	C5-C6-C7	118.86(13)
C3-N2	1.4632(17)	C5-C6-C24	119.93(14)
C3-C4	1.5154(19)	C7-C6-C24	121.21(14)
C3-C23	1.523(2)	C8-C7-C6	118.59(13)
C4-C5	1.390(2)	C8-C7-C25	120.92(13)
C4-C9	1.4100(18)	C6-C7-C25	120.48(13)
C5-C6	1.391(2)	C7-C8-C9	122.98(13)
C6-C7	1.400(2)	C8-C9-C4	118.02(12)
C6-C24	1.500(2)	C8-C9-C10	119.66(12)
C7-C8	1.392(2)	C4-C9-C10	122.29(12)
C7-C25	1.499(2)	C11-C10-C15	119.04(12)
C8-C9	1.3931(19)	C11-C10-C9	120.51(12)
C9-C10	1.4933(19)	C15-C10-C9	120.45(11)
C10-C11	1.3878(19)	C10-C11-C12	120.81(13)
C10-C15	1.4062(18)	O2-C12-C13	123.86(13)
C11-C12	1.393(2)	O2-C12-C11	116.03(12)
C12-O2	1.3680(16)	C13-C12-C11	120.11(13)
C12-C13	1.383(2)	C12-C13-C14	118.97(14)
C13-C14	1.389(2)	C15-C14-C13	121.63(13)
C14-C15	1.3825(19)	C14-C15-C10	119.23(12)
C15-C16	1.5115(18)	C14-C15-C16	122.07(12)
C16-N2	1.4719(16)	C10-C15-C16	118.68(12)
C16-C17	1.5077(19)	N2-C16-C17	101.37(10)
C17-C22	1.3838(19)	N2-C16-C15	110.82(11)
C17-C18	1.391(2)	C17-C16-C15	118.01(11)
C18-C19	1.389(2)	C22-C17-C18	120.27(13)
C19-C20	1.393(2)	C22-C17-C16	109.58(11)
C20-C21	1.380(2)	C18-C17-C16	130.04(13)
C21-C22	1.384(2)	C19-C18-C17	118.38(14)
C26-O2	1.4244(19)	C18-C19-C20	120.59(14)
		C21-C20-C19	121.04(15)
O1-C1-N2	125.80(13)	C20-C21-C22	118.02(15)
O1-C1-C22	128.48(13)	C21-C22-C17	121.69(13)
N2-C1-C22	105.72(11)	C21-C22-C1	129.28(13)
N2-C3-C4	110.68(11)	C17-C22-C1	109.00(12)
N2-C3-C23	110.64(12)	C1-N2-C3	123.25(11)
C4-C3-C23	113.42(12)	C1-N2-C16	114.31(11)
C5-C4-C9	118.95(13)	C3-N2-C16	122.42(11)
C5-C4-C3	117.71(12)	C12-O2-C26	116.80(11)

Table 30   Torsion angles [°].

N2-C3-C4-C5	118.94(13)	C19-C20-C21-C22	-0.2(2)
C23-C3-C4-C5	-116.02(14)	C20-C21-C22-C17	-0.5(2)
N2-C3-C4-C9	-63.73(16)	C20-C21-C22-C1	176.85(14)
C23-C3-C4-C9	61.31(17)	C18-C17-C22-C21	1.4(2)
C9-C4-C5-C6	-0.4(2)	C16-C17-C22-C21	177.89(13)
C3-C4-C5-C6	177.06(12)	C18-C17-C22-C1	-176.50(12)
C4-C5-C6-C7	-1.7(2)	C16-C17-C22-C1	0.03(15)
C4-C5-C6-C24	177.89(13)	O1-C1-C22-C21	3.5(2)
C5-C6-C7-C8	1.83(19)	N2-C1-C22-C21	-176.89(14)
C24-C6-C7-C8	-177.70(13)	O1-C1-C22-C17	-178.88(14)
C5-C6-C7-C25	-179.55(13)	N2-C1-C22-C17	0.76(15)
C24-C6-C7-C25	0.9(2)	O1-C1-N2-C3	0.3(2)
C6-C7-C8-C9	0.0(2)	C22-C1-N2-C3	-179.40(12)
C25-C7-C8-C9	-178.62(13)	O1-C1-N2-C16	178.35(13)
C7-C8-C9-C4	-2.0(2)	C22-C1-N2-C16	-1.31(15)
C7-C8-C9-C10	176.04(12)	C4-C3-N2-C1	-155.02(12)
C5-C4-C9-C8	2.17(18)	C23-C3-N2-C1	78.38(16)
C3-C4-C9-C8	-175.13(12)	C4-C3-N2-C16	27.03(17)
C5-C4-C9-C10	-175.83(12)	C23-C3-N2-C16	-99.56(14)
C3-C4-C9-C10	6.87(19)	C17-C16-N2-C1	1.29(14)
C8-C9-C10-C11	44.67(18)	C15-C16-N2-C1	-124.80(12)
C4-C9-C10-C11	-137.37(13)	C17-C16-N2-C3	179.40(11)
C8-C9-C10-C15	-135.19(13)	C15-C16-N2-C3	53.31(16)
C4-C9-C10-C15	42.78(18)	C13-C12-O2-C26	-1.2(2)
C15-C10-C11-C12	-1.58(19)	C11-C12-O2-C26	178.71(13)
C9-C10-C11-C12	178.57(12)		
C10-C11-C12-O2	177.33(12)		
C10-C11-C12-C13	-2.7(2)		
O2-C12-C13-C14	-175.59(13)		
C11-C12-C13-C14	4.5(2)		
C12-C13-C14-C15	-2.0(2)		
C13-C14-C15-C10	-2.3(2)		
C13-C14-C15-C16	179.41(12)		
C11-C10-C15-C14	4.02(19)		
C9-C10-C15-C14	-176.12(12)		
C11-C10-C15-C16	-177.61(11)		
C9-C10-C15-C16	2.25(18)		
C14-C15-C16-N2	106.51(14)		
C10-C15-C16-N2	-71.81(15)		
C14-C15-C16-C17	-9.68(18)		
C10-C15-C16-C17	172.00(11)		
N2-C16-C17-C22	-0.73(14)		
C15-C16-C17-C22	120.45(13)		
N2-C16-C17-C18	175.36(14)		
C15-C16-C17-C18	-63.46(19)		
C22-C17-C18-C19	-1.4(2)		
C16-C17-C18-C19	-177.10(14)		
C17-C18-C19-C20	0.6(2)		
C18-C19-C20-C21	0.2(2)		

2.4 Crystallographic data for 18-Azaoctacyclo[16.7.0.0^{2,7}.0^{8,16}.0^{9,14}.0^{10,12}.0^{11,15}.0^{20,25}] pentacosa-2,4,6,8(16),20(25),21,23-heptaen-19-one (252)

Table 31 Crystal data

Habitus, colour	prism, colourless
Crystal size	0.28 x 0.24 x 0.13 mm^3
Crystal system	Monoclinic
Space group	P 21/n Z = 4
Unit cell dimensions	a = 9.3805(10) Å α = 90°.
	b = 15.2125(11) Å β = 101.538(8)°.
	c = 11.7293(10) Å γ = 90°.
Volume	1640.0(3) Å^3
Cell determination	13342 peaks with Theta 2.2 to 26°.
Empirical formula	C$_{24}$H$_{19}$NO
Formula weight	337.40
Density (calculated)	1.367 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	712
Wavelength	0.71073 Å
Temperature	193(2) K
Theta range for data collection	2.22 to 25.00°.
Index ranges	-11<=h<=11, -18<=k<=18, -13<=l<=13
Reflections collected	13785
Independent reflections	2874 [R(int) = 0.0415]
Completeness to theta = 25.00°	99.9 %
Observed reflections	2262[I>2sigma(I)]
Reflections used for refinement	2874
Extinction coefficient	X = 0.0045(15)
Absorption correction	None
Largest diff. peak and hole	0.301 and -0.146 e.Å^{-3}
Refinement	Full-matrix least-squares on F^2
Treatment of hydrogen atoms	Located, isotropic refinemnet
Data / restraints / parameters	2874 / 0 / 312
Goodness-of-fit on F^2	1.040
R index (all data)	wR2 = 0.0870
R index conventional [I>2sigma(I)]	R1 = 0.0362

Table 32   Bond lengths [Å] and angles [°]

C1-O1	1.2281(18)	C22-C6-C5	119.39(14)
C1-N2	1.3566(19)	C7-C6-C5	122.07(14)
C1-C14	1.482(2)	C25-C7-C6	119.14(14)
C3-N2	1.456(2)	C25-C7-C8	121.81(14)
C3-C4	1.490(2)	C6-C7-C8	119.04(13)
C4-C5	1.348(2)	N2-C8-C9	101.15(12)
C4-C15	1.516(2)	N2-C8-C7	112.22(12)
C5-C6	1.466(2)	C9-C8-C7	115.93(13)
C5-C19	1.524(2)	C14-C9-C10	120.03(14)
C6-C22	1.404(2)	C14-C9-C8	109.70(13)
C6-C7	1.410(2)	C10-C9-C8	130.27(15)
C7-C25	1.389(2)	C11-C10-C9	118.36(16)
C7-C8	1.526(2)	C10-C11-C12	121.52(16)
C8-N2	1.4756(19)		
C8-C9	1.515(2)	C13-C12-C11	120.33(15)
C9-C14	1.386(2)	C12-C13-C14	117.92(16)
C9-C10	1.387(2)	C9-C14-C13	121.81(15)
C10-C11	1.385(2)	C9-C14-C1	108.81(13)
C11-C12	1.391(2)	C13-C14-C1	129.34(14)
C12-C13	1.385(2)	C4-C15-C20	102.69(13)
C13-C14	1.393(2)	C4-C15-C16	106.79(14)
C15-C20	1.543(2)	C18-C16-C17	60.71(12)
C15-C16	1.543(2)	C18-C16-C15	104.12(14)
C16-C18	1.494(3)	C17-C16-C15	108.35(15)
C16-C17	1.510(3)	C21-C17-C16	106.90(15)
C17-C21	1.501(3)	C21-C17-C18	106.64(14)
C17-C18	1.519(3)	C16-C17-C18	59.11(12)
C18-C19	1.538(2)	C16-C18-C17	60.18(12)
C19-C20	1.534(2)	C16-C18-C19	103.98(14)
C20-C21	1.514(2)	C17-C18-C19	108.89(14)
C22-C23	1.384(2)	C5-C19-C20	102.87(13)
C23-C24	1.386(2)	C5-C19-C18	107.62(13)
C24-C25	1.390(2)	C20-C19-C18	96.00(13)
		C21-C20-C19	106.90(14)
O1-C1-N2	125.06(14)	C21-C20-C15	105.54(14)
O1-C1-C14	128.69(14)	C19-C20-C15	93.56(13)
N2-C1-C14	106.24(13)	C17-C21-C20	97.91(14)
N2-C3-C4	115.01(13)	C23-C22-C6	121.42(15)
C5-C4-C3	130.59(15)	C22-C23-C24	119.82(15)
C5-C4-C15	107.54(14)	C23-C24-C25	119.40(15)
C3-C4-C15	120.19(13)	C7-C25-C24	121.64(15)
C4-C5-C6	128.32(15)	C1-N2-C3	120.48(13)
C4-C5-C19	106.66(14)	C1-N2-C8	113.98(12)
C6-C5-C19	124.03(14)	C3-N2-C8	123.91(12)
C22-C6-C7	118.54(14)		

Table 33   Torsion angles [°]

N2-C3-C4-C5	-36.0(3)	C17-C16-C18-C19	-104.00(15)
N2-C3-C4-C15	160.78(14)	C15-C16-C18-C19	-0.64(17)
C3-C4-C5-C6	4.5(3)	C21-C17-C18-C16	-100.06(16)
C15-C4-C5-C6	169.33(15)	C21-C17-C18-C19	-4.4(2)
C3-C4-C5-C19	-164.34(16)	C16-C17-C18-C19	95.63(15)
C15-C4-C5-C19	0.50(17)	C4-C5-C19-C20	-32.14(16)
C4-C5-C6-C22	-146.38(17)	C6-C5-C19-C20	158.42(14)
C19-C5-C6-C22	20.7(2)	C4-C5-C19-C18	68.52(16)
C4-C5-C6-C7	32.6(2)	C6-C5-C19-C18	-100.91(17)
C19-C5-C6-C7	-160.36(15)	C16-C18-C19-C5	-66.29(16)
C22-C6-C7-C25	2.2(2)	C17-C18-C19-C5	-129.13(15)
C5-C6-C7-C25	-176.77(14)	C16-C18-C19-C20	39.28(15)
C22-C6-C7-C8	-176.58(14)	C17-C18-C19-C20	-23.56(17)
C5-C6-C7-C8	4.5(2)	C5-C19-C20-C21	154.63(14)
C25-C7-C8-N2	114.51(15)	C18-C19-C20-C21	44.99(16)
C6-C7-C8-N2	-66.75(18)	C5-C19-C20-C15	47.21(14)
C25-C7-C8-C9	-1.0(2)	C18-C19-C20-C15	-62.43(13)
C6-C7-C8-C9	177.73(13)	C4-C15-C20-C21	-155.47(13)
N2-C8-C9-C14	-1.57(16)	C16-C15-C20-C21	-46.76(16)
C7-C8-C9-C14	120.06(14)	C4-C15-C20-C19	-46.83(14)
N2-C8-C9-C10	178.44(15)	C16-C15-C20-C19	61.88(13)
C7-C8-C9-C10	-59.9(2)	C16-C17-C21-C20	-31.25(18)
C14-C9-C10-C11	-1.9(2)	C18-C17-C21-C20	30.77(17)
C8-C9-C10-C11	178.10(15)	C19-C20-C21-C17	-48.79(17)
C9-C10-C11-C12	1.1(2)	C15-C20-C21-C17	49.94(16)
C10-C11-C12-C13	0.5(2)	C7-C6-C22-C23	-1.6(2)
C11-C12-C13-C14	-1.2(2)	C5-C6-C22-C23	177.37(15)
C10-C9-C14-C13	1.2(2)	C6-C22-C23-C24	-0.4(2)
C8-C9-C14-C13	-178.83(14)	C22-C23-C24-C25	1.7(2)
C10-C9-C14-C1	-176.89(14)	C6-C7-C25-C24	-0.9(2)
C8-C9-C14-C1	3.11(17)	C8-C7-C25-C24	177.87(15)
C12-C13-C14-C9	0.4(2)	C23-C24-C25-C7	-1.1(2)
C12-C13-C14-C1	178.05(15)	O1-C1-N2-C3	-10.4(2)
O1-C1-C14-C9	175.34(15)	C14-C1-N2-C3	168.51(13)
N2-C1-C14-C9	-3.48(16)	O1-C1-N2-C8	-176.34(14)
O1-C1-C14-C13	-2.5(3)	C14-C1-N2-C8	2.53(16)
N2-C1-C14-C13	178.65(15)	C4-C3-N2-C1	-171.52(14)
C5-C4-C15-C20	31.08(17)	C4-C3-N2-C8	-7.0(2)
C3-C4-C15-C20	-162.20(15)	C9-C8-N2-C1	-0.70(16)
C5-C4-C15-C16	-69.13(17)	C7-C8-N2-C1	-124.89(14)
C3-C4-C15-C16	97.59(17)	C9-C8-N2-C3	-166.14(14)
C4-C15-C16-C18	67.20(17)	C7-C8-N2-C3	69.68(19)
C20-C15-C16-C18	-37.97(16)		
C4-C15-C16-C17	130.58(15)		
C20-C15-C16-C17	25.41(17)		
C18-C16-C17-C21	99.61(16)		
C15-C16-C17-C21	3.4(2)		
C15-C16-C17-C18	-96.24(15)		
C15-C16-C18-C17	103.36(15)		

2.5 Crystallographic data for 6,7-dimethyl-11,15b-dihydro-9*H*-benzo[5,6]naphtha-[2',1':3,4]azepino[2,1-*a*]isoindol-11-one (246)

Table 34 Crystal data

Habitus, colour	plate, colourless	
Crystal size	0.27 x 0.21 x 0.06 mm^3	
Crystal system	Monoclinic	
Space group	P 2$_1$/c	Z = 4
Unit cell dimensions	a = 12.1052(10) Å	α = 90°.
	b = 8.2123(6) Å	β = 90.287(6)°.
	c = 19.4947(13) Å	γ = 90°.
Volume	1938.0(2) Å^3	
Cell determination	14442 peaks with Theta 1.6 to 25°.	
Empirical formula	C$_{27}$H$_{21}$NO	
Formula weight	375.45	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	792	
Wavelength	0.71073 Å	
Temperature	193(2) K	
Theta range for data collection	1.68 to 25.00°.	
Index ranges	-14<=h<=14, -9<=k<=9, -23<=l<=23	
Reflections collected	22133	
Independent reflections	3417 [R(int) = 0.0521]	
Completeness to theta = 25.00°	99.9 %	
Observed reflections	2337[I>2sigma(I)]	
Reflections used for refinement	3417	
Extinction coefficient	X = 0.021(2)	
Absorption correction	None	
Largest diff. peak and hole	0.166 and -0.152 e.Å^{-3}	
Refinement	Full-matrix least-squares on F^2	
Treatment of hydrogen atoms	Located, isotropic refinement	
Data / restraints / parameters	3417 / 0 / 347	
Goodness-of-fit on F^2	0.952	
R index (all data)	wR2 = 0.0930	
R index conventional [I>2sigma(I)]	R1 = 0.0371	

Table 35   Bond lengths [Å] and angles [°]

C1-O1	1.230(2)	C18-C5-C6	120.99(15)
C1-N2	1.354(2)	C7-C6-C19	119.55(14)
C1-C14	1.480(2)	C7-C6-C5	119.20(14)
C3-N2	1.463(2)	C19-C6-C5	121.24(14)
C3-C4	1.509(2)	C6-C7-C26	120.16(15)
C4-C5	1.395(2)	C6-C7-C8	117.62(14)
C4-C15	1.396(2)	C26-C7-C8	122.22(14)
C5-C18	1.402(2)	N2-C8-C9	101.56(13)
C5-C6	1.492(2)	N2-C8-C7	110.80(13)
C6-C7	1.395(2)	C9-C8-C7	120.66(14)
C6-C19	1.435(2)	C10-C9-C14	120.40(15)
C7-C26	1.408(2)	C10-C9-C8	130.36(15)
C7-C8	1.516(2)	C14-C9-C8	109.02(14)
C8-N2	1.470(2)	C9-C10-C11	117.82(17)
C8-C9	1.506(2)	C12-C11-C10	121.56(18)
C9-C10	1.381(2)	C11-C12-C13	120.83(17)
C9-C14	1.391(2)	C14-C13-C12	117.78(18)
C10-C11	1.393(2)	C13-C14-C9	121.59(16)
C11-C12	1.375(3)	C13-C14-C1	129.11(16)
C12-C13	1.386(3)	C9-C14-C1	109.26(14)
C13-C14	1.383(2)	C16-C15-C4	122.19(18)
C15-C16	1.386(2)	C15-C16-C17	118.92(16)
C16-C17	1.407(3)	C15-C16-C27	119.84(19)
C16-C27	1.507(3)	C17-C16-C27	121.23(18)
C17-C18	1.394(2)	C18-C17-C16	118.75(15)
C17-C28	1.503(2)	C18-C17-C28	120.13(18)
C19-C20	1.419(2)	C16-C17-C28	121.10(18)
C19-C24	1.424(2)	C17-C18-C5	122.25(17)
C20-C21	1.366(3)	C20-C19-C24	118.21(15)
C21-C22	1.404(3)	C20-C19-C6	122.53(15)
C22-C23	1.362(3)	C24-C19-C6	119.23(14)
C23-C24	1.417(2)	C21-C20-C19	121.19(18)
C24-C25	1.412(2)	C20-C21-C22	120.47(18)
C25-C26	1.373(3)	C23-C22-C21	119.97(19)
		C22-C23-C24	121.38(19)
O1-C1-N2	125.97(16)	C25-C24-C23	122.04(17)
O1-C1-C14	128.34(15)	C25-C24-C19	119.17(15)
N2-C1-C14	105.69(14)	C23-C24-C19	118.77(16)
N2-C3-C4	109.37(13)	C26-C25-C24	120.87(17)
C5-C4-C15	119.42(15)	C25-C26-C7	120.88(16)
C5-C4-C3	119.80(16)	C1-N2-C3	124.98(14)
C15-C4-C3	120.73(16)	C1-N2-C8	114.28(13)
C4-C5-C18	118.44(16)	C3-N2-C8	120.72(13)
C4-C5-C6	120.45(14)		

Table 36   Torsion angles [°]

N2-C3-C4-C5	-68.1(2)	C7-C6-C19-C20	-174.51(15)
N2-C3-C4-C15	109.01(18)	C5-C6-C19-C20	4.8(2)
C15-C4-C5-C18	-1.6(2)	C7-C6-C19-C24	3.7(2)
C3-C4-C5-C18	175.62(15)	C5-C6-C19-C24	-176.99(15)
C15-C4-C5-C6	-177.68(15)	C24-C19-C20-C21	1.1(2)
C3-C4-C5-C6	-0.5(2)	C6-C19-C20-C21	179.34(16)
C4-C5-C6-C7	54.0(2)	C19-C20-C21-C22	-0.6(3)
C18-C5-C6-C7	-122.00(17)	C20-C21-C22-C23	0.2(3)
C4-C5-C6-C19	-125.31(17)	C21-C22-C23-C24	-0.5(3)
C18-C5-C6-C19	58.7(2)	C22-C23-C24-C25	-177.22(18)
C19-C6-C7-C26	-3.2(2)	C22-C23-C24-C19	1.0(3)
C5-C6-C7-C26	177.50(15)	C20-C19-C24-C25	176.97(15)
C19-C6-C7-C8	176.05(14)	C6-C19-C24-C25	-1.3(2)
C5-C6-C7-C8	-3.3(2)	C20-C19-C24-C23	-1.3(2)
C6-C7-C8-N2	-69.38(18)	C6-C19-C24-C23	-179.59(15)
C26-C7-C8-N2	109.81(17)	C23-C24-C25-C26	176.56(17)
C6-C7-C8-C9	172.31(14)	C19-C24-C25-C26	-1.7(3)
C26-C7-C8-C9	-8.5(2)	C24-C25-C26-C7	2.3(3)
N2-C8-C9-C10	178.78(16)	C6-C7-C26-C25	0.2(3)
C7-C8-C9-C10	-58.4(2)	C8-C7-C26-C25	-178.98(15)
N2-C8-C9-C14	4.28(17)	O1-C1-N2-C3	1.8(3)
C7-C8-C9-C14	127.14(15)	C14-C1-N2-C3	-177.83(15)
C14-C9-C10-C11	0.4(2)	O1-C1-N2-C8	-179.47(16)
C8-C9-C10-C11	-173.54(16)	C14-C1-N2-C8	0.86(18)
C9-C10-C11-C12	0.4(3)	C4-C3-N2-C1	-142.85(16)
C10-C11-C12-C13	-0.5(3)	C4-C3-N2-C8	38.5(2)
C11-C12-C13-C14	-0.2(3)	C9-C8-N2-C1	-3.14(17)
C12-C13-C14-C9	1.0(2)	C7-C8-N2-C1	-132.52(14)
C12-C13-C14-C1	178.66(16)	C9-C8-N2-C3	175.62(14)
C10-C9-C14-C13	-1.1(2)	C7-C8-N2-C3	46.24(19)
C8-C9-C14-C13	174.01(15)		
C10-C9-C14-C1	-179.21(15)		
C8-C9-C14-C1	-4.08(18)		
O1-C1-C14-C13	4.5(3)		
N2-C1-C14-C13	-175.83(16)		
O1-C1-C14-C9	-177.58(16)		
N2-C1-C14-C9	2.07(18)		
C5-C4-C15-C16	1.7(2)		
C3-C4-C15-C16	-175.49(16)		
C4-C15-C16-C17	-0.3(3)		
C4-C15-C16-C27	178.46(19)		
C15-C16-C17-C18	-1.2(2)		
C27-C16-C17-C18	-179.89(18)		
C15-C16-C17-C28	177.08(16)		
C27-C16-C17-C28	-1.6(3)		
C16-C17-C18-C5	1.3(2)		
C28-C17-C18-C5	-177.01(16)		
C4-C5-C18-C17	0.1(2)		
C6-C5-C18-C17	176.21(15)		

2.6 Crystallographic data for 7-methoxy-11,15b-dihydro-9*H*-dibenzo[3,4:5,6]azepino [2,1-*a*]isoindol-11-one (247)

Table 37   Crystal data

Empirical formula	$C_{22}H_{17}N\ O_2$
Formula weight	327.37
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 2_1/c
Unit cell dimensions	$a = 14.4089(12)$ Å $\alpha = 90°$.
	$b = 13.0610(9)$ Å $\beta = 107.902(7)°$.
	$c = 9.1016(8)$ Å $\gamma = 90°$.
Volume	1629.9(2) Å^3
Z	4
Density (calculated)	1.334 Mg/m^3
Absorption coefficient	0.085 mm^{-1}
F(000)	688
Crystal size	0.50 x 0.20 x 0.08 mm^3
Theta range for data collection	1.49 to 27.06°.
Index ranges	-18<=h<=18, -16<=k<=14, -10<=l<=11
Reflections collected	16403
Independent reflections	3563 [R(int) = 0.0482]
Completeness to theta = 27.06°	99.4 %
Refinement	Full-matrix least-squares on F^2
Data / restraints / parameters	3563 / 0 / 295
Goodness-of-fit on F^2	0.835
Final R indices [I>2sigma(I)]	$R_1 = 0.0364$, $wR_2 = 0.0819$
R indices (all data)	$R_1 = 0.0664$, $wR_2 = 0.0890$
Extinction coefficient	0.029(2)
Largest diff. peak and hole	0.132 and -0.156 e.Å^{-3}

Table 38   Bond lengths [Å] and angles [°]

N-C20	1.3566(16)	C4-C5-C21	120.75(12)
N-C19	1.4566(18)	C4-C5-C6	129.64(12)
N-C6	1.4667(17)	C21-C5-C6	109.59(11)
O1-C20	1.2298(16)	N-C6-C5	101.57(10)
O2-C16	1.3773(16)	N-C6-C7	110.63(11)
O2-C22	1.4293(18)	C5-C6-C7	118.33(11)
C1-C2	1.385(2)	C8-C7-C12	119.68(12)
C1-C21	1.3861(19)	C8-C7-C6	122.41(11)
C2-C3	1.388(2)	C12-C7-C6	117.90(11)
C3-C4	1.3877(19)	C9-C8-C7	120.76(13)
C4-C5	1.3804(19)	C10-C9-C8	119.83(14)
C5-C21	1.3852(18)	C9-C10-C11	120.07(15)
C5-C6	1.5049(18)	C10-C11-C12	121.11(13)
C6-C7	1.5134(18)	C11-C12-C7	118.54(12)
C7-C8	1.3904(18)	C11-C12-C13	120.41(11)
C7-C12	1.4083(17)	C7-C12-C13	121.02(12)
C8-C9	1.387(2)	C14-C13-C18	117.68(12)
C9-C10	1.380(2)	C14-C13-C12	120.95(13)
C10-C11	1.385(2)	C18-C13-C12	121.36(11)
C11-C12	1.3959(19)	C15-C14-C13	122.35(14)
C12-C13	1.4891(18)	C16-C15-C14	118.95(13)
C13-C14	1.3940(19)	O2-C16-C15	125.01(12)
C13-C18	1.4057(19)	O2-C16-C17	115.06(13)
C14-C15	1.389(2)	C15-C16-C17	119.93(12)
C15-C16	1.381(2)	C18-C17-C16	120.92(14)
C16-C17	1.3922(19)	C17-C18-C13	120.15(12)
C17-C18	1.3818(18)	C17-C18-C19	118.67(13)
C18-C19	1.5059(19)	C13-C18-C19	121.14(12)
C20-C21	1.4802(19)	N-C19-C18	112.00(12)
C20-N-C19	123.78(12)	O1-C20-N	124.96(12)
C20-N-C6	113.94(10)	O1-C20-C21	129.01(12)
C19-N-C6	121.77(10)	N-C20-C21	106.03(11)
C16-O2-C22	117.23(13)	C5-C21-C1	121.52(13)
C2-C1-C21	117.68(14)	C5-C21-C20	108.84(11)
C1-C2-C3	120.92(14)	C1-C21-C20	129.64(12)
C4-C3-C2	121.06(14)		
C5-C4-C3	118.07(13)		

Table 39   Torsion angles [°]

C21-C1-C2-C3	0.1(2)	C17-C18-C19-N	118.52(15)
C1-C2-C3-C4	0.2(2)	C13-C18-C19-N	-63.98(18)
C2-C3-C4-C5	0.0(2)	C19-N-C20-O1	6.1(2)
C3-C4-C5-C21	-0.4(2)	C6-N-C20-O1	178.07(13)
C3-C4-C5-C6	-178.45(15)	C19-N-C20-C21	-174.04(13)
C20-N-C6-C5	1.53(15)	C6-N-C20-C21	-2.05(15)
C19-N-C6-C5	173.70(12)	C4-C5-C21-C1	0.7(2)
C20-N-C6-C7	-124.95(12)	C6-C5-C21-C1	179.06(13)
C19-N-C6-C7	47.22(16)	C4-C5-C21-C20	-179.22(13)
C4-C5-C6-N	177.87(14)	C6-C5-C21-C20	-0.82(16)
C21-C5-C6-N	-0.34(15)	C2-C1-C21-C5	-0.5(2)
C4-C5-C6-C7	-60.9(2)	C2-C1-C21-C20	179.38(14)
C21-C5-C6-C7	120.92(13)	O1-C20-C21-C5	-178.39(14)
N-C6-C7-C8	107.62(14)	N-C20-C21-C5	1.74(15)
C5-C6-C7-C8	-8.9(2)	O1-C20-C21-C1	1.7(2)
N-C6-C7-C12	-71.49(15)	N-C20-C21-C1	-178.12(14)
C5-C6-C7-C12	172.01(12)		
C12-C7-C8-C9	-0.9(2)		
C6-C7-C8-C9	-179.98(13)		
C7-C8-C9-C10	-0.2(2)		
C8-C9-C10-C11	0.6(2)		
C9-C10-C11-C12	0.1(2)		
C10-C11-C12-C7	-1.1(2)		
C10-C11-C12-C13	176.66(14)		
C8-C7-C12-C11	1.53(19)		
C6-C7-C12-C11	-179.34(13)		
C8-C7-C12-C13	-176.25(13)		
C6-C7-C12-C13	2.88(19)		
C11-C12-C13-C14	48.67(19)		
C7-C12-C13-C14	-133.59(14)		
C11-C12-C13-C18	-130.29(15)		
C7-C12-C13-C18	47.45(19)		
C18-C13-C14-C15	0.5(2)		
C12-C13-C14-C15	-178.45(13)		
C13-C14-C15-C16	0.7(2)		
C22-O2-C16-C15	2.6(2)		
C22-O2-C16-C17	-177.23(15)		
C14-C15-C16-O2	179.33(13)		
C14-C15-C16-C17	-0.8(2)		
O2-C16-C17-C18	179.61(13)		
C15-C16-C17-C18	-0.2(2)		
C16-C17-C18-C13	1.5(2)		
C16-C17-C18-C19	179.02(14)		
C14-C13-C18-C17	-1.6(2)		
C12-C13-C18-C17	177.38(12)		
C14-C13-C18-C19	-179.08(13)		
C12-C13-C18-C19	-0.1(2)		
C20-N-C19-C18	-153.49(13)		
C6-N-C19-C18	35.13(19)		

2.7 Crystallographic data for [2-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-5,6-dimethyl-3-phenyl-cyclohexa-2,5-dienyl]-phenyl-acetic acid methyl ester (287)

Table 40   Crystal data

Empirical formula	$C_{32}H_{29}NO_4$	
Formula weight	491.56	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 2_1/c	Z = 4
Unit cell dimensions	a = 13.5297(14) Å	α = 90°.
	b = 11.2367(8) Å	β = 92.643(11)°.
	c = 16.8739(16) Å	γ = 90°.
Volume	2562.6(4) Å^3	
Density (calculated)	1.274 g/cm^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	1040	
Crystal size	0.40 x 0.30 x 0.08 mm^3	
Theta range for data collection	1.51 to 26.03°.	
Index ranges	-16<=h<=16, -13<=k<=13, -20<=l<=20	
Reflections collected	17654	
Independent reflections	4983 [R(int) = 0.0429]	
Completeness to theta = 26.03°	98.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4983 / 0 / 343	
Goodness-of-fit on F^2	1.070	
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.0983	
R index (all data)	R1 = 0.0770, wR2 = 0.1054	
Extiction index	0.0058(8)	
Largest diff. Peak and hole	0.502 and –0.212 eA^3	

Table 41   Bond lengths [Å] and angles [°]

O1-C1	1.211(2)	C8-C7-C17	113.72(17)
O2-C18	1.206(2)	C7-C8-C9	115.25(16)
O3-C32	1.201(2)	C4-C9-C10	123.61(16)
O4-C32	1.325(2)	C4-C9-C8	121.45(16)
O4-C33	1.451(2)	C10-C9-C8	114.92(15)
N2-C1	1.395(2)	C11-C10-C15	117.36(18)
N2-C18	1.398(2)	C11-C10-C9	120.54(17)
N2-C3	1.467(2)	C15-C10-C9	121.99(17)
C1-C24	1.483(3)	C10-C11-C12	121.66(19)
C3-C4	1.516(2)	C13-C12-C11	120.28(19)
C4-C9	1.331(2)	C12-C13-C14	119.05(19)
C4-C5	1.514(2)	C13-C14-C15	120.7(2)
C5-C6	1.508(3)	C14-C15-C10	120.9(2)
C5-C25	1.591(2)	O2-C18-N2	124.69(17)
C6-C7	1.340(3)	O2-C18-C19	129.35(17)
C6-C16	1.512(3)	N2-C18-C19	105.95(15)
C7-C8	1.497(3)	C20-C19-C24	121.30(17)
C7-C17	1.502(3)	C20-C19-C18	130.75(17)
C8-C9	1.500(3)	C24-C19-C18	107.95(15)
C9-C10	1.496(2)	C19-C20-C21	117.61(19)
C10-C11	1.376(3)	C22-C21-C20	120.94(19)
		C21-C22-C23	121.50(19)
C32-O4-C33	115.80(17)	C24-C23-C22	117.26(18)
C1-N2-C18	111.62(14)	C23-C24-C19	121.38(17)
C1-N2-C3	123.29(15)	C23-C24-C1	130.23(17)
C18-N2-C3	124.09(15)	C19-C24-C1	108.38(15)
O1-C1-N2	124.79(17)	C26-C25-C32	117.25(16)
O1-C1-C24	129.23(17)	C26-C25-C5	112.64(15)
N2-C1-C24	105.96(15)	C32-C25-C5	110.56(14)
N2-C3-C4	113.50(14)	C31-C26-C27	118.36(17)
C9-C4-C5	121.48(16)	C31-C26-C25	123.05(17)
C9-C4-C3	121.19(16)	C27-C26-C25	118.44(17)
C5-C4-C3	117.08(15)	C28-C27-C26	120.7(2)
C6-C5-C4	113.33(15)	C27-C28-C29	119.91(19)
C6-C5-C25	112.59(14)	C30-C29-C28	119.96(19)
C4-C5-C25	108.79(14)	C29-C30-C31	120.5(2)
C7-C6-C5	121.46(16)	C30-C31-C26	120.55(19)
C7-C6-C16	123.09(17)	O3-C32-O4	123.83(18)
C5-C6-C16	115.30(16)	O3-C32-C25	122.67(18)
C6-C7-C8	121.43(17)	O4-C32-C25	113.49(16)
C6-C7-C17	124.68(18)		

Table 42   Torsion angles [°]

C18-N2-C1-O1	-174.50(17)	C18-C19-C20-C21	-179.05(19)
C3-N2-C1-O1	-5.6(3)	C19-C20-C21-C22	-0.9(3)
C18-N2-C1-C24	3.93(19)	C20-C21-C22-C23	0.3(3)
C3-N2-C1-C24	172.88(15)	C21-C22-C23-C24	0.3(3)
C1-N2-C3-C4	108.05(19)	C22-C23-C24-C19	-0.3(3)
C18-N2-C3-C4	-84.4(2)	C22-C23-C24-C1	178.49(18)
N2-C3-C4-C9	136.94(17)	C20-C19-C24-C23	-0.4(3)
N2-C3-C4-C5	-48.7(2)	C18-C19-C24-C23	179.62(17)
C9-C4-C5-C6	-23.4(2)	C20-C19-C24-C1	-179.37(17)
C3-C4-C5-C6	162.30(15)	C18-C19-C24-C1	0.61(19)
C9-C4-C5-C25	102.69(19)	O1-C1-C24-C23	-3.3(3)
C3-C4-C5-C25	-71.64(19)	N2-C1-C24-C23	178.39(18)
C4-C5-C6-C7	21.1(2)	O1-C1-C24-C19	175.62(19)
C25-C5-C6-C7	-102.92(19)	N2-C1-C24-C19	-2.72(19)
C4-C5-C6-C16	-163.22(15)	C6-C5-C25-C26	62.7(2)
C25-C5-C6-C16	72.8(2)	C4-C5-C25-C26	-63.8(2)
C5-C6-C7-C8	-2.4(3)	C6-C5-C25-C32	-70.6(2)
C16-C6-C7-C8	-177.75(17)	C4-C5-C25-C32	162.89(16)
C5-C6-C7-C17	172.59(17)	C32-C25-C26-C31	57.8(2)
C16-C6-C7-C17	-2.7(3)	C5-C25-C26-C31	-72.2(2)
C6-C7-C8-C9	-15.1(3)	C32-C25-C26-C27	-126.83(19)
C17-C7-C8-C9	169.40(16)	C5-C25-C26-C27	103.18(19)
C5-C4-C9-C10	-171.54(15)	C31-C26-C27-C28	1.6(3)
C3-C4-C9-C10	2.6(3)	C25-C26-C27-C28	-174.01(17)
C5-C4-C9-C8	6.7(3)	C26-C27-C28-C29	-0.6(3)
C3-C4-C9-C8	-179.17(16)	C27-C28-C29-C30	-0.2(3)
C7-C8-C9-C4	12.9(3)	C28-C29-C30-C31	0.1(3)
C7-C8-C9-C10	-168.73(16)	C29-C30-C31-C26	0.9(3)
C4-C9-C10-C11	78.6(2)	C27-C26-C31-C30	-1.7(3)
C8-C9-C10-C11	-99.7(2)	C25-C26-C31-C30	173.68(17)
C4-C9-C10-C15	-105.4(2)	C33-O4-C32-O3	-0.3(3)
C8-C9-C10-C15	76.2(2)	C33-O4-C32-C25	178.78(18)
C15-C10-C11-C12	2.2(3)	C26-C25-C32-O3	177.24(19)
C9-C10-C11-C12	178.34(19)	C5-C25-C32-O3	-51.8(3)
C10-C11-C12-C13	0.0(3)	C26-C25-C32-O4	-1.8(2)
C11-C12-C13-C14	-1.7(4)	C5-C25-C32-O4	129.15(17)
C12-C13-C14-C15	1.2(4)		
C13-C14-C15-C10	1.0(4)		
C11-C10-C15-C14	-2.7(4)		
C9-C10-C15-C14	-178.8(2)		
C1-N2-C18-O2	175.28(17)		
C3-N2-C18-O2	6.4(3)		
C1-N2-C18-C19	-3.57(19)		
C3-N2-C18-C19	-172.41(15)		
O2-C18-C19-C20	2.9(3)		
N2-C18-C19-C20	-178.31(19)		
O2-C18-C19-C24	-177.06(19)		
N2-C18-C19-C24	1.71(19)		
C24-C19-C20-C21	0.9(3)		

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