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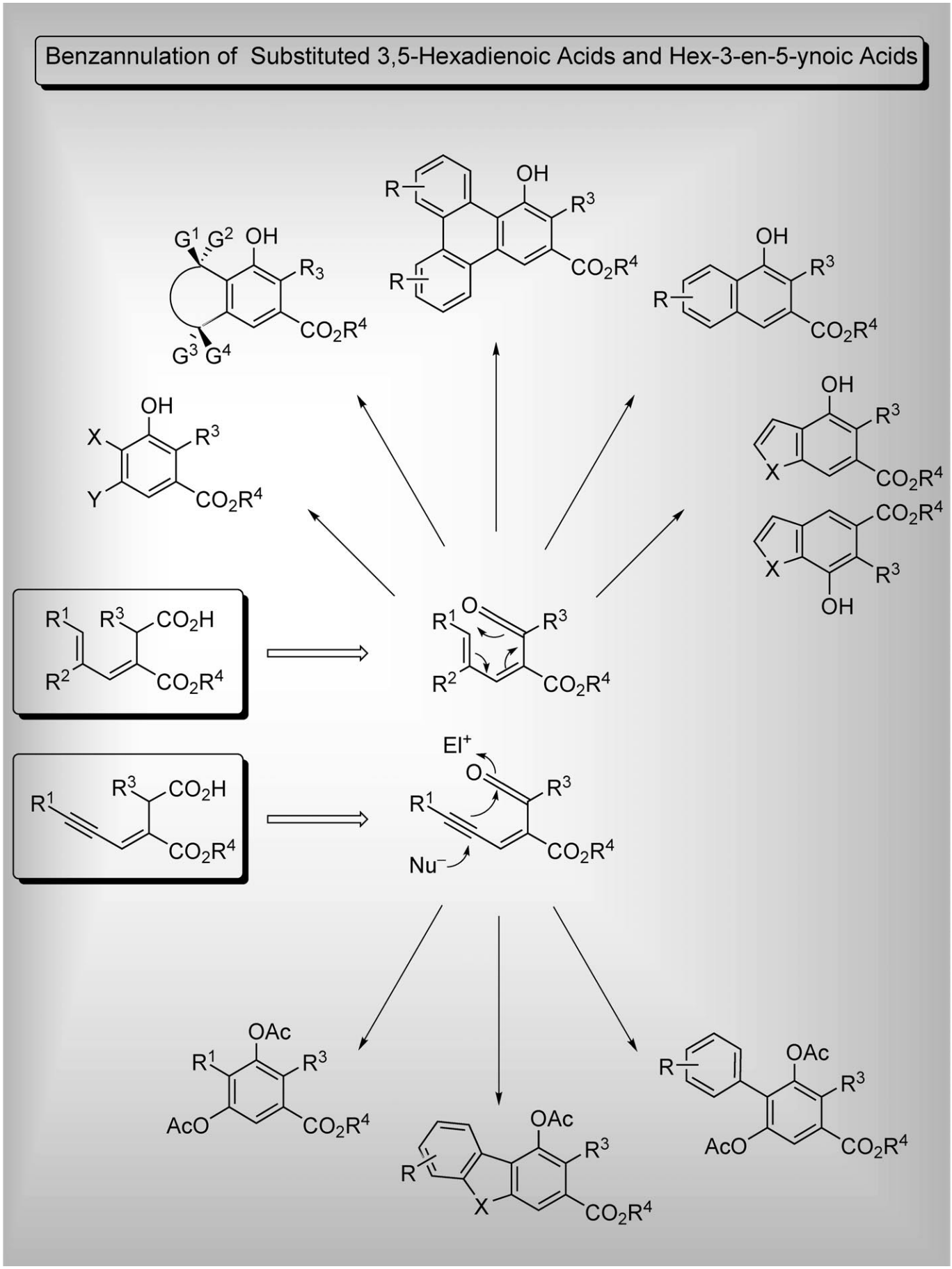

Recent Advances in the Benzannulation of Substituted 3-Alkoxycarbonyl-3,5-hexadienoic Acids and 3-Alkoxycarbonylhex-3-en-5-ynoic Acids to Polysubstituted Aromatics

Stefano Serra,*[a] Claudio Fuganti,[b] and Elisabetta Brenna[b]

Abstract: The benzannulation reactions of substituted 3-alkoxycarbonyl-3,5-hexadienoic and 3-alkoxycarbonylhex-3-en-5-ynoic acids offer a straightforward access to various polysubstituted aromatic compounds. The process is very flexible, and can be applied to the regiospecific preparation of oligoaryls, naphthalenes, ring-fused heterocycles, chiral tetrahydronaphthalenes, *C*-aryl-glycosides and many natural products of different structure. In this Concept article, we highlight the potential of this annulation reaction by illustration of our recent contribution to this field, as well as the studies previous reported by others.

Keywords: annulation · aromaticity · heterocycles · natural products · polycycles

Introduction

The regiospecific preparation of polyfunctionalized aromatic compounds is one of the challenging problems in organic synthesis. The classic approach exploits readily available benzene derivatives and pivots on aromatic substitution in which the substituents are introduced into a preexisting arene. A great variety of synthetic methodologies based on this route have been developed. The best known are electrophilic or nucleophilic substitutions,[1] recently complemented by catalysed coupling reactions,[2] and metalation–functionalization reactions.[3] The main restriction of this approach lies in the activation/deactivation and orienting effects of the substituents that limit the application of the synthetic methods. Other approaches that build up the aromatic moiety starting from acyclic precursors[4–12] in a single step, with substituents already in place are called benzannulation methods. These last reactions have received growing interest, since the preparation of highly substituted compounds in only few steps and the avoidance of *ortho*/*meta*/*para* mixtures obtained in conventional aromatic synthesis show several advantages. These general features are common in the most useful benzannulation routes based on the Diels–Alder [4+2] cycloaddition;[5] transition-metal-catalysed [2+2+2] and [4+2] cycloaddition,[6] the Dötz reaction;[7] [3+3],[8] [4+2][9] and [5+1][10] benzannulation and on different methods of ring closure of acyclic precursors.[11,12] These last methodologies show different features in term of efficiency, selectivity and synthetic applicability, as a result of their specific mechanism, of the experimental conditions used and of the availability of the starting materials. The more regioselective pathways are usually those involving an electrocyclic ring closure as a key step and, among this class, the 1,6-electrocyclic annulation[12] of dienylketenes[13] have come to play a leading role. In this context, we focus our attention on the benzannulation reactions of substituted 3-alkoxycarbonyl-3,5-hexadienoic and 3-alkoxycarbonylhex-3-en-5-ynoic acids that afford various polysubstituted phenol derivatives following the mechanism described above. Few studies on the cyclization of the former kind of acids and none on the latter have been reported before the publication of our work. In this account, we illustrate the recent developments in this field, mainly based on the researches succeeded in our laboratory. The different classes of compounds that can be prepared by the above-mentioned reactions and some selected syntheses of natural products will be described to exemplify the synthetic potential of this benzannulation approach.

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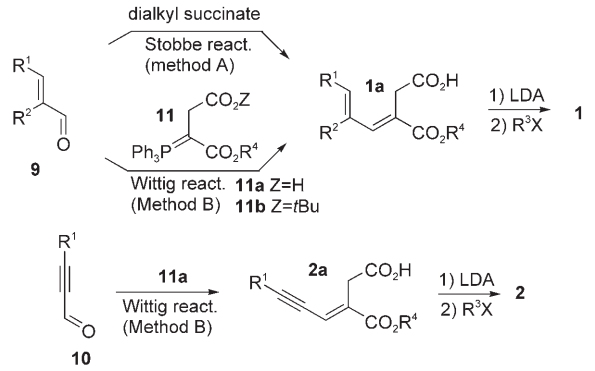
General Features in Benzannulation and Preparation of 3-Alkoxycarbonyl-3,5-hexadienoic and 3-Alkoxycarbonylhex-3-en-5-ynoic Acids

The benzannulation of 3-alkoxycarbonyl-3,5-hexadienoic (**1**) and 3-alkoxycarbonylhex-3-en-5-ynoic acids (**2**) requires experimental conditions that might change markedly on the basis of their general structure (type **1** or **2**), on the degree of substitution and on the nature of substituents. Despite this fact, only two mechanisms, which are very similar, are involved in the reactions (Scheme 1). In all cases, the acids **1** or **2** were treated with a suitable activating agent in presence of an excess of base. The so-formed intermediates **3** and **4** are unstable in the reaction environment and are converted into the vinylketenes **5** and **6**, respectively, by base-induced elimination.

The intermediate **5** readily cyclizes through a 1,6-electrocyclic reaction to give phenols **7**. In this case, the overall ring closure process is very fast and compound **3** could be isolated only in the presence of less than one equivalent of base. The benzannulation procedure is usually performed at low temperature (from −30 to 20°C) with diphenylphosphinic chloride,[14] ethyl chloroformate[15] or trifluoroacetic anhydride[16] as activating agents and a tertiary amine (triethyl amine, *N*-methylmorpholine) as base. Otherwise, stronger conditions are necessary to induce the cyclization of ynenylketene **6**. Electrophilic attack of the ketene moiety and nucleophilic addition to the triple bond must work in concerted fashion and require the simultaneous presence of electrophilic and nucleophilic species. We found that these requirements are complied with the use of an anhydride as activating agent and of its corresponding carboxylic acid salt as base.[17] The treatment of acid **2** in a refluxing mixture of acetic anhydride and sodium acetate is the most simple procedure to prepare the symmetrical phenol derivatives **8** ($El = CH_3CO^+$; $Nu = CH_3COO^-$).

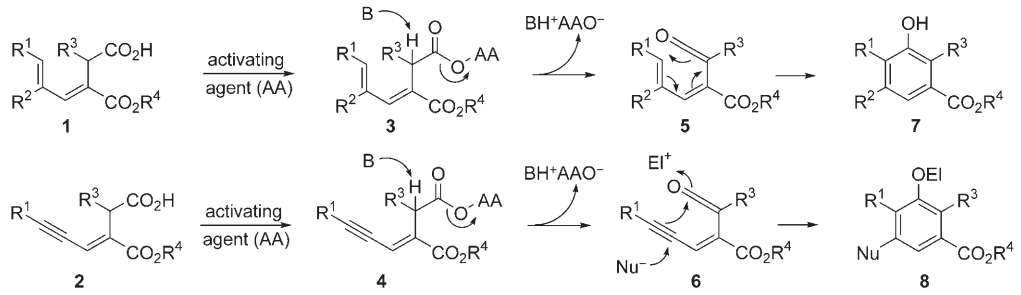
Concerning the access to acids **1** and **2**, two suitable methods have been employed (Scheme 2). The first approach is based on the Stobbe condensation[18] of dialkyl succinates with α,β-unsaturated aldehydes **9** (Method A). In this case, a stoichiometric amount of sodium methylate or potassium *tert*-butoxide is required and the resulting strong basic conditions limit the range of the aldehydes available. Very good conversion is possible when the R^1 and/or R^2 groups are aromatic or heteroaromatic, while aldehydes **9** with a different substitution pattern or propargylic aldehydes **10** afford acids **1a** and **2a**, respectively, in lower yields. A second milder method is based on the condensation of aldehydes **9** or **10** with the Wittig reagents of type **11**[19] to give acids **1a** and **2a**, respectively, in very good yields (Method B). Both procedures are stereoselective[19b] and afford the 3-(*E*)-alkylidene-succinic acid monoalkyl esters, that is, isomers that are suitable for the annulation step. Moreover, the generation of the dilithium enolate of acids **1a** and **2a** followed by regioselective alkylation in the 2-position with alkyl halides[16] gives access to acids **1** and **2** and therefore makes possible a further functionalization of phenols **7** and **8**, respectively.



Scheme 2. Preparation of 3-alkoxycarbonyl-3,5-hexadienoic acids **1** and of 3-alkoxycarbonylhex-3-en-5-ynoic acids **2**.

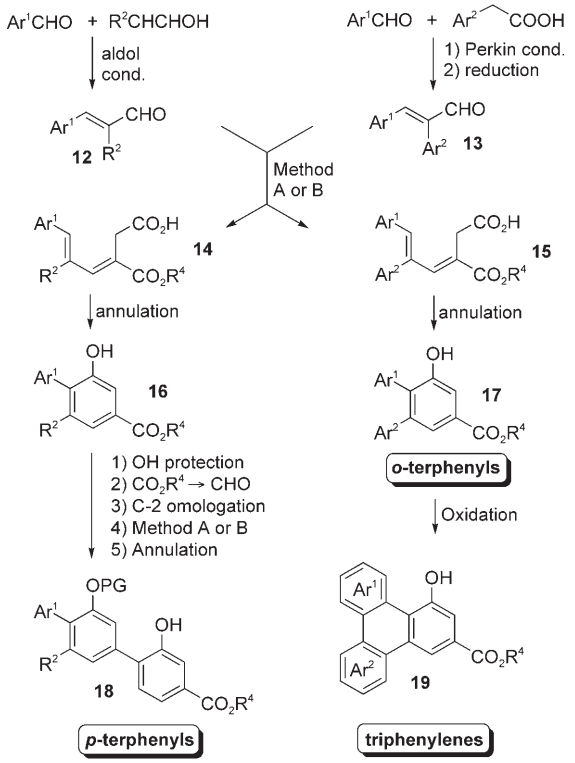
Preparation of Biaryls, Terphenyls, Triphenylenes and Heterosubstituted Phenols

The first preparation of substituted *m*-hydroxybenzoic acids by benzannulation of 3-methoxycarbonyl-3,5-hexadienoic acids (**1**; $R^3 = H$, $R^4 = Me$) was by Ramage et al.[14] These authors prepared the above-mentioned acids by Wittig reaction of ylide **11b** with α,β-unsaturated aldehydes, followed by regioselective acid hydrolysis of the *tert*-butyl ester. The cyclisation step was performed with diphenylphosphinic chloride as activating agent and *N*-methylmorpholine as base to give the corresponding phenol derivatives in moderate yields (47–62%). Since some of the starting aldehydes



Scheme 1. Proposed mechanisms of benzannulation of 3-alkoxycarbonyl-3,5-hexadienoic acids **1** and of 3-alkoxycarbonylhex-3-en-5-ynoic acids **2**.

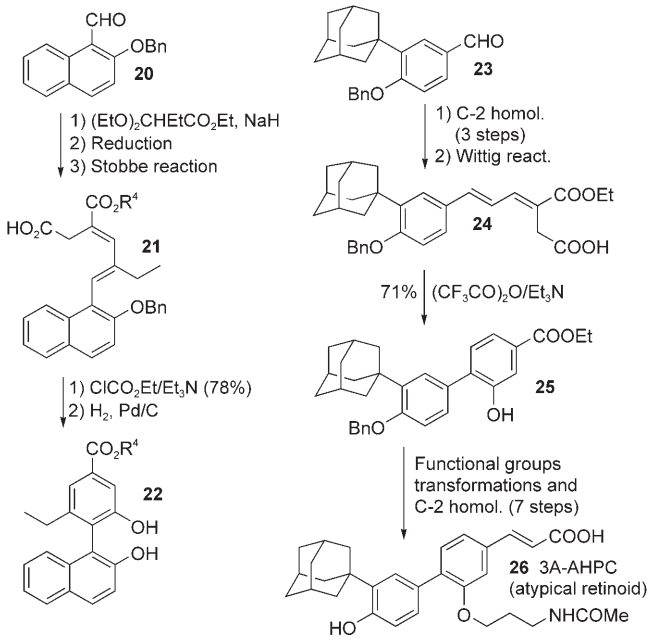
were aromatic, the method indicated the possibility to prepare biaryl compounds by annulation. Later, we improved[15] this synthetic way by a number of modifications to dienoic acid preparation and to the annulation step procedure. Primarily, we found that hexadienoic acids of type **1** and **2** can be easily prepared without the use of ylide **11b**. In the latter case the removal of *tert*-butyl protective group need strong acid conditions and some concomitant polymerisation lowered the efficiency of the process. In contrast, substituted cinnamic aldehydes **12** and **13** (Scheme 3) can be converted



Scheme 3. Synthesis of biaryls, terphenyls and triphenylenes from α,β-unsaturated aldehydes.[15,20]

into substituted dienoic acids **14** and **15**, respectively, both by Stobbe condensation or Wittig reaction with ylide **11a**. Moreover the cyclization step could be performed by the use of ethyl chloroformate as the activating agent. This reagent is less dangerous to handle, less expensive and more effective than diphenylphosphinic chloride, thus allowing an increase in the isolated yields of aromatic derivatives. According to our finding, substituted benzaldehydes were condensed with substituted acetaldehydes to give cinnamic aldehydes **12**, which can be converted into acids **14**.

Similarly, Perkin condensation of substituted benzaldehydes with substituted phenylacetic acids, followed by reduction of acidic functionality, gives aldehydes **13**, which can be transformed into acids **15**.[20] The application of the annulation process on **14** and **15** affords biaryls of type **16** and *o*-terphenyls of type **17**, respectively. The mild cyclization conditions allow the presence of different substituents on the starting aromatic ring, which could be also heteroaromatic. Moreover, this last arylation procedure can be applied iteratively. Protection of phenol group, transformation of the ester functionality into aldehyde, C-2 homologation, conversion in the dienoic acid and the annulation procedure gives the *p*-terphenyls of type **18**. It is worth noting that both *p*-terphenyls **18** and triphenylenes **19**, which are obtainable by oxidative coupling of the two *ortho*-aromatic rings of **17**, are of outstanding interest in the field of material science, because of their use as liquid crystal components.[21] Two further applications to biaryl synthesis are outlined in Scheme 4. The protected aldehyde **20**, easily obtained from



Scheme 4. Preparation of the atropoisomeric biaryl **22** and of the atypical retinoid 3A-AHPC **26**.[15,23]

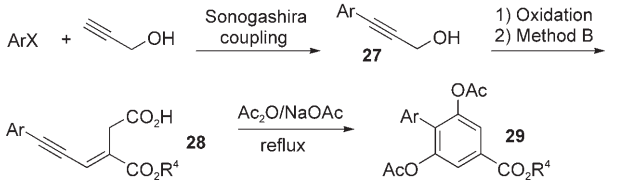
β-naphthol by Reimer–Tiemann formylation followed by benzylation, can be converted into acid **21** with an ethyl group in the 5-position of the dienoic framework. The annulation procedure and deprotection of the phenol group gives biaryl **22**, which proved to be a 1:1 mixture of atropoisomers configurationally stable at room temperature.[15,22] Compound **22** could be regarded as a binol analogue belonging to the *C*1 symmetry point group, showing the advantage of a carboxylic acid functionality. This acidic function was exploited[22] for the resolution of the chiral compound itself, according to the classical scheme of fractional crystallisation of diastereoisomeric salts.

Enantioenriched **22** was then successful used as a ligand for stereoselective Keck allylation of prochiral aldehydes. Similarly, the benzannulation of the 6-aryl-hexadienoic acid (**24**) is the key step in the preparation of the atypical retinoid 3A-AHPC (**26**).[23] The synthesis of this chemotherapeutic agent starts from the protected 3-adamantil-4-hydroxybenzaldehyde (**23**), which is homologated to the corre-

sponding cinnamaldehyde and then converted to the acid **24** by Wittig reaction. The annulation procedure affords biaryl **25** in good yield, which can be converted into target compound **26** by a number of further chemical transformations.

The annulation of 6-aryl-hex-3-en-5-ynoic acids of type **28** (Table 1) represents an additional new pathway to phenolic

Table 1. Preparation of 4-aryl-3,5-dihydroxybenzoic acid derivatives ($R^4 = Et$).[17]



Ar	Yield [%][a]	Ar	Yield [%][a]
phenyl	85	4-F-phenyl	88
2-Cl-phenyl	68	3,4-dimethoxyphenyl	81
4-nitrophenyl	76	3-thienyl	83

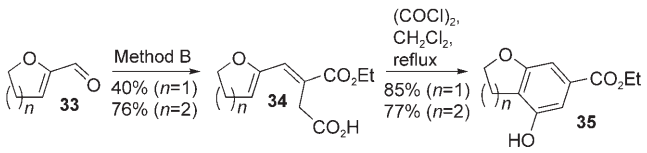
[a] Based on the isolated biaryl.

biaryl compounds. Accordingly, the starting materials are aromatic halides and propynol that can be transformed into propargylic alcohols **27** by Sonogashira coupling. Oxidation of alcohols **27** to the corresponding propargylic aldehydes followed by Wittig reaction gives acids **28**, which can be cyclized by heating with acetic anhydride in presence of sodium acetate. The resulting 4-aryl-3,5-dihydroxybenzoic acid derivatives **29** were obtained in good yields[17] and different kinds of substituents on the starting aryl ring are allowed.

Interestingly, when a heteroatom is linked directly to the hexadienoic acids framework, the annulation procedure affords heterosubstituted phenols.[16] Readily available 2- and 3-heterosubstituted α,β-unsaturated aldehydes **30** can be converted into the 4- and 5-heterosubstituted 3-hydroxybenzoic acid derivatives **32**, respectively, via intermediate acids **31** (Table 2).

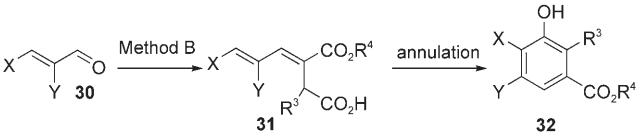
Both Et_3N/ClCOOEt and Et_3N/$(CF_3CO)_2O$ activating agents give good results and the heteroatom can be halogen, oxygen, sulfur and silicon. In addition, the heteroatom can be part of an aliphatic ring. Some studies in this field were reported by Paquette et al.[24] in their synthesis of tricyclic subunit of the austalides. They converted the dihydrofuran and dihydropyran aldehydes of type **33** to dienic acids **34** by Wittig reaction (Scheme 5).

These last compounds can be treated with oxalyl chloride in refluxing CH_2Cl_2 to give phenol derivatives **35**. In such



Scheme 5. Paquette pathway to dihydrobenzofuran and chromane derivatives.[24]

Table 2. Synthesis of heterosubstituted phenols from heterosubstituted α,β-unsaturated aldehydes.[16]



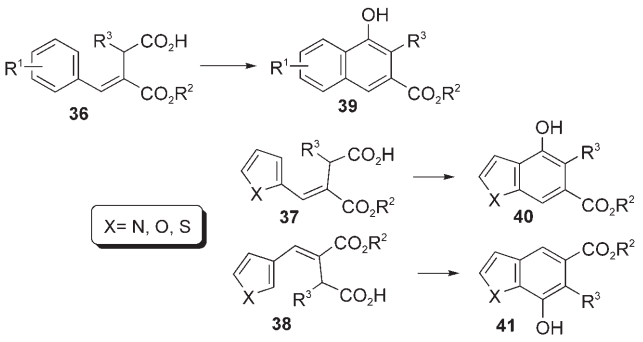
X	Y	R^3	R^4	Yield [%][a]
Ph	Br	H	Et	78
Br	Me	H	Et	89
*n*Pr	Br	H	Et	72
I	H	H	Et	91
Ph	OMe	H	Et	88
H	OMe	H	Et	70
OEt	H	H	Et	90
*n*Pr	OMe	H	Et	89
PhS	H	H	Et	70
PhS	Me	H	Et	86
Me_3Si	H	H	Et	60
PhS	Me	Me	Et	95

[a] After isolation of the product.

cases, the addition of base is not necessary, since the annulation process is mediated by intramolecular nucleophilic attack of the neighbouring enol ether.

Preparation of Aromatic and Heteroaromatic Ring-Fused Compounds

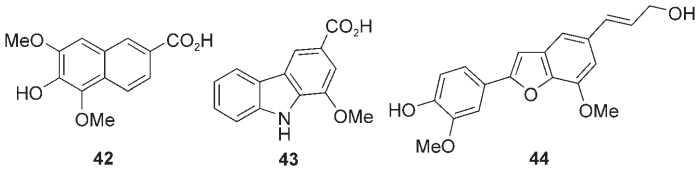
The benzannulation reaction of substituted hexadienoic acids **1** and **2** is also suitable for the preparation of different aromatics with ring-fused structures. The first relevant case regards the cyclization of acids **36–38** (Scheme 6) in which the double bond in the 5-position of the 3-alkoxycarbonyl-3,5-hexadienoic acids is part of an aromatic or heteroaromatic ring.



Scheme 6. Ring-fused aromatics: synthesis of naphthol, indole, benzofurane and benzothiophene derivatives.[25–29]

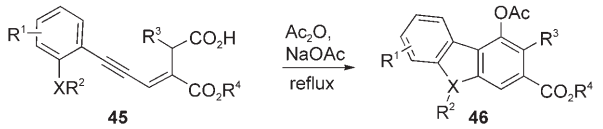
Such compounds are easily prepared from the corresponding aromatic aldehydes both by Stobbe and Wittig condensation. The annulation process was investigated in 1959[25] with acetic anhydride as activating agent. These pioneering studies showed good results mostly in the naphthol

synthesis, since the harsh conditions used were not compatible with different heterocyclic systems. More recently, these reactions were reinvestigated.[4b,26–29] We found that both the Et_3N/ClCOOEt and Et_3N/$(CF_3CO)_2O$ reagents are suitable activating agents. Naphthols **39** are obtained from acids **36** with good yields, particularly when the substituent group R activates the aromatic ring toward the electrophilic attack of the ketene. The same reagents are also effective in the annulation of the acids **37** and **38** to afford indoles, benzofuranes and benzothiophenes (**40** and **41**). The features of mildness of this method extended its synthetic applications especially for the preparation of natural products. Different natural products such as naphtoic acid **42**,[26] the carbazole alkaloid mukonine **43**[28] and the neolignan ailanthoidol **44**[29] were synthesised with this annulation as a key step



A further significant procedure to ring-fused heterocycles is based on the 6-arylhex-3-en-5-ynoic acids of type **45** (Table 3). Such compounds are analogous to acids **28** that give biaryl by benzannulation procedure. Otherwise, if the 6-aryl substituent shows a further *ortho* substitution with oxygen, sulfur or nitrogen, the heteroatom could act as nucleophile to give addition to the triple bond. We found that treatment of the acids **45** with refluxing acetic anhydride and sodium acetate gave heteroaromatic systems with ring-fused structures. Both the heterocyclic ring and the phenolic ring are built up in the cyclization step to afford compounds of type **46**, which are substituted dibenzofurans,[30] dibenzothiophenes[31] and carbazoles[32] depending of the heteroatom involved. When the heterosubstituents are methoxy or thiomethyl groups the reaction affords dibenzofurans and dibenzothiophenes with concomitant evolution of methyl acetate. Otherwise, since acetamide functionality is not an adequate nucleophile to promote the annulation step, a protecting/activating group is necessary when the substituent is nitrogen. In this case the *p*-tosyl group leads to N-protected carbazoles in very good yields.

Table 3. Ring-fused aromatics: synthesis of dibenzofuran,[30] dibenzothiophene[31] and carbazole[32] derivatives.



$R^{1[a]}$	R^2	R^3	R^4	Yield [%][b]
X = O (dibenzofurans)				
H	Me	H	Et	92
7-Me,8-OMe	Me	H	Et	97
8-NO_2	Me	H	Et	93
8-COOMe	Me	H	Et	95
7-I, 8-OMe	Me	H	Et	89
8–9-fused aromatic ring	Me	H	Et	87
6-Me, 9-*i*Pr	Me	H	Et	77
X = S (dibenzothiophenes)				
H	Me	H	Et	95
H	Me	Me	Et	91
7-Me	Me	H	Et	92
X = N (carbazoles)				
H	Ts	H	Et	89
6-Me	Ts	H	Et	90
7-OMe	Ts	H	Et	82
6-COOEt	Ts	H	Et	87
6-F	Ts	H	Et	91
6-NO_2	Ts	H	Et	77

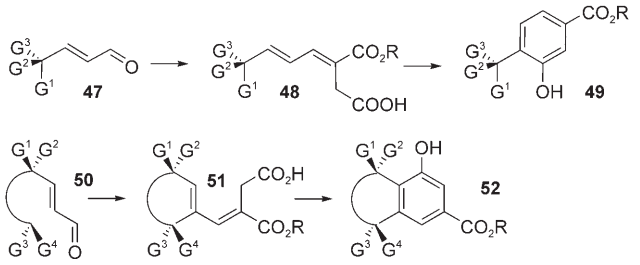
[a] Dibenzofuran, dibenzothiophene and carbazole numbering. [b] After isolation of the product.

Synthesis of Chiral Compounds with Benzylic Stereocentres

The stereoselective construction of compounds bearing a stereogenic benzylic carbon atom is a demanding synthetic transformation. Many relevant natural products and biologically active compounds show these structural features and a variety of methods for their enantioselective preparations have been developed. These approaches are based essentially on three pathways: the use of an appropriate aromatic precursor on which the stereocentre is built-up, the enantioselective addition of an aromatic reagent on an aliphatic precursor and the construction of the aromatic framework starting from a chiral aliphatic precursor. The last approach (benzannulation) could overcome many of the drawbacks of the other two and will be the more valuable one as the starting chiral compounds are easily available.

In this context, the cyclisation of 3-alkoxycarbonyl-3,5-hexadienoic acids has proved to be a very useful synthetic method. According to Scheme 7, α,β-unsaturated aldehydes **47** containing a stereocentre in the γ-position are convertible into acids **48** that afford phenol derivatives **49** after annulation reaction.

In the same way two benzylic stereocentres can be created by the employment of α,β-unsaturated aldehydes containing two allylic stereocentres. Moreover, when the double



Scheme 7. Benzannulation pathway to phenols bearing benzylic stereocentres. G = generic substituent or H.

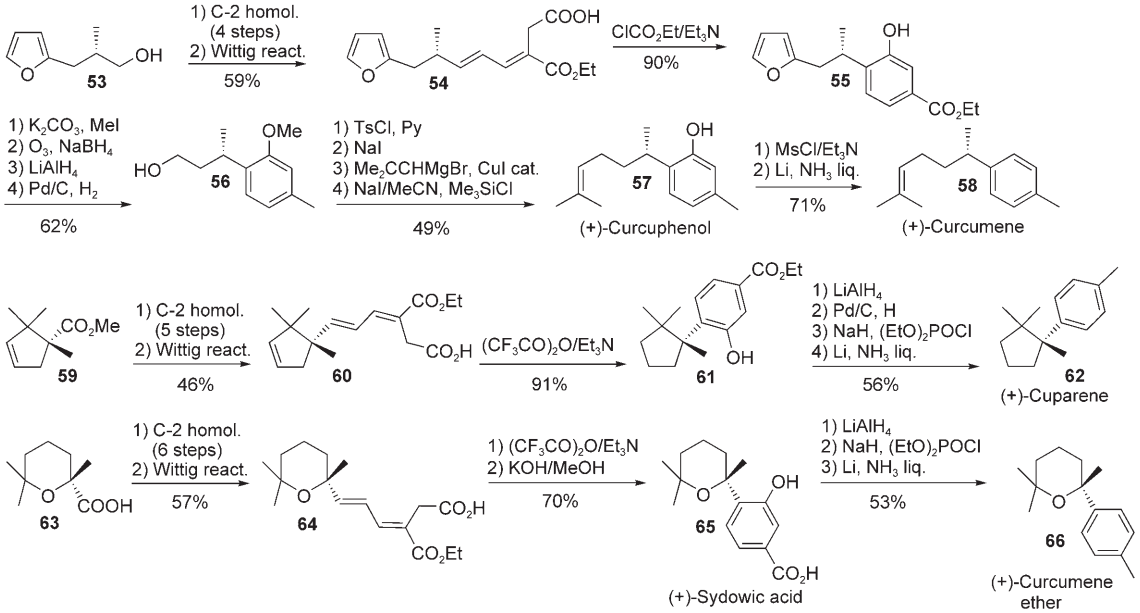
bond of the starting aldehyde **50** is part of a carbocyclic ring, the annulated product **52** is a chiral ring-fused aromatic. Overall, all the processes work in mild conditions and neither Et_3N/ClCOOEt nor Et_3N/$(CF_3CO)_2O$ activating agents produce racemization. These general features have been verified experimentally during the preparation of different chiral compounds.

The most relevant applications regard the enantiospecific synthesis of natural products. In this area, aromatic sequiterpenes are a challenging target, since they are components of many essential oils and their phenolic derivatives show different biological activities. This is the case of curcuphenol (**57**), in which the (*S*)-(+)-enantiomer (Scheme 8) inhibits the activity of gastric H, K-ATPase, and (*S*)-(+)-curcumene (**58**), which is a flavour component of *Curcuma* and *Zingiber* species. We performed the synthesis of this last compounds[33] using (*R*)-(−)-3-furyl-2-methylpropanol (**53**; 99% *ee*), easily available by enzymatic reduction of 2-methyl-3-furylacrolein, as the starting chiral building block. The hydroxyl group can be straightforwardly manipulated to obtain the hexadienoic acid **54**, which can be smoothly annulated to phenol **55** with Et_3N/ClCOOEt as an activating agent. The phenolic moiety was protected as ether and the furyl group was converted into the acid group by ozonolysis. Further functional group transformations afforded alcohol **56**, which can be converted into the related iodide and coupled with isobutenyl/magnesium bromide in the presence of copper(I) iodide to obtain a product that has the whole C-15 bisabolane skeleton. The following deprotection of methyl ether gives enantiopure (+)-curcuphenol (**57**), which can be reductively deoxygenated to afford (+)-curcumene (**58**).

Subsequent work shows that a similar pathway could be easily applied also to the synthesis of compounds containing quaternary benzylic stereocentes. The preparation of the cuparene framework was first investigated.[34] The enantiopure ester **59** is obtained in few steps from the cheap (1*R*,3*S*)-(+)-camphoric acid, available from the pool of chirality, and is transformed into suitable dienoic acid **60**. The annulation reaction affords phenol **61**, with a yield that depends on the activating agent used, and the subsequent reductive deoxygenation gives (+)-cuparene (**62**) without loss of optical purity. When ethyl chloroformate is used, the phenolic derivative (70%) is obtained together with a small amount of the diethyl ester of acid **60**. We assume that ethanol, derived from the decomposition of the mixed anhydride, reacts in competitively with the reactive dienylketene to give the ethyl ester. The same procedure performed with trifluoroacetic anhydride and a prolonged reaction time gives **61** in higher yield (91%). The different behaviour found in this last synthesis can be explained in terms of major steric hindrance around the position 6 of the hexadienoic system.

A similar situation was found during the synthesis of the two natural sesquiterpenes sydowic acid and curcumene ether.[35] In this case the starting C-9 chiral building block (*R*)-(−)-cinenic acid (**63**) is obtained by resolution of the easily available racemic material through fractional crystallization of its (*R*)-1-phenylethylamine salt. The conversion of this enantiopure acid into dienic acid **64** and the annulation reaction followed by saponification affords (+)-sydowic acid (**65**), which can be reduced and deoxygenated to give (+)-curcume ether (**66**). Again the Et_3N/$(CF_3CO)_2O$ activating agent is the reagent of choice in the cyclization step in which an oxygenated benzylic stereocentre is built from an alifatic precursor without loss of optical purity.

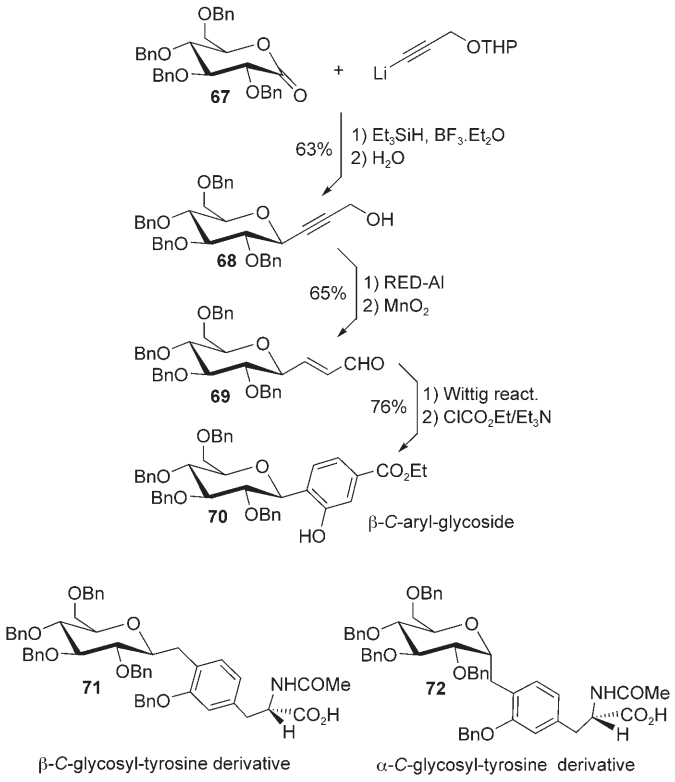
Yet another demanding target is the family of *C*-aryl glycosides. These compounds are natural, biologically active substances with an aromatic ring directly linked to the anomeric position. Many different synthetic approaches have been developed[36] and in most case these methods couple a carbohydrate derivative with a suitable aryl moiety.



Scheme 8. Enantioselective synthesis of aromatic sesquiterpenes.[33–35]

Since such processes are often not stereoselective and arenes bearing electron-withdrawing groups lack reactivity, alternative procedures in which the aromatic ring is constructed from a pre-existing *C*-glycoside could be more suitable.

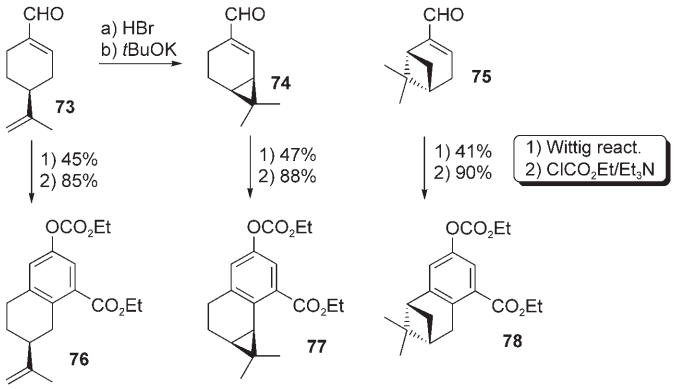
Accordingly, we reported a new pathway[37] to β-*C*-aryl-glycoside starting from easy available 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (**67**; Scheme 9). Compound **67** was condensed with the lithium salt of protected propynol to give an anomeric mixture of the related alcohol in almost quantitative yield. The mixture was treated with triethylsilane and boron trifluoride to afford exclusively the β-linked propargylic alcohol **68**. The triple bond was regioselectively reduced to the *trans* allylic alcohol, which was oxidised to the aldehyde **69**. Its conversion into 6-glucopyranose-3-ethoxycarbonyl-3,5-hexadienoic acid was performed by Wittig reaction and the following treatment with the Et_3N/ClCOOEt activating agent gave β-*C*-aryl-glycoside **70** in very good yield and as a single anomer. The described approach was then expanded by the regiospecific synthesis of further *C*-glycosides. Similarly, β and α-*C*-glycosyl-tyrosines derivatives **71** and **72**, respectively,[38] were prepared using the above mentioned benzannulation reaction as a key step.



Scheme 9. Stereoselective synthesis of *C*-aryl-glycosides.[37,38]

Synthesis of Chiral Tetrahydronaphtalenes

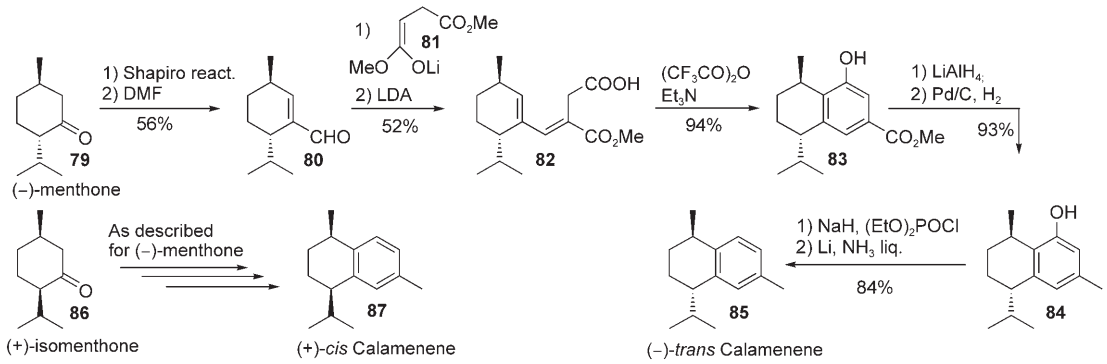
As shown in Scheme 7, when the double bond in the 5-position of the 3-alkoxycarbonyl-3,5-hexadienoic acids is part of a ring, the result of the annulation reaction is a ring-fused aromatic. The interest in various terpenoid natural products with a chiral tetrahydronaphthalene basic structure has recently stimulated the research of new methods for the aromatic annulation of aliphatic cyclohexanic precursors. An efficient route for the synthesis of these chiral tetrahydronaphthalenes has to have a high control on the regiochemistry of the cyclization step, and to preserve the configuration of the existing stereocentres. These requisites are conveniently satisfied by the synthetic procedure involving the 3-alkoxycarbonyl-3,5-hexadienoic acids. The first realisation of this concept was reported from our laboratories in 1998[39] during a work aimed to convert easily available chiral unsaturated aldehydes into chiral tetrahydronaphthalenes (Scheme 10).



Scheme 10. Preparation of chiral tetrahydronaphthalenes.[39]

Starting materials are the commercially available (−)-perillaldehyde (**73**) and (−)-myrtenal (**75**) together with the bicyclic substrate **74**, which is prepared from **73** by treatment with HBr in acetic acid, followed by reaction with potassium *tert*-butoxide. The conversion of aldehydes **73**–**75** into corresponding hexadienoic acids and the subsequent annulation procedure with an excess of ethyl chloroformate and triethylamine as activating agent gives the phenol derivatives **76**–**78**, respectively, in a stereospecific fashion.

Afterwards, a more challenging target was devised. The preparation of chiral sesqui- and diterpene compounds that contain the basic calamenene framework was investigated. These compounds are important natural products that have attracted considerable attention because of their remarkable properties. The sesquiterpene calamenene itself is widespread in plants and is a component of a number of essential oils. In addition, some structurally related oxygenated derivatives display a wide range of biological activities, as for example the serrulatane and pseudopterosin diterpenoids[40] that possess powerful anti-inflammatory activities. From a synthetic point of view, the major problem consists in the stereoselective construction of the two benzylic stereocentres that could originate four isomeric calamenene structures. The benzannulation approach[41] to the more simple member of this class is based on the use of (−)-menthone



Scheme 11. Benzannulation approach to the synthesis of calamenene sesquiterpenes.[41]

79 and (+)-isomenthone **86** as starting materials (Scheme 11).

The regioselective introduction of the double bond at the C2(3) carbon is performed by the Shapiro reaction followed by the DMF treatment of the lithium derivative to give the isomerically pure aldehyde **80**. A further essential aspect of the synthesis is the regioselective conversion of the menthones into the corresponding mono esters mono acids of type **82**. Since neither Wittig reaction nor Stobbe condensation took place under the usual conditions, the more nucleophilic lithium enolate **81** was employed to accomplish this homologation step. This behaviour is probably due to the steric hindrance of the isopropyl group. Accordingly, aldehydes **80** react with **81** at low temperature and the condensation intermediate can be treated with an equimolar amount of LDA to give acid **82**.

The homologated dienoic acids are obtained in good yields, although as a mixture of isomers in which the compound **82** was one of the major components. Since only 3-(*E*)-hexadienoic acids are able to give benzannulation reactions, the whole isomeric mixture can be treated with trifluoroacetic anhydride as activating agent, in the presence of an excess of triethylamine. Isomerically pure phenol **83** is obtained and the reaction yield indicates the quantitative conversion of starting acid **82**. The reduction of the ester group to a methyl substituent affords natural 8-hydroxy-calamenene (**84**), which can be converted in (−)-*trans*-calamenene (**85**). By the route way (+)-isomenthone (**86**) gives isomerically pure (+)-*cis* calamenene (**87**), clearly demonstrating that the benzannulation approach on the 3-oxygenated-*p*-menthane framework allows the straightforward construction of this kind of sesquiterpenes in stereospecific fashion.

Conclusion

According to the survey presented here, the specific preparation of different polysubstituted aromatics can be achieved by the benzannulation reaction of substituted hexadienoic acids precursors. Since these starting materials are easily prepared and the reaction mode for a given substrate can be easily predicted, the described procedures hold a general synthetic significance. This fact ensures that the described procedures can be added to the known range of benzannulation methods. Yet, there is ample possibility of more new unexpected routes to other aromatic structures, as only a restricted group of substituents of the 3,5-hexadienoic and hex-3-en-5-ynoic acids framework has been employed in the described studies. Moreover, our investigations have showed that the annulation protocol is very flexible and may be adapted to the synthesis of aromatics of different structural classes. These features indicate that studies on these kind of annulation are far from being complete and will be certainly be further expanded in the next years.

[1] a) G. A. Olah, *Acc. Chem. Res.* **1971**, *4*, 240–248; b) J. F. Bunnett, R. E. Zahler, *Chem. Rev.* **1951**, *49*, 273–412; c) J. F. Bunnett, *Acc. Chem. Res.* **1978**, *11*, 413–420.
[2] a) K. Tamao, in *Comprehensive Organic Synthesis, Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford (UK), **1991**, pp. 435–480; b) D. W. Knight, in *Comprehensive Organic Synthesis, Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford (UK), **1991**, pp. 481–520; c) K. Sonogashira, in *Comprehensive Organic Synthesis, Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford (UK), **1991**, pp. 521–549.
[3] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933.
[4] a) P. Bamfield, P. F. Gordon, *Chem. Soc. Rev.* **1984**, *13*, 441–488; b) C. B. de Koning, A. L. Rousseau, W. A. L. van Otterlo, *Tetrahedron* **2003**, *59*, 7–36.
[5] a) W. Oppolzer, in *Comprehensive Organic Synthesis, Vol. 5* (Eds: B. M. Trost, I. Fleming), Pergamon, Oxford (UK), **1991**, pp. 315–399; b) G. Brieger, J. N. Bennett, *Chem. Rev.* **1980**, *80*, 63–97; for Diels–Alder benzannulations not described in reference [4] see: c) D. L. Boger, M. D. Mullican, *J. Org. Chem.* **1984**, *49*, 4033–4044; d) R. L. Snowden, M. Wüst, *Tetrahedron Lett.* **1986**, *27*, 703–704; e) M. E. Hayes, H. Shinokubo, R. L. Danheiser, *Org. Lett.* **2005**, *7*, 3917–3920.
[6] a) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901–2915; b) M. Rubin, A. W. Sromek, V. Gevorgyan, *Synlett* **2003**, 2265–2291; c) T. J. Donohoe, A. J. Orr, M. Bingham, *Angew. Chem.* **2006**, *118*, 2730–2736; *Angew. Chem. Int. Ed.* **2006**, *45*, 2664–2670.
[7] K. H. Dötz, P. Tomuschat, *Chem. Soc. Rev.* **1999**, *28*, 187–198.
[8] a) A. R. Katritzky, J. Li, L. Xie, *Tetrahedron*, **1999**, *55*, 8263–8293; for [3+3] benzannulations not described in references [4a] or [8a] see: b) R. K. Dieter, Y. J. Lin, *Tetrahedron Lett.* **1985**, *26*, 39–42; c) P. Langer, G. Bose, *Angew. Chem.* **2003**, *115*, 4165–4168; *Angew. Chem. Int. Ed.* **2003**, *42*, 4033–4036.
[9] a) S. T. Perri, H. W. Moore, *J. Am. Chem. Soc.* **1990**, *112*, 1897–1905; b) R. L. Danheiser, R. G. Brisbois, J. J. Kowalczyk, R. F.

Miller, *J. Am. Chem. Soc.* **1990**, *112*, 3093–3100; c) A. Gurski, L. S. Liebeskind, *J. Am. Chem. Soc.* **1993**, *115*, 6101–6108; d) O. Barun, S. Nandi, K. Panda, H. Ila, H. Junjappa, *J. Org. Chem.* **2002**, *67*, 5398–5401; e) W. F. Austin, Y. Zhang, R. L. Danheiser, *Org. Lett.* **2005**, *7*, 3905–3908; f) A. Goel, D. Verma, M. Dixit, R. Raghunandan, P. R. Maulik, *J. Org. Chem.* **2006**, *71*, 804–807.

[10] X. Bi, D. Dong, Q. Liu, W. Pan, L. Zhao, B. Li, *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579.

[11] a) M. Iwasaki, Y. Kobayashi, J.-P. Li, H. Matsuzaka, Y. Ishii, M. Hidai, *J. Org. Chem.* **1991**, *56*, 1922–1927; b) K. K. Wang, *Chem. Rev.* **1996**, *96*, 207–222; c) C.-Y. Lee, C.-F. Lin, J.-L. Lee, C.-C. Chiu, W.-D. Lu, M.-J. Wu, *J. Org. Chem.* **2004**, *69*, 2106–2110; d) X. Zhang, S. Sarkar, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 236–243.

[12] V. A. Bakulev, *Russ. Chem. Rev.* **1995**, *64*, 99–124.

[13] a) H. W. Moore, O. H. W. Decker, *Chem. Rev.* **1986**, *86*, 821–830; b) T. T. Tidwell, *Angew. Chem.* **2005**, *117*, 5926–5933; *Angew. Chem. Int. Ed.* **2005**, *44*, 5778–5785.

[14] K. Clinch, C. J. Marquez, M. J. Parrott, R. Ramage, *Tetrahedron* **1989**, *45*, 239–258.

[15] E. Brenna, C. Fuganti, V. Perozzo, S. Serra, *Tetrahedron* **1997**, *53*, 15029–15040.

[16] S. Serra, C. Fuganti, A. Moro, *J. Org. Chem.* **2001**, *66*, 7883–7888.

[17] S. Serra, C. Fuganti, *Synlett* **2002**, 1661–1664.

[18] W. S. Johnson, G. H. Daub, in *Organic Reactions, Vol. 6* (Ed.: A. Adam), Wiley, New York, **1951**, pp. 1–73.

[19] a) R. F. Hudson, P. A. Chopard, *Helv. Chim. Acta* **1963**, *46*, 2178–2185; b) E. Röder, H. Krauss, *Liebigs Ann. Chem.* **1992**, 177–181.

[20] E. Brenna, C. Fuganti, S. Serra, *J. Chem. Soc. Perkin Trans. 1* **1998**, 901–904.

[21] M. D. Watson, A. Fechtenkötter, K. Müllen, *Chem. Rev.* **2001**, *101*, 1267–1300.

[22] E. Brenna, L. Scaramelli, S. Serra, *Synlett* **2000**, 357–358.

[23] E. Brenna, C. Fuganti, G. Fronza, F. G. Gatti, F. Sala, S. Serra, *Tetrahedron* **2007**, *63*, 2351–2356.

[24] L. A. Paquette, M. M. Schulze, D. G. Bolin, *J. Org. Chem.* **1994**, *59*, 2043–2051.

[25] a) A. M. El-Abbady, L. S. El-Assal, *J. Chem. Soc.* **1959**, 1024–1026; b) S. M. Abdel-Wahhab, L. S. El-Assal, *J. Chem. Soc. C* **1968**, 867–869; c) S. M. Abdel-Wahhab, N. R. El-Rayyes, *J. Chem. Soc. C* **1971**, 3171–3173; d) S. M. Abdel-Wahhab, N. R. El-Rayyes, *J. Prakt. Chem.* **1972**, *314*, 213–219; e) N. R. El-Rayyes, *J. Prakt. Chem.* **1973**, *315*, 295–299; f) N. R. El-Rayyes, *J. Prakt. Chem.* **1973**, *315*, 300–306; g) N. R. El-Rayyes, N. A. Al-Salman, *J. Prakt. Chem.* **1976**, *318*, 816–822.

[26] C. Fuganti, S. Serra, *J. Chem. Res. Synop.* **1998**, 638–639.

[27] M. Kim, E. Vedejs, *J. Org. Chem.* **2004**, *69*, 6945–6948.

[28] E. Brenna, C. Fuganti, S. Serra, *Tetrahedron* **1998**, *54*, 1585–1588.

[29] C. Fuganti, S. Serra, *Tetrahedron Lett.* **1998**, *39*, 5609–5610.

[30] S. Serra, C. Fuganti, *Synlett* **2003**, 2005–2008.

[31] S. Serra, Unpublished results.

[32] S. Serra, C. Fuganti, *Synlett* **2005**, 809–812.

[33] C. Fuganti, S. Serra, *Synlett* **1998**, 1252–1254.

[34] C. Fuganti, S. Serra, *J. Org. Chem.* **1999**, *64*, 8728–8730.

[35] S. Serra, *Synlett* **2000**, 890–892.

[36] C. Jaramillo, S. Knapp, *Synthesis* **1994**, 1–20.

[37] C. Fuganti, S. Serra, *Synlett* **1999**, 1241–1242.

[38] E. Brenna, C. Fuganti, P. Grasselli, S. Serra, S. Zambotti, *Chem. Eur. J.* **2002**, *8*, 1872–1878.

[39] E. Brenna, C. Fuganti, S. Serra, *Synlett* **1998**, 365–366.

[40] T. J. Heckrodt, J. Mulzer, *Top. Curr. Chem.* **2005**, *244*, 1–41.

[41] S. Serra, C. Fuganti, *Tetrahedron Lett.* **2005**, *46*, 4769–4772.

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